KMJ
KUWAIT MEDICAL JOURNAL
The Official Journal of The Kuwait Medical Association

EDITORIAL

Magical Mem-Brain-Biology's Holy Grail 173
Belle M Hegde

REVIEW ARTICLE

Osteoarthritis of the Knee: Review of Risk Factors and Treatment Programs with Special Reference to Evidence-Based Research 176
Ali Al Mukaimi, Ehab El Salawi, Anders Lindstrand

ORIGINAL ARTICLES

Re-appraisal of Vaginal Delivery after Previous Two Cesarean Sections 189
Lulu Abdullah Al Nuaim

Characterization of Acrylamide Mediated Testicular Toxicity in Rat: Light and Electron Microscopic Study 196
Nesreen Rajeh, Samar Al Saggaf, Nasra Ayuob, Sufian ElAssouli

Complications of Brucellosis in Adults: An Experience from a State Hospital in Southeastern Anatolia Region of Turkey 206
Mehmet Ulug, Nuray Can-Ulug

Combination of Ballistic Lithotripsy and Transurethral Plasmakinetic Resection for Treating 200 Men with Bladder Calculi and Benign Prostatic Hyperplasia: A Trial with 2-Year Follow-Up 213
Jiansong Wang, Haifeng Wang, Yigang Zuo, Delin Yang, Mingxia Ding, Ruping Yan

Correlation of Fine Needle Aspiration Cytologic Features of Extrapulmonary Tuberculous Lesions with detection of Acid Fast Bacilli – Mubarak Al-Kabeer Hospital, Kuwait Experience 216
Kusum Kapila, Bahiyah E Haji, Sara S George, Mohammad Jaragh, Taiba A Alansary, Eiman E Mokaddas

Evaluation of Insulin Resistance by the Homeostasis Model Assessment in Female Patients with Primary Sjögren's Syndrome 220
Gonca Karabulut, Fulden Sarac, Gul Kitapcioglu, Candeger Yılmaz, Yasemin Kabasakal

CASE REPORTS

Duodenal Diverticulum Mimicking Pancreatic Abscess 224
Khaleda Dashti, Ammar Aljumah, Sarah Almutawa

Fenofibrate-Induced Rhabdomyolisis in a Dialysis Patient with Subclinical Hypothyroidism– Case Report 227
Funda Sari, Metin Sarikaya, Ramazan Cetinkaya

Splenic Vein Thrombosis: A Rare Complication of Coeliac Disease 230
Anwar QKHS Alenezi, Jamal Monzer Hilal, Ali Mahmoud Behbehani

Traumatic Anterior Hip Dislocation (Perineal) with Ipsilateral Avulsion Fracture of the Greater and Lesser Trochanter in an Adolescent 234
Janko Heberle

Acquired Factor VIII Inhibitor in A Patient with Mixed Connective Tissue Disease: A Case Report 238
Ekhlas Alhumoud, Hani Al-Humoud, Hana Mohammad Abdulla

Appendicitis Caused by Accidentally Ingested Metallic Pin: A Case Report 241
Lamya Al-Sarraf, Venugopal Naik Keluth Chavan, Renu Gupta

Complex Regional Pain Syndrome in a Child; The First Case Report from Kuwait 244
Aida Abdul-Malik, Zaid Al-Harbash, Khalid Al-Othman

KU ISSN 0023-5776

Continued inside

Vol. 43 No. 3 SEPTEMBER 2011

KUWAIT MEDICAL JOURNAL

CONTENTS

Continued from cover

SELECTED ABSTRACTS OF ARTICLES PUBLISHED ELSEWHERE BY AUTHORS IN KUWAIT 247

FORTHCOMING CONFERENCES AND MEETINGS 251

WHO-FACTS SHEET 259

1. **Hepatitis C**
2. **Yellow fever**
3. **Disability and Health**
4. **Environmental and Occupational Cancers**
5. **Chronic Obstructive Pulmonary Disease (COPD)**

❊ ❊ ❊

Open access for articles at: ***www.kma.org.kw/KMJ***

Indexed and abstracted in:

EMBASE (*The Excerpta Medica Database*)

Science Citation Index Expanded (also known as **SciSearch®)**

Journal Citation Reports/Science Edition

IMEMR Current Contents (*Index Medicus* for the Eastern Mediterranean Region; available online at: www.emro.who.int/EMRJorList/online.aspx

PUBLISHER: The Kuwait Medical Journal (KU ISSN-0023-5776) is a quarterly publication of THE KUWAIT MEDICAL ASSOCIATION. Address: P.O. Box 1202, 13013 Safat, State of Kuwait; Telephone: 1881181 Fax: 25317972, 25333276. E-mail : kmj@kma.org.kw

INSTRUCTIONS FOR AUTHORS: Authors may submit manuscripts prepared in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. These Requirements are published in each issue of the Kuwait Medical Journal.

CHANGE OF ADDRESS: Notice should be sent to the Publisher six weeks in advance of the effective date. Include old and new addresses with mail codes.

KUWAIT MEDICAL JOURNAL (previously The Journal of the Kuwait Medical Association) is added to the list of journals adhering to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals", American College of Physicians, Independence Mall West, Sixth Street at Race, Philadelphia, PA 19106-1572, USA, and can be located at http://www.icmje.org/jrnlist.html

Kuwait Medical Journal (KMJ)

Published by the Kuwait Medical Association
Previously known as The Journal of the Kuwait Medical Association (Est. 1967)

EDITORIAL OFFICE

Editorial Manager : Babichan K Chandy
Language Editor : Abhay U Patwari

EDITORIAL ADDRESS

P.O. Box: 1202, 13013-Safat, Kuwait
Telephone: (00-965) 1881181(Ext. 201) - Fax: (00-965) 25317972, 25333276
E-mail: kmj@kma.org.kw
Website: www.kma.org.kw/KMJ

KUWAIT MEDICAL JOURNAL (KMJ)
Instructions for Authors

INTRODUCTION

Formerly known as 'The Journal of the Kuwait Medical Association', the Kuwait Medical Journal (KMJ) was established in the year 1967. It is the official publication of the Kuwait Medical Association and published quarterly and regularly in March, June, September and December.

AIMS AND SCOPE

KMJ aims to publish peer-reviewed manuscripts of international interest. Submissions on clinical, scientific or laboratory investigations of relevance to medicine and health science come within the scope of its publication. Original articles, case reports, brief communications, book reviews, insights and letters to the editor are all considered. Review articles are solicited. Basic medical science articles are published under the section 'Experimental Medicine'.

GENERAL

The Kuwait Medical Journal is a signatory journal to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, the fifth (1997) revision of a document by the international Committee of Medical Journal Editors. A description of important features of this document is available on the Lancet website at http://www.thelancet.com. Alternatively, you may consult the following: N Engl J Med 1997; 336:307-315 or order the leaflet "Uniform Requirements for Manuscripts Submitted to Biomdical Journals" by writing to the Editor of the British Medical Journal (BMJ), BMA House, Tavistock Square, London WC1H 9JR, UK.

To present your original work for consideration, one complete set of the manuscript, written in English (only), accompanied by tables, and one set of figures (if applicable), should be submitted to the Editor. Authors should also provide the manuscript on an IBM compatible medium such as floppy, CD (in MS word format) or pen-drive, if not submitted through e-mail. The KMJ editorial office uses Microsoft 'Office 2007' word processing and 'Excel' programs. Details of the type of computer used, the software employed and the disk system, if known, would be appreciated.

ELECTRONIC SUBMISSIONS

A manuscript could be submitted through e-mail as an attached word-document **(.doc), together with a scanned copy of the signed consent letter of the author(s).** The consent letter could otherwise be faxed to the journal office at (00965) 25317972 or 25333276. **Figures/photographs, photomicrogrphs etc, if any, need to be in .jpg/.jpeg/.bmp format with 300 dpi resolution and illustrations such as drawings, charts etc., as Excel files. All the figures including illustrations should be saved as Fig. 1, Fig. 2, etc in running sequence and submitted as seperate attachments along with the manuscript.** Incomplete/improper submissions will not be processed, and will be returned.

Following a peer review process, the corresponding author will be advised of the status; acceptance/recommendation for revision or rejection of the paper, in a formal letter sent through post and/or e-mail. A galley proof will be forwarded to the corresponding author through e-mail before publication of the accepted papers which must be returned to the journal office within 48 hours with specific comments, if any. Corrections in the galley proof, in case any, must be limited to typographical errors, or missing contents only.

ETHICAL CONSIDERATIONS

Where human investigations or animal experiments are part of the study, the design of the work has to be approved by local ethics committee. A relevant statement of approval should be added in the 'Subjects and Methods' section of the manuscript.

PREPARATION OF THE MANUSCRIPT

The manuscript should be typed as 'normal text' in single column, with no hyphenation and no hard returns within paragraphs (use automatic word wrap) on A4 size (29.7 x 21 cm) paper in single column format, preferably in font size no.12. Cell format for paragraphs, artwork and/or special effects for the text and/or table(s) are not acceptable. Italics shall be used only for foreign/Latin expressions and/or special terminologies such as names of micro organisms. Maintain a minimum of 2 cm margin on both sides of the text and a 3 cm margin at the top and bottom of each page. No part of the text other than abbreviations and/or subtitles shall be written in upper case (ALL capital). Header/foot notes, end notes, lines drawn to separate the paragraphs or pages etc. are not acceptable. Do not submit articles written/saved in 'Track-change' mode

THE ORDER OF THE TEXT

Original Articles: Title page, Abstract (in structured format for original articles) of no more than 250 words, Key Words (no more than five), followed by Introduction, Subjects (or Materials) and methods, Results, Discussion, Conclusion, Acknowledgment/s (if any), References, Legends to figures, Tables, and Figures. Each section should begin on a new page.

Review Articles (solicited): Title Page, Abstract of no more than 250 words, Key Words (no more than

five), followed by Introduction, Methods/History (if applicable), Literature Review, Conclusion, Acknowledgment/s (if any), References, Legends to figures (if applicable), Tables, and Figures. Each section should begin on a new page.

Case Studies: Title page followed by Abstract (a short summary of not more than 200 words), Key Words, Introduction, Case history/report, Discussion, Conclusion, Acknowledgment/s (if any), References, Legends to figures (if applicable), Tables, and Figures.

Manuscript should be paginated consecutively, commencing with the title page. Main headings, introduction, subjects and methods, etc., should be placed on separate lines.

THE TITLE PAGE

Title page of the submitted manuscript should provide a clear title of the study followed by **full names of all authors**, the highest academic degree and affiliations if any, the name and address of **the institution/s where the work was done including the department, the name and complete address of the corresponding author** to whom proofs and correspondences shall be sent, **duly supported with contacts such as telephone, mobile/cell, fax and e-mail address**.

STRUCTURED ABSTRACT

A structured abstract of **no more than 250 words** is required for studies **under the section "Original Articles"**. It must provide an overview of the entire paper, and **should contain succinct statements on the following,** where appropriate: **Objective(s), Design, Setting, Subjects, Intervention(s), Main Outcome Measure(s), Result(s), and Conclusion(s).** (See: Haynes RB, Mulrow CD, Huth AJ, Altman DG, Gardner MJ. More informative abstracts revisited. Annals of Internal Medicine 1990; 113:69-76). **Abstract for all other category of submissions shall be a short summary not more than 200 words followed by Key words** and the report or review.

KEY WORDS

Key Words should be preferably MeSH terms, and shall not duplicate words already in the manuscript title; MesH terms can be checked at: <http://www.nlm.nih.gov/mesh/>.

TABLES

Tables typed on separate pages using table format **should follow the list of references**. All tables must be numbered consecutively and provided with appropriate titles. Contents of the table should be simple, and information therein not duplicated, but duly referred to, in the main text. Tables recording only a few values are not appreciated, since such information can be more accurately, usefully and concisely presented as a sentence or two in the text.

DESIGN OF THE WORK

This should be stated clearly. The rationale behind the choice of sample size should be given. Those about to begin randomized controlled studies may wish to study the CONSORT statement (JAMA 1996; 276:637-639).

ILLUSTRATIONS

Photographs, Photomicrographs, line drawings, transparencies, etc. must be of high quality and supplied in original (not photocopies or laser prints) of size 10 x 15 cm (4" x 6"). Regarding scanned image requirements, see 'Electronic Submissions'. Photographs should fit within a print area of 164 x 235 mm. All the figures must be numbered serially (Fig 1, Fig 2 etc.) and the figure number written on the back side of each (in case of hard copy submission) and an arrow drawn to indicate the top edge. Figures where patient's identity is not concealed, authors need to submit a written consent of the patient or of the patient's guardian, in case of minors. **Figure legends/titles should be listed separately after the 'References' section.** If any of the tables, illustrations or photomicrographs have been published elsewhere previously, a written consent for reproduction is required from the copyright holder along with the manuscript. Charts and drawings must be professionally done, duly titled and submitted in Excel format as separate files. When charts are submitted, the numerical data on which they were based should be supplied.

ABBREVIATIONS

Except for units of measurement, **abbreviations should be defined on first use** and then applied consistently throughout the article. Non-standard abbreviations or those appearing fewer than three times are not accepted. Use abbreviated units of measure, only when used with numbers. Abbreviations used as legends in tables and/or figures should be duly defined below the respective item.

NUMBERS AND UNITS

Measurements of length, height, weight and volume must be reported in metric units (meter, kilogram, liter etc.) or their decimal multiples. Temperature should be given in degrees Celsius. Blood pressure in mm Hg, and **hematological and biochemical measurements in Système International (SI) units**. For decimal values, use a point, and not a comma, e.g., 5.7. Use a comma for numbers > 10,000 (i.e., 10^3) and for numbers < 9999, do not use a comma (e.g., 6542).

DRUG NAMES

Non-proprietary (generic) names of product should be employed. If a brand name for a drug is used, the British or international non-proprietary (approved) name should be given in parentheses. The source of any new or experimental preparation should also be given.

REFERENCES

Indicate references in the text in sequence using Arabic numerals **within square brackets and as superscripts (e.g.,[1, 3-5] etc).** Do not quote additional data (like part of the title, year of publication etc.) from the references with citations in the text, unless very important. In the References section, list them in the same sequence as they appeared in the text. **Include the names and initials of all authors if not more than six (≤ 6); when authorship exceeds six, use *et al* after three author names. Do not use automatic numbering, end notes or footnotes for references.** References to manuscripts either in preparation or submitted for publication, personal communications, unpublished data, etc. are not acceptable.

The author's name should be followed by the title of the article, the title of the journal abbreviated in the style of the Index Medicus, the year of publication, the volume number and the first and last page numbers. References to books should give the title of the book, followed by the place of publication, the publisher, the year and the relevant pages. Journal titles should be abbreviated according to the style in Index Medicus. References should be limited to those relating directly to the contents of the paper and should be set out in Vancouver style, as shown in the examples below.

EXAMPLES

Article

Burrows B, Lebowitz MD. The βagonists dilemma (editorial). N Engl J Med 1992; 326:560-561.

Book

Roberts NK. The cardiac conducting system and His bundle electrogram. New York, Appleton-Century-Crofts, 1981; 49-56.

Book chapter

Philips SJ, Whisnam JP. Hypertension and stroke, In: Laragh JH, Bremner BM, editors. Hypertension: pathophysiology, diagnosis, and management. 2nd Ed. New York: Raven Press; 1995. p 465-478.

Weblinks

U.S. positions on selected issues at the third negotiating session of the Framework Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform, 2002. (Accessed June 4, 2003, at http://www.house.gov/reform/min/inves.tobacco/ index_accord.htm.)

AUTHORSHIP AND CONSENT FORM

All authors must give their signed consent for publication in a letter of submission, which should accompany the manuscript. This letter should contain the statement that *"This manuscript (write the title) is an unpublished work which is not under consideration elsewhere and the results contained in this paper have not been published previously in whole or part, except in abstract form. In consideration of the KMJ accepting my/our submission for publication, the author(s) undersigned hereby assign all copyrights ownership to the KMJ and shall have no right to withdraw its publication. It is expressly certified that I/we, have done/actively participated in this study and agree to the accuracy of contents of this manuscript. It was conducted in accordance with current ethical considerations and meets with the committee's approval. I/all of us agree to its publication in KMJ and to the authorship as expressed in this declaration and in the title page of our manuscript"*. The participation of the authors must include: conception, design, analysis, interpretation, or drafting the article for critically important intellectual content. A change in authorship after initial submission of a manuscript should be duly supported with a documented request from the main author, duly endorsed by the author removed and/or-added. No changes in authorship will be permitted after acceptance for publication of a manuscript.

More than six authors are not appreciated for an article and if listed, the authors may be asked to justify the contribution of each individual author. For case reports, not more than three authors are acceptable. Regarding contributions of authors over the limit mentioned above, read the 'Acknowledgment' section.

ACKNOWLEDGMENT

The objective of this section is to disclose affiliations with or association of any organization with a direct financial interest in the study. Otherwise, it will be considered as having no such interests. Contributions of others who have involved in the study, such as statisticians, radiologists etc. and/or those who have assisted in the preparation of the manuscript submitted could also be included in this section.

COPY RIGHT

SUBMISSION OF A MANUSCRIPT

Manuscripts to be submitted to:

The Editor
Kuwait Medical Journal
P.O. Box: 1202
Code-13013-Safat
Kuwait
Telephone (965) 1881181(Ext. 201)
Fax (965) 25317972; 25333276
E-mail: kmj@kma.org.kw
Website: www.kma.org.kw/KMJ

Editorial

Magical Mem-Brain- Biology's Holy Grail

Belle M Hegde
The Journal of the Science of Healing Outcomes, State College, Pennsylvania, USA and Mangalore, India*
Manipal University, Manipal India**
The Middlesex Medical School, University of London, UK#
Northern Colorado University, USA##

Kuwait Medical Journal 2011; 43 (3): 173-175

"The goal of life is living in agreement with nature."
Zeno
From Diogenes Laertius, Lives of Eminent Philosophers

I have lifted the first half of the caption directly from Bruce Lipton, the celebrated new biology's guru and a noted cell biologist. He was a tenured professor at Wisconsin School of Medicine. Modern medical physiology (biology included) follows the outmoded linear model of Newtonian physics of deterministic predictability[1]. Euclidean geometry is another blow to our thinking in biology. To cite one example there is no single organ in the human body, any animal or plant kingdom that fits the Euclidean geometry; the latter applies to inanimate integer structures like cones, squares, cubes etc[2]. Take the example of the human heart. This can never be measured by conventional Euclidean geometry but we still do and make management decisions based on that to the detriment of our patients. Humans fit into the new Fractal geometry, first introduced by a computer scientist, Benoit Mandelbrot in 1975[3].

Mandelbrot's equation is very simple. There is a basic equation of simple multiplication and addition. Take any number, multiply it by itself and, then add the original number to it. This simple equation can decipher all happenings in Nature. The equation needs to be repeated *ad infinitum* to get the desired results. Though it looks simple, it has a self similarity built into it, which is the crux of all that one sees in nature, be it a cloud, a leaf, kidney nephrons, bronchial branching or the branching of the vascular tree. This is the new science of Chaos and Fractals. The self-similar pattern makes for efficient functionality, in addition. One can understand why Nature has given us just about the same amount of genes as that of a rat. There is no need for a gene for every action. A single message can get million things done simultaneously in the Fractal science. Mandelbrot's equation results in a new science in place of Euclidean geometry, called Fractal geometry. Fractals are bits; they are non-integer[2]. Fractal geometry can measure the human heart, the length of the wavy border of a country like Ceylon or, for that matter, anything in Nature!

The next area that needs a relook is the time honored concept that the nucleus of the cell with its genes is the master of all that happens to us. While there are vital genes out with the nucleus in the mitochondria, genes are not our masters. Our bane has been the Darwin's theory of evolution which is flawed from the word go. Modern science has taught us that it is the environment which controls what happens to us and that is what determines the evolutionary process in principle[4]. It is the environmental happenstance that energizes us. The genes only play a secondary role dictated by the environment[5]. This latter concept fits in very well with Lamarckism. Evolution is not a fight for survival of the fittest but a co-operation for the growth of the whole. Darwin's fight is taken to heart by the present business tycoons to loot the common man. The world is divided between the "haves" and the "have-nots." This can not go on for ever. Until the basic needs of the lowest of the low are met there will be no lasting peace on this planet. That is what our body cell function tells us in such elegant language of Nature. The cell function also teaches us the nature of the Supreme Being, not the one that sits in our shrines, *but the real one, the super-consciousness, the all pervading energy that runs this world. Cell biology could teach a lesson or two to the non-believers. Do not get me wrong: I never meant that ritualistic religion is the truth; it is a myth for power.

Each cell in our body, which was a whole unicellular organism itself to begin with, in evolution billions of years ago. That cell had, perforce, to perform all the functions that a human being does now to survive.

Address correspondence to:
Prof. B. M. Hegde, MD, FRCP, FRCPE, FRCPG, FRCPI, FACC, FAMS, "Manjunath", Pais Hills, Bejai, Mangalore-575004. India.
Tel: +91 824 245 0450; E-mail: hegdebm@gmail.com; web site: www.bmhegde.com
**Editor in Chief, **Vice Chancellor (Retd), #Former Visiting Professor of Cardiology, ##AffiliateProfessorofHumanHealth.*
E-mail: hegdebm@gmail.com

The total responsibility of managing those functions rested with the membrane of a single cell: in short, the membrane was the cell's brain; the caption of the article[6]. The nuclear genes, the mitochondrial genes, the chromosomal proteins, and the other parts of the cell had to obey the dictates of the cell membrane to function, as the latter is the only communication facility that the cell interior had with the outer world. The cell wall is a bipolar phosphor-lipid (fat) coat which is basically hydrophobic but has important hydrophilic functions as well. The most important gates (receptors) built into the wall are the Integrated Membrane Proteins (IMPs) which have a central tunnel for things to come into the cell from outside like nutrition etc. and the excretory products to go out[5].

Just like the semiconductor silicon chips, the cell wall channels have gates (receptors) and channels. The gates work like a revolving door turning in one direction alone letting in certain things while blocking the rest. There are three very important areas where these channels work. Sodium-Potassium ATPase system is one. This will allow, with each revolution, three positively charged Sodium atoms to get out of the cell while throwing in two positively charged Potassium atoms into the cell from the environment[5]. These gates rotate like a revolving gate hundreds of times every second. Since the fat membrane does not allow the charge to get out of the cell keeping the inside of the cell negatively charged with the outside being positive. This membrane potential is the reason why each human cell is a very efficient self charging battery which supplies electricity (energy) for all bodily functions. Consequently, the cell wall uses up a large amount our daily expenditure of energy.

The second variety of effector proteins, called cytoskeletal proteins, regulate the shape and motility of cells. That is why we are called animate organisms with locomotion. The third type, the enzymes, breaks down or synthesizes all molecules. All three, when activated along with the channels, serve as signals which bind the chromosome's regulatory proteins that form a sleeve around the DNA of the cell, unlike in the older wisdom where the genes were to control their own activity. It is the membrane's effector proteins, which operate in response to external stimuli to the cell wall, which control the "reading of the genes so that worn out proteins could be cast off and new ones formed." In short, cell's operations are primary responsibility of the environmental signals coming in through the cell wall. Since gene survival depends on the ever changing environment, DNA blueprints can not control the operations of the cell. This makes the cell wall the "true brain" of the cell and, consequently, the organism.

To get smarter during evolution, the single cell organisms got together to result in multicellular organisms that we see today[5]. Now the advantage is that one could have trillions of IMPs stuck all over the cell walls to get better interaction with the environment. When the cells got together, they realized that it is better to have certain cells do exclusively some of the functions, instead of all the cells doing all the functions to economize on energy. That is how the nervous system with the brain developed to specially interact with the environment. There was further specialization in those cells also as we see today. Similarly, the other organs were formed for special tasks. However, the master of the orchestra still is the cell wall. The cell wall becomes a liquid crystal like your laptop computer screens. The cell thus becomes a programable chip whose working, including gene activity, are primarily controlled by the environmental signals and NOT genes[5]. This is the secret of life.

Bruce Lipton, writing in his celebrated classic-The Biology of Belief- has this to say, in addition. "Imagine a population of trillions of individuals living under one roof in a state of perpetual happiness. Such a community exists - it is called the human body." The same fact was illustrated by another quantum physicist, Fritz-Albert Popp, who showed that the photon light (Bio-Photons) from each DNA in the human body in health is in synch with one another and suffer also together when they do[6]. Even when an ointment is applied on the hand, the photon lights in the brain also change! Human body works better than human societies. There are no "have not's" in the human system. All are haves only. If mankind learns that lesson from the cells this world would be a better place to live in. For example, cancer cells are those "homeless, jobless" cells that live off other healthy cells in the human body, like the terrorists[5].

There is hope for mankind even in this "man-eating-man" world. This earth shaking research done by a Stanford biologist, published in PLOS biology in 2004 illustrates that truth. Writing an editorial on that study, Franz BM de Wall of Emery University has this to say "even the fiercest primates do not forever need to stay that way"[7]. This study showed elegantly how some of the ferocious baboons, genetically said to be programed for violence were tamed by the females to be co-operative and loving, proving once again the truth that environment shapes our genes and our future. There is hope for mankind. Humans need not be stuck with the greed to acquire more and more material possessions beyond what is necessary for sustenance, and the more dangerous obsession of ideological control of others. Most human violence is neither genetically mandated nor biologically necessary. We will be able to change that by altering the atmosphere which will become necessary with the explosive growth of the population and poisoning of the natural resources of the world. There will be a

day when the whole world would become one loving single community (*Vasudai Eva Kutumbakam*). This is the evolutionary need, if you follow the science of new biology very carefully. This should start at school where the students that are not that "bright" could be helped by those that are, for the common good of all. Bruce Lipton's study of Caribbean Island Medical School students proved this to be true[5].

Finally, a word about the environmental control that we have been harping on here so far. What is that control? That exactly is the super-consciousness or God, if you wish. Life is like a character in the TV screen. TV screen catches the image from the atmosphere. But the image is not inside the TV box! Similarly, human life on this planet is the essence (spirit in the western concept and *Atman* in the Indian ethos) of that super consciousness. Death, therefore becomes akin to your shutting off the TV screen where the image disappears from your view but the image is still there in the atmosphere. You could catch that in another TV screen. That could be the biological explanation for re-birth which has been a subject of study in at least three universities in the USA. One of them has been going on for sixty years in three generations of researchers with positive results[8]. Death, therefore, does not become the end of life but, a part of life, if one took life as a whole. Didn't we have to learn this lesson from a single cell wall that is the Director of this movie called life-the mem-Brain?

"Keep love in your heart. A life without it is like a sunless garden when the flowers are dead. The consciousness of loving and being loved brings a warmth and richness to life that nothing else can bring."

Oscar Wilde

REFERENCES

1. Hegde BM. Unconventional wisdom in medicine. JIACM 2007; 8:294-296.
2. Kaplan D, Glass L. Understanding non-linear dynamics. 1995 New York Springer-Verlog.
3. Lorenz E. The essence of Chaos. 1995 London UCL Press.
4. Bockris JOM. The new paradigm. 2005 A & M University Press, Texas.
5. Lipton BH. The biology of belief. 2009 Hay House Publications New York.
6. Popp FA. Bio-photons. energyallaround.blogspot.com/.../biophysicist-fritz-albert-popp-PhD.
7. de Waal FBM. Peace lessons from an unlikely source. PLoS Biol 2004; 2(4): e101. doi:10.1371/journal.pbio.0020101
8. Harpur T. (1998) "Life After Death: Reincarnation / The Testimony of Science" (video), Sleeping Giant Productions, Wellspring Media. http://www.amazon.com/exec/obidos/ASIN/B000007QTQ

Review Article

Osteoarthritis of the Knee: Review of Risk Factors and Treatment Programs with Special Reference to Evidence-Based Research

Ali Al Mukaimi[1], Ehab El Salawi[1], Anders Lindstrand[2]
[1]Al Razi Orthopedic Hospital, Kuwait
[2]Department of Orthopedics, Clinical Sciences, Lund University, Lund, Sweden

Kuwait Medical Journal 2011; 43 (3): 176-188

ABSTRACT

Osteoarthritis is a widespread disease leading to physical disability affecting quality of life. It is primarily regarded as a cartilage disease but affect all tissues of a joint. Osteoarthritis can be regarded as an organ failure. Knee osteoarthritis is common in Kuwait, especially in women. The main symptoms are pain, stiffness and weakness affecting knee function. The diagnosis is made by history and clinical examination. A weight-bearing radiograph will fully establish the diagnosis. Many of the patients are also obese, diabetic, hypertensive or affected by other organ failures. The aim is to reduce knee pain and improve knee function which is also beneficial for the other diseases.

Initially, we recommend self-management by information about knee osteoarthritis, daily exercise of any type which is pleasant for the individual like walking 10-30 minutes once or twice daily in order to induce light to moderate cartilage load. Further, regular muscle training to increase especially pelvis and lower leg strength and realistic programs to reduce weight is advised.

Regular support by a primary care doctor, a physiotherapist or a coach is beneficial. The program is demanding, as it means a change of life-style. Different modalities of non-operative treatment are physiotherapy, pharmacological treatment by analgesics / NSAIDs / glucosamine and injection of steroids or hyaluronic acid. The effect of the pharmacological treatment programs vary. Often the outcome, by evidence based research, is low or at best moderate. If self-management and non-operative treatment fails and the symptoms are pronounced, surgery is an option. Knee prosthesis is the main alternative.

KEY WORDS: knee, osteoarthritis, review, risk factors, treatment

INTRODUCTION AND RISK FACTORS

Arthritis is a chronic disease which is estimated to affect about 15 % of the population and is the leading cause of functional dependency in the activities of daily living in elderly[1] (Fig. 1).

There are several reviews of risk factors and pathogenesis including the repair process as well as treatment programs of knee osteoarthritis (OA)[2-5]. In essence, there are two possible pathways for initiation of OA disease, overload or injury of normal cartilage or normal load of weak cartilage. Risk factors for development of knee OA are rheumatoid arthritis and other inflammatory conditions, knee infection, knee trauma often sustained in sports[5-7], unfavourable loading[8], heavy physical activity[5, 9], resting in a squatting or kneeling position[8,10] and also obesity[5,11,12]. Poor muscle function, especially in women, influences the disease progress and severity of symptoms[13-15]. Increasing age is a major risk factor for OA[16]. Female sex[17] and heredity[18,19] are other known risk factors. OA may also occur in a knee joint where the cartilage is weak, for example due to disuse atrophy, and therefore, already sensitive to activities of daily life[17].

Thus, the etiology of OA is dependant on several factors of constitutional and environmental type. Some of these factors can be affected by treatment programs which, if effective, will slow down the symptoms of the disease. In many instances today, due to better knowledge of risk factors, the cause of knee OA can be identified and fewer patients have idiopathic OA. The earlier classification of knee OA, into secondary (known etiology) and primary (unknown etiology) is no longer recommended as most knee OA can be identified by risk factors.

KNEE OSTEOARTHRITIS AND FOOTBALL

OA can develop as a late consequence of knee trauma resulting in cruciate ligament, collateral

Address correspondence to:
Anders Lindstrand, MD PhD, Department of Orthopedics, Clinical Sciences, Lund University, 221 85 Lund, Sweden. E-mail: lindstrand5@telia.com

ligament, meniscal or cartilage injuries. These injuries occur during high activity level, often in contact sports which include acceleration/deceleration or rotation/pivoting movements. One example of such a contact sport is football; the most common sport of the world. Especially, after anterior cruciate ligament and meniscal injuries, there is an increased risk of developing clinical and radiological signs of OA. In a review article Lohmander *et al*[6] identified 127 published articles from 1970 – 2007, 10 - 20 years after an anterior cruciate ligament injury. These articles were found in a Medline search by the key words "anterior cruciate ligament, injury, osteoarthritis and follow-up". The prevalence of OA was found to be 50% even after isolated anterior cruciate ligament injuries. The Lohmander group presented, in the same report as mentioned before[6], a review of radiologic long term follow-up of isolated meniscal injuries and found in 41 publications a prevalence of 50% OA after 10 – 20 years. In another review article, Oiestad *et al*[7] identified 31 anterior cruciate ligament injury articles by a search in three computer data bases (PubMed, Embase and AMED). The number of articles retrieved originally was 2000 but the authors made a quality scoring of the study designs and included only 31 articles with the highest quality score. After a mean 13.7 (10 - 27) years follow-up, 0 - 13% of isolated anterior cruciate ligament injuries had developed knee OA. In combined anterior cruciate ligament and meniscal injuries, the prevalence of OA was 21 - 48%. Even if these two review articles are not in full agreement about the prevalence of OA after isolated anterior cruciate ligament injuries, the risk of long term OA is pronounced. Definitely there is a high price for the joy of playing football. Especially as the post-traumatic OA disease starts earlier in life compared to most other types of OA which have a later onset.

The innervation of the the anterior cruciate ligament injured patient is often long-term deficient as proprioception is affected after an injury. About 1/3 of the anterior cruciate ligament injured patients, independent of reconstruction, do not regain the normal muscular function of the injured limb. There are, however, occasional reports, on non-operated anterior cruciate ligament injured patients, who were treated by intensive rehabilitation and recommended a low activity level, where the long-term muscular function was normalized[20] and long-term knee OA was low[21]. Not only knee joint injury, but also knee joint overload, is a risk factor for knee OA. In top football, there is constant knee joint overload due to the character of the game. In elite football players, even without a documented knee injury, knee OA was found in 30%, 10 - 20 years after the end of the football career, while recreational football players had the same low incidence as non-football players after the same follow-up time[22]. Therefore, daily overload of the knee in elite football is a negative factor for the joint but occasional football, even in organized league on a low level, has no such drawback.

In general, sports can be divided into low, moderate or high demands of the knee joint where, apart from European and American football, also basketball and handball are examples of high knee load while swimming and golf are examples of lower knee load[23].

CARTILAGE AND BONE TISSUE

OA is regarded not only as mainly a cartilage disease, but also one that affects other tissues of a joint, especially the bone, by subchondral sclerosis, osteophytes and cyst formation and also the synovium by synovitis and often increased amount of joint fluid. Also, the ligaments are involved by time.

The bony ends, constituting the knee joint, are covered by hyaline cartilage. This tissue has a favourable friction coefficient which is an advantage during load transmission[24]. The thickness of articular cartilage varies with the pressure. The higher the peak pressure, the thicker the cartilage and it is interesting to note that patellar articular cartilage is the thickest in the human body[25]. This cartilage tissue constitutes of cartilage cells and extracellular matrix including water, proteglycans and collagen[24,25]. There are four different zones of articular cartilage; superficial, middle, deep and calcified[26]. These layers have a different composition of collagen formation and cell morphology. During weight-bearing, water is pressed out of the extra-cellular matrix, while the water returns at rest. There is a continuous turnover in normal cartilage tissue constituting a balance. This is a fine-tuned mechanism which is distorted in OA when the cartilage becomes fibrillated and by time cleft formation and areas of necrosis appear. Mechanically mediated and cytokine-mediated pathways of cartilage degeneration have been identified in the pathogenesis of OA[3, 24]. The possible OA healing mechanism / response has been studied[27-30]. There is no vascular supply or innervation of cartilage which affect the healing properties. In the very early stage of the OA disease, the tissue changes can not be seen by inspection (arthroscopy) or by MRI (radiography). Microscopy of a bone/cartilage biopsy would, however, show early osteoarthritic findings. By time, cartilage fibrillation and fissures will develop, which can be seen by arthroscopy or MRI. There are several systems used for grading of cartilage disease, such as the Mankin´s criteria (microscopy) or the Outerbridge classification (inspection).

The bone tissue is affected in the early and especially the late phase of OA. The micro-architecture of the bone is deteriorated in all types of OA. In cancellous bone, the form of the trabeculae are changed and the density

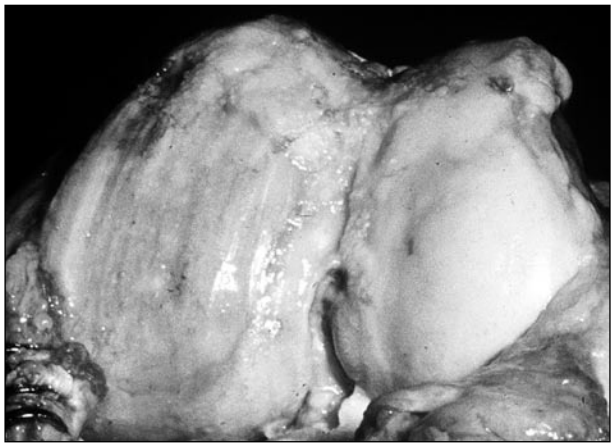

Fig. 1: Operative photograph of the left knee
To the left: OA of the medial femoral condyle (MFC) with centrally bare bone
To the right: almost normal cartilage of the lateral femoral condyle (LFC)

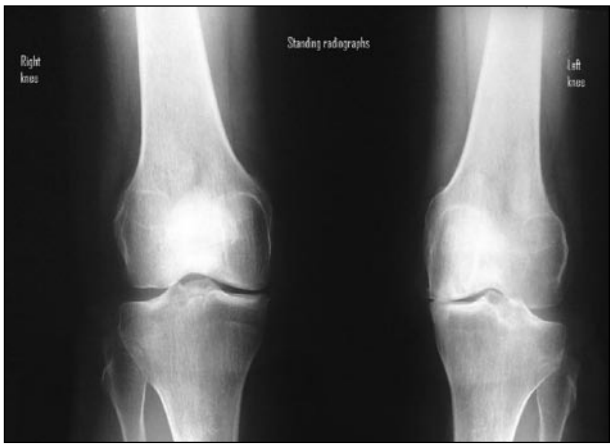

Fig. 2: Osteoarthritis on antero-posterior standing radiograph of both knees. The distance between the bony ends of femur and tibia on the medial side is abnormal. On the left side it is medial bone contact (Ahlback grade 2) and on the right side the medial cartilage is reduced (Ahlback grade 1).

(bone volume) is increased. The subchondral bone plate[31] will also be affected and by time, sclerosis will be found there. Experimentally, by using alendronate to affect bone remodelling, the subchondral bone density was increased and different amount of cartilage degeneration (OA) was observed[32]. It is also shown that subchondral bone collagen metabolism is increased in OA[33]. The role of bone tissue and especially the subchondral bone in the OA process is, however, not fully known but this structure probably plays an essential role in the onset and development of OA.

The concentration of certain cartilage matrix components in joint fluid, serum and urine can be measured[34-36]. The idea is to monitor the degradation and reparation of the cartilage. This technique is presently mainly used in research but in the future, if reliable, could be a better instrument than radiology, to identify and follow the OA process.

SYMPTOMS AND SIGNS

Three common complaints due to knee OA are pain, stiffness and weakness. In the long perspective, quality of life is affected[1] and even psychological stress symptoms can occur[3, 37].

The pain is mainly on weight bearing but by time, pain at rest disturbing sleep may also develop. Early in the disease, there is mild knee pain after long walks or other exertions. The onset is gradual and intermittent with better or worse periods. There is, by time, often joint swelling and excessive joint fluid is produced which is best palpated in the suprapatellar pouch or posteriorly as a Baker cyst.

During disease progress, the pain on weight-bearing becomes more pronounced and disturbs ordinary activities of daily living (ADL). The maximum walking time becomes shorter by about 10 - 20 minutes, and often a stick or a crutch is used. There is also pain on palpation[38]. Clinical accuracy of diagnosing meniscal injuries in existing knee OA is difficult as most menisci, by time, are affected by degeneration due to the OA disease. The range of motion will be reduced especially in advanced OA. For example, in advanced knee OA (Ahlbach grade IV - V)[39] 10 degrees of extension defect and 30 degrees of reduced flexion is a common finding. The muscle power is reduced[40] leading to weakness and even giving way. Gradually a deformity will develop; varus in medial OA and valgus in lateral OA. Especially the valgus deformity is bothering, as it may lead to knock-knee which means that the knees, during walking, collide and are in the way of each other.

RADIOLOGY

Ten or even twenty years may elapse after the debut of knee OA before obvious radiographic OA findings are present on plain radiographs. It is often a long radiographic silent period when subjective symptoms are present on-and-off and standing radiographs are normal OA can be seen by inspection during surgery (Fig. 1). Joint space narrowing based on weight-bearing radiographs, indicating cartilage wear, is a diagnostic finding in OA (Fig. 2). A weight-bearing postero-anterior radiograph, obtained in 45 degrees flexion, can better identify early cartilage wear[41]. Joint space narrowing and, by time, bone attrition is used in the Ahlback classification in five stages[39]. However, even if joint space reduction is not present on weight-bearing radiographs, other signs of early OA like osteophytes, bone sclerosis or cyst formation may be seen on plain radiographs[42]. Structural changes are the basis for the early stage of the Kjellgren and Lawrence radiographic classification based on plain radiographs. An MRI, on

the other hand, will show early cartilage wear and often there is a concomitant degenerative meniscal injury. This meniscal injury is more a sign of the early OA disease and less a sign of a traditional meniscus rupture. In a long-term study, MRI predictors for a rapid OA progression were meniscus extrusion beyond the tibial margins, a major medial meniscus tear and bone edema[43]. Also, subchondral bone attrition, as found on MRI, is a sign of compartment specific mechanical load[44]. Information from MRI can be enhanced by gadolinium[45]. The future goal, by specialized MRI, related to articular cartilage is to detect abnormalities even before early morphological changes occur. The idea is to implement treatment programs early.

The radiographic findings often have a slow but consistent progress. However, research has shown that some patients do not have such a radiographic progression during a long time period. There is no consensus on which radiographic classification system to use which makes comparison between studies more difficult. There is, therefore, a need for one internationally accepted, reliable and validated radiographic classification based on plain radiographs[7] in order to be able to compare the outcome of studies using different interventions (Table 1).

Table 1: Radiographs in Knee OA

- Weight-bearing plain radiographs will establish the OA diagnosis
- Specialized radiography like MRI is usually not necessary
- A degenerative meniscal injury on MRI is more a sign of the early OA disease and less a sign of a traditional meniscal rupture

KNEE OSTEOARTHRITIS IN KUWAIT

In Kuwait, females are more affected by symptomatic knee OA than males. This is documented in the operation statistics, as nowadays, six out of seven operated patients in this country are female[17]. This difference is higher here than in other countries, where six out of ten operated patients are female[46]. The onset of severe symptoms indicating surgery is not only earlier in life for females than males, but also earlier than females in other countries[17].

There are certain specific risk factors for the early onset of OA in Kuwait. Many individuals are obese which increase the load on the joint during walking. Overweight has been shown to have a large impact on symptoms of knee OA[43]. However, even slight weight loss is beneficial for self-reported function and pain[47]. There is also a low ambulatory activity level due to frequent use of cars[17] which will, by time, cause disuse atrophy of the cartilage and also weaker lower limb muscles. The cartilage, which needs daily regular activity in order to maintain its properties, becomes more vulnerable[25]. However, the precise amount of joint load needed in order to maintain healthy articular cartilage is not fully known[25], but it demands a more active life-style. Also the cultural habits of sitting and kneeling in Kuwait are risk factors for knee OA[8]. Hormonal and metabolic factors are probably involved and there may also be hereditary traits, which are not fully known in the Arab population, but are reported for other populations[18,19].

NON-OPERATIVE TREATMENT

Most of the patients with knee OA are treated by non-operative programs, and surgery by knee prosthesis is often not indicated at least not in the early course of the disease. The non-operative treatment is often called conservative treatment, but the non-operative treatment should not be conservative, rather active, patient-directed non-operative treatment. The development of the symptoms of the OA disease is very individual and it is difficult to predict the outcome for a specific person. It is until now not proven, that it is possible to reverse the cartilage destruction by pharmacological means, but there are ways to affect the symptoms of knee OA. Knowledge of the natural history of the OA disease allows the patient for better confidence, as certain OA patients do not experience progress of symptoms during the years to come.

The key points of the non-operative treatment are self-management by:

1. Patient education about the OA disease
2. Physical activity, which is individual regarding type and time, but often involves daily walking with (stick, crutch) or without support. Despite suffering from pain, every knee OA patient needs to walk daily, sometimes to the limit of their capacity, in order to keep up their ability to walk.
3. Muscle training of the pelvis and lower limb. Thigh strength (quadriceps) training is essential.
4. Realistic program for weight reduction by implementing certain diet plan and follow-up

These active, patient-directly-involved, non-operative treatment programs differ from, out of the patient's perspective, passive non-operative treatments like medicine or injection therapy.

This basic program needs to be implemented early by the primary care doctor and needs regular follow-up as regards any changes in life-style. Physiotherapists can be involved in a structural way, not only for physiotherapy treatment programs, but also to assist the patient in self-management. Sometimes, a personal trainer or a coach can follow and support the patient. In order to implement and follow-up such a program well and get a reasonable compliance, a national computer file program for the health care system involving all hospitals and all primary care units is an advantage. A few simple variables like length, weight and a functional tests like chair stand test[15,48] and / or a walking test[15] may be used for follow-up.

INTERNATIONAL RESEARCH

The Osteoarthritis Research Society International (OARSI)[49], the National Institute of Health and Clinical Excellence (NICE)[50], the American Academy of Orthopedic Surgeons (AAOS)[51] and European League Against Rheumatism (EULAR)[52] have recommendations for the management of knee OA. They are generally in agreement that self-management is the basis for the OA treatment. Self-management means that the patient, by own activity, gets information about the natural history of the OA disease, in order to understand the disease pattern better. It also relates to daily ADL routines, type and frequency of exercise activity and nutritional questions.

If self-management is not successful and the symptoms are pronounced, a treatment program may be started. The scientific result of an intervention can be evaluated by effect size (ES) which is the standard mean difference between groups and compares treatment and placebo groups for pain and function. Clinically, an ES = 0.2 means a minor positive effect, ES = 0.5 means intermediate positive effect and an ES = 0.8 means a major positive effect of the treatment[49]. When evaluating effect size in different publications, it should be noted that the effect is based on different number of studies / patients, the effect is often present for a short time period, a publication bias may exist (studies with a negative result will less often be published) and the risk of side-effects varies between the treatment programs.

One late update of treatment programs for Knee OA is from 2010 in the journal Osteoarthritis and Cartilage[49], where the OARSI group recommendations for the management of hip and knee osteoarthritis was published. In this article, the OARSI group had performed a literature search in Medline, EMBASE, CINAHL, AMED, Science Citation Index and the Cochrane library to analyse the quality of the studies. This search identified 64 systematic reviews, 266 randomized clinical trials and 21 economic evaluations which met the inclusion criteria for a high quality study during the years 2006 - 2009 regarding knee and hip OA. This article is recommended for more detailed information regarding non-operative treatment of knee osteoarthritis.

NON-OPERATIVE TREATMENT PROGRAM

Self-management: information

Information about knee OA is a central part of self-management and recommended by all expert groups, *viz*, OARSI, NICE, AAOS and EULAR. Ravaud *et al*[53] conducted a study where information about OA, exercise and weight reduction was compared to standard treatment. There was a small short-term superior benefit in minor weight reduction and time spent in exercise activity in the information group, but no significant pain reduction. Buszewicz *et al*[54] gave verbal information during six sessions on management of OA including a booklet compared to a control group where only the booklet information was given. The intervention group had reduced anxiety, better perceived self efficacy, but no significant difference in pain or function. Thus, information alone can reduce disease anxiety and improve self efficacy, but it is not effective in order to reduce pain or to improve function in knee OA. So information needs to be combined with other treatment.

Self-management: Exercise

Reduced muscle power of the lower limb is crucial as a weak or exhausted muscle increase the risk of overloading the joint. If this is present during long-time periods, like years, it will have a negative impact on knee OA. Exercise can be performed by individual treatment, exercise classes or home-based programs.

There are several meta-analyses on randomized studies for exercise therapy which include control groups of non-exercising patients. In a Cochrane database analysis, including 32 studies comprising 3800 patients, Fransen *et al*[55] found that therapeutic exercise, had at least short term benefit in reducing knee pain and improving physical function for people with knee OA. The effect was small, but comparable to reports for non-steroidal anti-inflammatory drugs. There was no difference between individual treatment, exercise classes or home-based programs. However, the more are supervision occasions, the better the outcome.

In a metaanalytic review by Devos-Comby *et al*[56] 16 studies on exercise and self management interventions were analyzed. In comparison to control conditions, exercise regimes improved physical health and overall impact of knee OA. Self-management programs significantly improved psychological outcomes. Both patient education and exercise regimes had a modest influence on patient's well-being. There are, however, reports that a simple home based exercise program and also aerobic walking can significantly reduce knee pain[57,58]. The patient compliance of such programs is probably important and will affect the outcome (Table 2).

Table 2: Active self-management of OA by the patient

- Find and get information about knee osteoarthritis
- Perform daily exercise of any type which is pleasant for the individual; for example walking 10 - 30 minutes once or twice daily
- Do regular muscle training
- Use realistic programs to reduce weight.

Self-management is demanding as it often means a change of life-style

Physical therapy

Jamtvedt *et al*[59] conducted an overview of systematic reviews on physical therapy for knee OA during the period 2000 – 2007. Twenty-three reports were included. The authors found highest quality evidence that exercise in combination with weight reduction reduced pain and improved function in knee OA. There was moderate quality evidence that acupuncture, trans-cutaneous nerve stimulation or laser therapy also reduced pain. One essential question is, whether the exercise training itself negatively affects the knee OA progress due to overload of the diseased joint. It seems to be the opposite, as in a randomized study, the glucosamine content was favourably affected by exercise training in knee OA patients[60]. Interestingly, Manninen *et al*[61] reported that the risk of knee OA requiring knee arthroplasty decreased with increasing hours of recreational physical therapy. The later studies should be regarded as hypothesis-generated reports which need to be repeated in future research.

Water-based training

In a cochrane database report[62], it was found that there is a lack of high quality studies regarding water-based training and only a small beneficial effect was found regarding pain relief early after training. However, all six included studies except one were related to both knee and hip OA. The study on knee OA alone compared water-based exercise with land-based exercise and showed a large effect on pain immediately after training. The authors, however, conclude that more research is needed before the effect of aquatic exercise for knee OA can be stated.

Weight reduction and training

The two keystones in the treatment of knee OA are weight-reduction and regular training. Overweight indicates a need for a special dietary program[63,64] and a dietician and / or psychological support may be an advantage in order to comply successfully with such a program. Even a minor decrease of the weight (5 - 6 kg) may have a beneficial effect on knee symptoms. In a meta-analytic study on weight reduction[65] only four out of 35 randomized clinical trials were of acceptable quality and included. The best effect was achieved, if the weight is reduced by 5% with 0.25% / week during a 20-week program[65]. It has been found that a combination of weight reduction and training is more beneficial than one of these programs only[47]. The program can be directed by a physiotherapist or a coach but the individual patient is the only one who can affect the final result due to compliance with the program. It has been suggested that weight-reduction in the obese carries a risk of increased mortality. In a study by Shea *et al*[64] no such relation was found. On the contrary, a reduced mortality rate was indicated by the outcome of the study.

Pharmacological treatment

Acetaminophen (paracetamol) is used frequently. A Cochrane database study by Towheed *et al*[66] included 15 randomized clinical trials where seven studies compared acetaminophen to placebo. Five of the seven studies had better pain relief by acetaminophen and the same safety profile as placebo. The authors conclude, however, that the effect of acetaminophen is of a questionable clinical significance. Another meta-analytic study, an analysis, showed that the pain relief with acetaminophen was small and the effect was mainly within the first month[67]. Despite this low effect size of acetaminophen in recent studies, the drug is still recommended as the primary choice of pharmacological pain relief by OARSI, NICE, AAOS and EULAR in knee OA. However, if high doses of acetaminophen are used the risk of liver failure and other side effects is increased. Then a short-term low dose NSAIDs eventually combined with a proton pump inhibitor is an alternative. However, the general health of the invidual patient has to be taken into account and it is well-known that certain cardiovascular diseases can compromise the use of NSAIDs.

NSAIDs have a mild positive effect on knee OA pain[67]. In a meta-analysis by Bjordal *et al* that included 63 randomized placebo controlled trials and a total of 14,060 patients receiving different pharmacologic treatments, they concluded that oral NSAIDs treatment in patients with moderate to severe pain had a small effect with maximum efficacy compared to placebo at 2 - 4 weeks. In an earlier meta-analytic report by the same group of authors 2004[68], 10,845 patients were studied. They reported an effect size of 0.32 for oral NSAIDs and if doubtful studies were excluded, the remaining effect size was 0.23. Only short term use was recommended by the authors. In the study by Towheed *et al*[66], apart from acetaminophen, oral NSAIDs were also studied. NSAIDs were superior to acetaminophen for knee pain. The authors conclude, however, that the effect size was modest, and the trial duration was only six weeks, and therefore, special considerations need to be taken when making the decision between using acetaminophen and/or NSAIDs. In summary, in OA subjects with moderate-to-severe levels of pain, NSAIDs have only a small effect. The relative efficacy of cox 2- inhibitors was studied in a meta-analysis by Lee *et al*[69] and the authors found that the effect size for these coxib group of drugs was small. However, the studies showed that significant heterogeneity was observed indicating systematic differences among published trials emphasizing the need for more studies with direct-comparison.

Gastrointestinal (GI) side effects by NSAIDs

The gastrointestinal (GI) side effects of acetaminophen and oral NSAIDs were studied in 644,183 patients over the age of 65 in Canada[70]. The risk for hospitalization due to bleeding, ulceration or perforation was higher in patients on NSAIDs compared to patients on acetaminophen. The combination of the two drugs highly increased the risk of such a GI event. Also the risk of an adverse GI event was twice as high for standard NSAIDs compared to cox-2 agents or a standard NSAID with a proton pump inhibitor.

Topical NSAIDs

In a meta-analysis of randomized controlled trials, topical NSAIDs (locally applied) were more effective than placebo[71] during the first two weeks of treatment. The effect size was 0.41 (first week) and 0.40 (second week). The effect on pain relief was slightly better than oral NSAIDs. On the other hand, topical NSAIDs were inferior to oral NSAIDs during the first week of treatment and associated with more local side effects such as rash, itch or burning[71]. Most data on the use of topical NSAIDs are limited to short term use and there was no clinical effect after two weeks. The main drawback is temporary skin irritation.

Opioids

More potent analgesics such as opioids, have a large efficacy in pain relief[72]. This meta-analysis comprised 18 randomized placebo-controlled trials including 3244 patients. However Bjordal *et al* in their meta-analysis[67] had only mild pain relief by opioids. Opioids should be used with caution and there is a clear risk of addiction.

Oral glucosamine

The effect of oral glucosamine for knee and hip OA are mixed. Earlier meta-analyses indicated moderate to large effect by chondroitin. Recently, chondroitin sulphate[73] was presented in a meta-analysis comprising 20 trials including in total 3846 patients. The quality of the studies was very heterogeneous and many were small trials with unclear allocation. Trials that were not analyzed properly showed larger effects in favour of chondroitin than did the remaining trials. When the analysis was reduced to three trials with large sample size and the best quality, there was no effect regarding pain relief. It seems probable that the effect of chondroitin sulphate is minimal or none. Block *et al*[74] analyzed the science of how to interpret the effect of oral glucosamine on joint health. The authors lack certain basic data and emphasize the need for "standardized and clinically relevant *in vitro* assay systems and *in vivo* animal models for testing, as well as development of new outcome measures for inflammation and pain pathways in human OA". They postulate that a change of research approach is needed. In a meta-analysis[75], glucosamine hydrochloride had no positive effect while glucosamine sulphate had a moderate effect. Effect size ranged from 0.05 - 0.16 in studies without industry involvement and 0.47 – 0.55 in studies with industry involvement. These studies on glucosamine show heterogenicity. There is possible allocation, analysis and publication bias[75]. Therefore, a cautious attitude regarding the effect of these drugs was recommended.

Another way of presenting results of pharmacological treatment is the need for later total knee arthroplasty[76] after treatment of knee OA with glucosamine sulphate for minimum 12 months and maximum 36 months. This resulted in half the incidence of total knee arthroplasties after five years compared to placebo. This study should be regarded as a hypothesis generated report which needs further research in order to be proven.

Intra-articular steroid injections

Intra-articular steroid injections have short term beneficial effect in the treatment of knee OA[67] and use of single dose is also effective[77]. The later study is a Cochrane database systematic review where 28 randomized controlled trials compared intra-articular corticosteroids to most often placebo. The positive effect regarding pain relief is best seen after 2 - 3 weeks. After 4 - 24 weeks no such positive effect regarding pain relief was seen. There are few side effects[77] where the most serious is septic arthritis. Geirson *et al*[78] have shown an incidence of 0.037% after arthrocenteses.

Intra-articular injection by visco-supplementation by hyaluronic acid

Hyaluronic acid can relieve symptoms of knee OA[79, 80]. The first study is a Cochrane database report by Bellamy *et al*, comprising 76 trials, where 40 was versus placebo. The report concludes that visco-supplementation is an effective treatment for OA of the knee with beneficial effect on knee pain, function and patients global assessment especially 5 - 13 weeks post injection. The effect is, however, different for different visco-supplementation products and time points. There is also heterogenicity of outcomes between trials. When analyzing only high quality studies there is no clear effect regarding relief of pain. In the report by Arrich *et al*, published in 2005, which is a systematic review and meta-analysis, comprising 22 randomized clinical trials, they concluded that intra-articular hyaluronic injections have not been proven clinically effective. The authors recommend more efficient research with clinically relevant and uniform endpoints in order to clarify the risk-benefit ratio. The major side effects of visco-supplementation are incidents of pain and swelling as well as septic arthritis (Table 3).

Table 3: Examples and effect of pharmacologic treatment

Pharmacological treatment
- Analgesics/NSAIDs
- Glucosamine
- Intra-articular injection by steroids or hyaluronic acid

Often the effect of pharmacological treatment, is low or at best intermediate.
This is shown by evidence based research.
Side effects, sometimes serious, are common.
The same effect as by pharmacological treatment can be achieved by self-management and physiotherapy.
Side-effects of such treatment are low. However, it is demanding as it means a change of life-style.

Acupuncture

Acupuncture has no clear effect regarding pain relief for OA[81]. In this meta-analysis, 11 randomized trials met the selection criteria and nine out of those reported sufficient data for pooling. Sham-controlled acupuncture had a small, clinically irrelevant, positive effect on pain relief while waiting-list patients had clinically relevant effect which may be due to placebo. The effect of pulsed electromagnetic therapy on knee OA has been evaluated[82]. In this systematic review, five randomized controlled trials were identified which compared pulsed electromagnetic therapy with placebo. No beneficial effects regarding pain relief was found.

Braces, orthoses or lateral wedge shoe inserts

These are also used for the treatment of knee OA[83]. In this Cochrane database systematic review, four randomized controlled clinical trials were identified for medial compartment knee OA. The conclusion indicates limited evidence that braces, orthotic devices or lateral wedge shoe inserts were beneficial in knee OA.

Other substances

Vitamins[84], Selen[84], avocado soyabean[85] , green-lipped mussel[86], rosehip powder[87], diacerhein[88], SAM-e[89] or African devils claw[90] are substances which have been suggested to reduce pain associated with OA. However, evidence based research is limited and more studies are recommended. As an example, we like to comment on the study on rosehip powder (Rosa canina). Christensen *et al* performed a meta-analysis comprising three randomized controlled trials including 287 patients[87]. Rosehip powder showed a reduction in pain scores with an ES of 0.37. Test for homogeneity seemed to support that the efficacy was consistent across trials. Thus it seems reasonable to assume that the three studies were measuring the same overall effect. Therefore, it is twice as likely that a patient allocated to rosehip powder would respond to therapy, compared to placebo. However, in general the series for rosehip powder and for most of these substances are small and more proof is necessary to confirm the effect.

Osteoarthritis School

In general, OA information / training is regarded as positive for the knee OA patients. By a literature review, improvement of arthritis by 15 - 30% was found after patient education[1]. Today, many patients have access to Internet and get information about OA. However, it is difficult to get correct and complete information.

Group training in an OA school has been proposed[91]. The school usually includes 5 - 6 lessons, where a small group of patients are informed and treated by different medical professionals. A physiotherapist, an occupational therapist or a specialized nurse are usually organizing the lectures under the supervision of a primary care doctor. Different other specialists are recruited during certain lessons, for example, a dietician or an orthopedic surgeon. The lessons are patient oriented and two-way communication, teaching and learning, is essential. Inclusion criteria were radiographic verified OA or clinical signs of OA in one or more joints. The patient should be positive for treatment in a group. The main issue is help for self-help. Usual issues for information / discussion are disease information, types of exercise, methods of training, orthotic bandage, diet questions, pharmacologic therapy and surgical information. We believe that such an OA school should be beneficial for the OA patients in Kuwait. A change of life-style needs information and repetition of information.

OPERATIVE TREATMENT

If non-operative treatment fails certain patients are candidates for major knee surgery by osteotomy or knee prosthesis. Minor arthroscopic procedures like shaving cartilage, partial meniscectomy or washing of the joint are ineffective and are no longer recommended in early OA[49, 92, 93]. In a prospective randomized trial, arthroscopic surgery was not better compared to a training program in the treatment of degenerative meniscal tears[94]. It is important to understand that an MRI diagnosed meniscal injury in middle-aged or elderly persons is most often an early sign of OA and not equal to a traumatic meniscal injury in a young person. Autologous transplantation of chondrocytes or mosaicplasty are used for local cartilage defects but not for early OA changes.

Osteotomy is performed in unicompartmental femoro-tibial OA in order to change the load from the affected compartment to the healthy compartment. Most often, it is done in early medial OA. It is performed in proximal tibia preferably proximal to the insertion of the patellar tendon. The traditional closed wedge high tibial osteotomy means that the tibial bone is cut, a lateral wedge is removed, and the osteotomy is

closed and fixed by staples or a plate[95, 96]. In the callus distraction technique, a tibial osteotomy is performed and the osteotomy is locked by an external fixator. The correction is performed after surgery by slowly opening the osteotomy by adjusting a screw located on the external fixator, about 1 mm each day, until the full correction is achieved[97]. The results by high tibial osteotomy are almost as good as those by total knee arthroplasty and complications are few if the procedure is performed by experienced surgeons[98]. As most of the OA is medially located (bow leg) a tibial osteotomy converts a knee from mild varus to mild valgus. The draw back for the patient is a certain postoperative valgus of the limb as some overcorrection of the hip knee ankle axis is intended. This is, however, the aim of the procedure, to move the lower limb axis from the diseased medial cartilage to the more healthy lateral cartilage.

Modern principles of knee arthroplasty are in use for more than 30 years[99]. The results of the first total condylar knee was favorable[100] and local series have shown similar results[101]. In national registers, the pain relief is good and the incidence of revision is low (around 5% after 10 years)[46]. The incidence of deep infection is around 0.5%[46]. In the early days, the prosthetic designs were of hinged or linked surface replacements but now, all primary prostheses are surface replacements of total or occasionally unicompartmental knee design. Most designs are femoral and tibial components of metal with a plastic insert fixed on the tibial component[99]. The metal material is mostly vitallium which is composed of chrome, cobalt and molybdenum while the plastic insert is made of high density polyethylene. The standard fixation of the metal components to bone is by special cement, a two component glue, which is mixed during surgery, and becomes hard and fully stabilizes the components after 10 - 15 minutes. There are guide instruments for bone cutting and occasionally computer navigation may be used. The correct patient selection for the procedure is now better understood. A young patient with a potential for high activity level postoperatively has a relative high risk for a premature loosening / material failure. On the other hand, a biologically old patient with a limited ability to take part in the postoperative rehabilitation will not benefit from a knee replacement, as there is often, too little muscular motor power to drive the artificial knee[99].

From 1984 until 2007, 577 knee prosthetic operations were performed in Al-Razi Orthopedic Hospital in Kuwait[17]. An increase in the number of these operations occurred during the last years and in 2007 there were almost 100 knee arthroplasties performed. There are no certain statistics of the annual incidence of knee arthroplasty operated Kuwaiti people as patients are also operated in private hospitals within and outside the country. It is estimated that about 200 - 250 knee prosthetic operations are performed on Kuwaitis annually. In order get more exact epidemiological data and in order to improve the quality assurance of knee prosthetic replacements in Kuwait, we have proposed that a national register of knee prosthesis is organized[17]. Similar national registers are in use in many other countries.

SUMMARY

Knee OA has a slow disease progress and it is the final result of many different disease patterns which occur in the knee joint. OA primarily affects the cartilage but involves by time, the bone, ligaments, muscles and the joint capsule. Often the patients are affected by other diseases like obesity, diabetes, hypertension or other organ failures. Symptoms of knee OA are pain, stiffness and muscle weakness. The main symptom is pain on walking which is often intermittent with better or worse periods.

The basic treatment of knee OA is self-management by information about the disease, regular exercise usually walking, muscle training and weight control. Patient participation in an OA school is an advantage and OA schools are therefore recommended to be introduced in Kuwait. An OA school is best organized by the primary care doctor, but actually all doctors, nurses and other health care employees can be involved in the implementation of the treatment program. If the compliance of the program is good many patients are satisfied with self-management / OA School. The key issue is an active lifestyle where level walking is the easiest and most natural activity. Mankind has in earlier times always been used to daily labour and our loco-motor system is planned for such a life. At that time long level walks, almost to the level of the capacity of the individual, gave the joints the necessary loading. Exercise also has a positive effect for most organs, not the least for the psychological well-being. Today, in many countries, exercise practice is written down by a doctor, in the same way as a prescription for drugs. Physiotherapy is recommended for a limited time period and one main issue is to encourage the patient to find a personal activity program.

However, OA patients of today are used to tablets of different types as a quick solution for their problem. The pharmacological modalities of non-operative treatment are analgesics / NSAIDs, injection by steroids / hyaloronic acid and glucosamine. Most of these pharmacological treatment programs have a temporary and usually a small, maximum intermediate, effect on the pain due to knee OA. The same type of effect can be achieved by self-management / physiotherapy and weight reduction (Table 4).

Table 4: Early osteoarthritis in primary care

- Early osteoarthritis is recommended to be seen in the primary care
- A primary care doctor can implement and follow up self-management
- Self-management needs regular support
- Support by a physiotherapist or a coach can also be beneficial
- Osteoarthritis schools is recommended in kuwait

If non-operative treatment fails, surgery is an option. This is most often done by total knee prosthesis. The outcome of such an operation is usually favorable. However, the patients should be informed about individual risk factors and possible complications. In otherwise healthy patients, the risk of complications is small.

CONCLUSION

Self-management is a simple and out of the patients perspective, an active treatment, which often leads to certain improvements of the knee OA disease. Self-management means that the patient gets information about knee OA, has an individual daily activity program, performs regular muscle training and has a sound diet. Such a program means usually a change of the life-style which can be further implemented by an OA School. Such a school can also deal with concurrent diseases like obesity, diabetes, hypertension or other organ failures.

REFERENCES

1. Hirano PC, Laurent DD, Lorig K. Arthritis patient education studies, 1987-1991: a review of the literature. Patient Educ Couns 1994; 24:9-54.
2. Brandt KD, Dieppe P, Radin E. Etiopathogenesis of osteoarthritis. Med Clin North Am 2009; 93:1-24, xv.
3. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet 2005; 365:965-973.
4. Michael JW, Schluter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. Dtsch Arztebl Int 2010; 107:152-162.
5. Toivanen AT, Heliovaara M, Impivaara O, *et al*. Obesity, physically demanding work and traumatic knee injury are major risk factors for knee osteoarthritis - a population-based study with a follow-up of 22 years. Rheumatology (Oxford) 2010; 49:308-314.
6. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. Am J Sports Med 2007; 35:1756-1769.
7. Oiestad BE, Engebretsen L, Storheim K, Risberg MA. Knee osteoarthritis after anterior cruciate ligament injury: a systematic review. Am J Sports Med 2009; 37:1434-1443.
8. Felson DT, Hannan MT, Naimark A, *et al*. Occupational physical demands, knee bending, and knee osteoarthritis: results from the Framingham Study. J Rheumatol 1991; 18:1587-1592.
9. McAlindon TE, Wilson PW, Aliabadi P, Weissman B, Felson DT. Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham study. Am J Med 1999; 106:151-157.
10. Dahaghin S, Tehrani-Banihashemi SA, Faezi ST, Jamshidi AR, Davatchi F. Squatting, sitting on the floor, or cycling: are life-long daily activities risk factors for clinical knee osteoarthritis? Stage III results of a community-based study. Arthritis Rheum 2009; 61:1337-1342.
11. Sowers MR, Karvonen-Gutierrez CA. The evolving role of obesity in knee osteoarthritis. Curr Opin Rheumatol 2010; 22:533-537.
12. Stevens-Lapsley JE, Kohrt WM. Osteoarthritis in women: effects of estrogen, obesity and physical activity. Womens Health (Lond, Engl) 2010; 6:601-615.
13. Hurley MV. The role of muscle weakness in the pathogenesis of osteoarthritis. Rheum Dis Clin North Am 1999; 25:283-298, vi.
14. Slemenda C, Heilman DK, Brandt KD, *et al*. Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? Arthritis Rheum 1998; 41:1951-1959.
15. Thorstensson CA, Petersson IF, Jacobsson LT, Boegard TL, Roos EM. Reduced functional performance in the lower extremity predicted radiographic knee osteoarthritis five years later. Ann Rheum Dis 2004; 63:402-407.
16. Aigner T, Haag J, Martin J, Buckwalter J. Osteoarthritis: aging of matrix and cells - going for a remedy. Curr Drug Targets 2007; 8:325-331.
17. Al Mukaimi A, El Salawi E, Lindstrand A. Knee arthroplasty in Kuwait during 25 years: A national presentation and an international review. Kuwait Medical Journal 2008; 40:269-274.
18. Chitnavis J, Sinsheimer JS, Clipsham K, *et al*. Genetic influences in end-stage osteoarthritis. Sibling risks of hip and knee replacement for idiopathic osteoarthritis. J Bone Joint Surg Br 1997; 79:660-664.
19. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. BMJ 1996; 312:940-943.
20. Ageberg E, Pettersson A, Friden T. 15-year follow-up of neuromuscular function in patients with unilateral nonreconstructed anterior cruciate ligament injury initially treated with rehabilitation and activity modification: a longitudinal prospective study. Am J Sports Med 2007; 35:2109-2117.
21. Neuman P, Englund M, Kostogiannis I, Friden T, Roos H, Dahlberg LE. Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. Am J Sports Med 2008; 36:1717-1725.
22. Roos H, Lindberg H, Gardsell P, Lohmander LS, Wingstrand H. The prevalence of gonarthrosis and its relation to meniscectomy in former soccer players. Am J Sports Med 1994; 22:219-222.
23. Buckwalter JA, Lane NE. Athletics and osteoarthritis. Am J Sports Med 1997; 25:873-881.
24. Pearle AD, Warren RF, Rodeo SA. Basic science of articular cartilage and osteoarthritis. Clin Sports Med 2005; 24:1-12.

25. Koval. General Knowledge, Articular Cartilage. Orthopaedic Knowledge Update 7, page 5-7. 2002.
26. Mow V, Proctor C, Kelly M. Basic Biomechanics of the Musculoskeletal System (eds: Nordin, Frankel). Lea & Febiger. 1989:31-57.
27. O´Driscol. The healing and regeneration of articular cartilage. J Bone Joint Surg Am 1998; 80:1795-1812.
28. Nakamura N, Horibe S, Toritsuka Y, *et al*. The location-specific healing response of damaged articular cartilage after ACL reconstruction: short-term follow-up. Knee Surg Sports Traumatol Arthrosc 2008; 16:843-848.
29. Shim IK, Yook YJ, Lee SY, *et al*. Healing of articular cartilage defects treated with a novel drug-releasing rod-type implant after microfracture surgery. J Control Release 2008; 129:187-1891.
30. Nishitani K, Shirai T, Kobayashi M, *et al*. Positive effect of alendronate on subchondral bone healing and subsequent cartilage repair in a rabbit osteochondral defect model. Am J Sports Med 2009; 37:139S-147S.
31. Radin EL, Rose RM. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop Relat Res 1986; 213:34-40.
32. Ding M, Danielsen CC, Hvid I. The effects of bone remodeling inhibition by alendronate on three-dimensional microarchitecture of subchondral bone tissues in guinea pig primary osteoarthrosis. Calcif Tissue Int 2008; 82:77-86.
33. Mansell JP, Bailey AJ. Abnormal cancellous bone collagen metabolism in osteoarthritis. J Clin Invest 1998; 101:1596-1603.
34. Otterness IG, Weiner E, Swindell AC, Zimmerer RO, Ionescu M, Poole AR. An analysis of 14 molecular markers for monitoring osteoarthritis. Relationship of the markers to clinical end-points. Osteoarthritis Cartilage 2001; 9:224-231.
35. Berry PA, Maciewicz RA, Wluka AE, *et al*. Relationship of serum markers of cartilage metabolism to imaging and clinical outcome measures of knee joint structure. Ann Rheum Dis 2010; 69:1816-1822.
36. van Spil WE, DeGroot J, Lems WF, Oostveen JC, Lafeber FP. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. Osteoarthritis Cartilage 2010; 18:605-612.
37. Hawley DJ. Psycho-educational interventions in the treatment of arthritis. Baillieres Clin Rheumatol 1995; 9:803-823.
38. Thompson LR, Boudreau R, Hannon MJ, *et al*. The knee pain map: reliability of a method to identify knee pain location and pattern. Arthritis Rheum 2009; 61:725-731.
39. Ahlback S. Osteoarthrosis of the knee. A radiographic investigation. Acta Radiol Diagn (Stockh) 1968; 277:7-72.
40. Verweij LM, van Schoor NM, Deeg DJ, Dekker J, Visser M. Physical activity and incident clinical knee osteoarthritis in older adults. Arthritis Rheum 2009; 61:152-157.
41. Mason RB, Horne JG. The posteroanterior 45 degrees flexion weight-bearing radiograph of the knee. J Arthroplasty 1995; 10:790-792.
42. Altman R, Asch E, Bloch D, *et al*. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986; 29:1039-1049.
43. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, *et al*. Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with clinical symptoms and radiographic changes. Arthritis Res Ther 2006; 8:21.
44. Neogi T, Nevitt M, Niu J, *et al*. Subchondral bone attrition may be a reflection of compartment-specific mechanical load: the MOST Study. Ann Rheum Dis 2010; 69:841-844.
45. Burstein D, Velyvis J, Scott KT, *et al*. Protocol issues for delayed Gd(DTPA)(2-)-enhanced MRI (dGEMRIC) for clinical evaluation of articular cartilage. Magn Reson Med 2001; 45:36-41.
46. Lidgren L, Robertsson O. The Swedish Knee Arthroplasty Register. Annual Report (http://wwwortluse/knee) 2010.
47. Messier SP, Loeser RF, Miller GD, *et al*. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. Arthritis Rheum 2004; 50:1501-1510.
48. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport 1999; 70:113-119.
49. Zhang W, Nuki G, Moskowitz RW, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage 2010; 18:476-499.
50. Osteoarthritis. NCCFCC. National clinical guideline for care and management in adults. Royal College of Physicians, 2008.
51. AAOS. Treatment of osteoarthritis of the knee (non-arthroplasty). American Society of Orthopedic Surgeons. 2008; (http://www.aaos.org/research/guidelines/GuidelineOAKnee.asp)
52. Jordan KM, Arden NK, Doherty M, *et al*. EULAR Recommendations 2003: an evidence based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis 2003; 62:1145-1155.
53. Ravaud P, Flipo RM, Boutron I, *et al*. ARTIST (osteoarthritis intervention standardized) study of standardised consultation versus usual care for patients with osteoarthritis of the knee in primary care in France: pragmatic randomised controlled trial. BMJ 2009; 338: b421.
54. Buszewicz M, Rait G, Griffin M, *et al*. Self management of arthritis in primary care: randomised controlled trial. BMJ 2006; 333:879.
55. Fransen M, McConnell S. Land-based exercise for osteoarthritis of the knee: a metaanalysis of randomized controlled trials. J Rheumatol 2009; 36:1109-1117.
56. Devos-Comby L, Cronan T, Roesch SC. Do exercise and self-management interventions benefit patients with osteoarthritis of the knee? A metaanalytic review. J Rheumatol 2006; 33:744-756.

57. Thomas KS, Muir KR, Doherty M, Jones AC, O'Reilly SC, Bassey EJ. Home based exercise programme for knee pain and knee osteoarthritis: randomised controlled trial. BMJ 2002; 325:752.
58. Roddy E, Zhang W, Doherty M. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. Ann Rheum Dis 2005; 64:544-548.
59. Jamtvedt G, Dahm KT, Christie A, *et al*. Physical therapy interventions for patients with osteoarthritis of the knee: an overview of systematic reviews. Phys Ther 2008; 88:123-136.
60. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. Arthritis Rheum 2005; 52:3507-3514.
61. Manninen P, Riihimaki H, Heliovaara M, Suomalainen O. Physical exercise and risk of severe knee osteoarthritis requiring arthroplasty. Rheumatology (Oxford) 2001; 40:432-437.
62. Bartels EM, Lund H, Hagen KB, Dagfinrud H, Christensen R, Danneskiold-Samsoe B. Aquatic exercise for the treatment of knee and hip osteoarthritis. Cochrane Database Syst Rev 2007: CD005523.
63. Miller GD, Rejeski WJ, Williamson JD, *et al*. The Arthritis, Diet and Activity Promotion Trial (ADAPT): design, rationale, and baseline results. Control Clin Trials 2003; 24:462-480.
64. Shea MK, Houston DK, Nicklas BJ, *et al*. The effect of randomization to weight loss on total mortality in older overweight and obese adults: the ADAPT Study. J Gerontol A Biol Sci Med Sci 2010; 65:519-525.
65. Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 2007; 66:433-439.
66. Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G. Acetaminophen for osteoarthritis. Cochrane Database Syst Rev 2006: CD004257.
67. Bjordal JM, Klovning A, Ljunggren AE, Slordal L. Short-term efficacy of pharmacotherapeutic interventions in osteoarthritic knee pain: A meta-analysis of randomised placebo-controlled trials. Eur J Pain 2007; 11:125-138.
68. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ 2004; 329:1317.
69. Lee C, Hunsche E, Balshaw R, Kong SX, Schnitzer TJ. Need for common internal controls when assessing the relative efficacy of pharmacologic agents using a meta-analytic approach: case study of cyclooxygenase 2-selective inhibitors for the treatment of osteoarthritis. Arthritis Rheum 2005; 53:510-518.
70. Rahme E, Barkun A, Nedjar H, Gaugris S, Watson D. Hospitalizations for upper and lower GI events associated with traditional NSAIDs and acetaminophen among the elderly in Quebec, Canada. Am J Gastroenterol 2008; 103:872-882.
71. Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. BMJ 2004; 329:324.
72. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2007; 15:957-965.
73. Reichenbach S, Sterchi R, Scherer M, *et al*. Meta-analysis: chondroitin for osteoarthritis of the knee or hip. Ann Intern Med 2007; 146:580-590.
74. Block JA, Oegema TR, Sandy JD, Plaas A. The effects of oral glucosamine on joint health: is a change in research approach needed? Osteoarthritis Cartilage 2010; 18:5-11.
75. Vlad SC, LaValley MP, McAlindon TE, Felson DT. Glucosamine for pain in osteoarthritis: why do trial results differ? Arthritis Rheum 2007; 56:2267-2277.
76. Bruyere O, Pavelka K, Rovati LC, *et al*. Total joint replacement after glucosamine sulphate treatment in knee osteoarthritis: results of a mean 8-year observation of patients from two previous 3-year, randomised, placebo-controlled trials. Osteoarthritis Cartilage 2008; 16:254-260.
77. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006:CD005328.
78. Geirsson AJ, Statkevicius S, Vikingsson A. Septic arthritis in Iceland 1990-2002: increasing incidence due to iatrogenic infections. Ann Rheum Dis 2008; 67:638-643.
79. Bellamy N, Campbell J, Robinson V, Gee T, Bourne R, Wells G. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database Syst Rev 2006:CD005321.
80. Arrich J, Piribauer F, Mad P, Schmid D, Klaushofer K, Mullner M. Intra-articular hyaluronic acid for the treatment of osteoarthritis of the knee: systematic review and meta-analysis. CMAJ 2005; 172:1039-1043.
81. Manheimer E, Linde K, Lao L, Bouter LM, Berman BM. Meta-analysis: acupuncture for osteoarthritis of the knee. Ann Intern Med 2007; 146:868-877.
82. McCarthy CJ, Callaghan MJ, Oldham JA. Pulsed electromagnetic energy treatment offers no clinical benefit in reducing the pain of knee osteoarthritis: a systematic review. BMC Musculoskelet Disord 2006; 7:51.
83. Brouwer RW, Jakma TS, Verhagen AP, Verhaar JA, Bierma-Zeinstra SM. Braces and orthoses for treating osteoarthritis of the knee. Cochrane Database Syst Rev 2005:CD004020.
84. Canter PH, Wider B, Ernst E. The antioxidant vitamins A, C, E and selenium in the treatment of arthritis: a systematic review of randomized clinical trials. Rheumatology (Oxford) 2007; 46:1223-1233.
85. Christensen R, Bartels EM, Astrup A, Bliddal H. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2008; 16:399-408.
86. Brien S, Prescott P, Coghlan B, Bashir N, Lewith G. Systematic review of the nutritional supplement Perna Canaliculus (green-lipped mussel) in the treatment of osteoarthritis. QJM 2008; 101:167-179.
87. Christensen R, Bartels EM, Altman RD, Astrup A, Bliddal H. Does the hip powder of Rosa canina (rosehip) reduce

pain in osteoarthritis patients?--a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2008; 16:965-972.
88. Fidelix TS, Soares BG, Trevisani VF. Diacerein for osteoarthritis. Cochrane Database Syst Rev 2006: CD005117.
89. Soeken KL, Lee WL, Bausell RB, Agelli M, Berman BM. Safety and efficacy of S-adenosylmethionine (SAMe) for osteoarthritis. J Fam Pract 2002; 51:425-430.
90. Wegener T, Lupke NP. Treatment of patients with arthrosis of hip or knee with an aqueous extract of devil's claw (Harpagophytum procumbens DC.). Phytother Res 2003; 17:1165-1172.
91. Hansson EE, Sorensson E, Ronnheden AM, Lundgren M, Bjarnung A, Dahlberg LE. Arthritis school in primary health care. A pilot study of 14 years of experience from Malmo. Lakartidningen 2008; 105:2175-177.
92. Moseley JB, O'Malley K, Petersen NJ, *et al*. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2002; 347:81-88.
93. Kirkley A, Birmingham TB, Litchfield RB, *et al*. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. N Engl J Med 2008; 359:1097-1107.
94. Herrlin S, Hallander M, Wange P, Weidenhielm L, Werner S. Arthroscopic or conservative treatment of degenerative medial meniscal tears: a prospective randomised trial. Knee Surg Sports Traumatol Arthrosc 2007; 15:393-401.
95. Magyar G, Toksvig-Larsen S, Lindstrand A. Changes in osseous correction after proximal tibial osteotomy: radiostereometry of closed- and open-wedge osteotomy in 33 patients. Acta Orthop Scand 1999; 70:473-477.
96. Magyar G, Ahl TL, Vibe P, Toksvig-Larsen S, Lindstrand A. Open-wedge osteotomy by hemicallotasis or the closed-wedge technique for osteoarthritis of the knee. A randomised study of 50 operations. J Bone Joint Surg Br 1999; 81:444-448.
97. Magyar G, Toksvig-Larsen S, Lindstrand A. Open wedge tibial osteotomy by callus distraction in gonarthrosis. Operative technique and early results in 36 patients. Acta Orthop Scand 1998; 69:147-151.
98. Magyar G, Toksvig-Larsen S, Lindstrand A. Hemicallotasis open-wedge osteotomy for osteoarthritis of the knee. Complications in 308 operations. J Bone Joint Surg Br 1999; 81:449-451.
99. Lindstrand A, Al Mukaimi A. Knee Arthroplasty. Kuwait Med J 2008; 40:267-268.
100. Insall J, Scott WN, Ranawat CS. The total condylar knee prosthesis. A report of two hundred and twenty cases. J Bone Joint Surg Am 1979; 61:173-180.
101. Al-Rowaih A, Pospula W, Abdul-Moez O, Lindstrand A. Duracon total knee replacement in Kuwait: A clinical and radiographic analysis of 52 knees followed for 2 - 5 years. . Med Princ Pract 1999; 8:98-104.

Original Article

Re-appraisal of Vaginal Delivery after Previous Two Cesarean Sections

Lulu Abdullah Al Nuaim
Department of Obstetrics and Gynecology, King Khalid University Hospital, Riyadh, Saudi Arabia

Kuwait Medical Journal 2011; 43 (3): 189 -195

ABSTRACT

Objective: To study the outcome of offering a trial of labor to women with history of two previous cesarean sections (CS) after appropriate counseling
Design: Retrospective
Setting: Obstetric Unit at King Khalid University Hospital, Riyadh, Saudi Arabia, over a period of seven years (1993 – 1999)
Subjects: A total of 40 women with two previous CS requested a trial of labor
Intervention: Trial of labor despite having two previous CS based on specific predetermined criteria
Main Outcome Measure(s): (1) The rate of vaginal delivery, (2) The rate of repeat CS and (3) Neonatal outcome
Results: This group represents 8% of women with a history of two previous CS out of which 50% had primary CS and 25% had repeated CS in their previous pregnancies. Spontaneous labor occurred in 95% and augmentation in 45%. There was no uterine dehiscence or rupture in this study. There were five intrauterine deaths, six babies admitted to the NICU; four for prematurity and breech delivery and two for grunting. There was no birth asphyxia or neonatal death. Five of these cases are presented in detail.
Conclusion: The favorable outcome in this study shows that trial of labor can be safely offered to a selected group of women with two previous CS after proper counseling. This goal can be achieved without limiting childbirth options for women who sincerely wish to avoid multiple cesarean deliveries. Larger trials are needed in our community to support finding in this study.

KEY WORDS: pregnancy outcome, repeat CS, vaginal birth after cesarean

INTRODUCTION

The rate of cesarean delivery has increased steadily over the past 30 years world wide, with current rates of > 25%[1-4] and the repeat cesarean section (CS) rate for low risk women of all ages and racial groups is now 88.7%[5]. Studies conducted in 1980's have shown that the primary reason for the continuing escalation of cesarean delivery rate is the performance of elective repeat CS[6], since the relative safety of cesarean delivery had promoted a more liberal approach to its use[7]. However, this has resulted in considerable concern as a public health issue. Studies conducted later have reported that the procedure though common, presents a high maternal morbidity and mortality[8-10]. Attention had been focused on the alternative to cesarean birth for some time[11]. Several studies performed in the 1970's and 1980's confirmed the safety of vaginal birth after a CS (VBAC)[12-13].

In addition, studies in the 1990's have supported that VBAC is an acceptable option to routine elective repeat surgery[14-16]. This has been approved by the American College of Obstetricians and Gynecologists, provided certain criteria are fulfilled[3]. Most authorities now agree that VBAC should be encouraged, in order to reduce the rising cesarean delivery rate[6]. The success rate for VBAC is up to 79%[17]. The benefits of VBAC, in terms of reduced costs and maternal morbidity, without jeopardizing fetal outcome have been well-documented[18]. Women with previous cesarean births now represent a relatively large proportion of the obstetric population and this is likely to increase even more, if the present cesarean birth rate continues. Since women's and physicians' interest in VBAC is increasing, the obvious question of whether such management alternative should be extended to women with two previous cesarean deliveries is being raised more frequently[19,20], especially for women whose initial CS were performed for clearly non-repetitive indications.

Data is now accumulating on vaginal birth after two CS[19-25]. Uterine scar separation does not appear to be affected by the number of previous uterine incisions

Address correspondence to:
Dr. Lulu A. Al Nuaim, MRCOG, MSc, Associate Professor and Consultant, Department of Obstetrics and Gynecology, College of Medicine & King Khalid University Hospital, King Saud University, P O Box 2925, Riyadh, 11461, KSA. Tel: + 966 (1) 4920260, Fax: + 966 (1) 4920520
E-mail: lulu.alnuaim@gmail.com

during a trial of labor[19,26]. There is increasing evidence that VBAC is safe and successful, and the dictum of once a CS, always a CS is no longer applicable[27]. Evidence is accumulating in western countries with regard to the safety and success of VBAC after multiple previous incisions in the lower segment[28]. Therefore, women in our community with two previous CS should at least be assessed individually, counseled and offered VBAC attempts.

The objective of this study is to present evidence that trial of labor can be accomplished safely in women with two previous cesarean births. The obstetric and neonatal outcome of forty women with previous two CS with different indications and of unknown scars, and who, after counseling, preferred to have vaginal birth is presented.

SUBJECTS AND METHODS

This retrospective study included forty women with two previous CS, and who delivered vaginally at the Obstetric Unit of King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia, over a period of seven years (1993 - 1999). The study group was selected for trial of labor despite having two previous CS, based on criteria such as the request of the couple during antenatal counseling for vaginal delivery, the estimated fetal size of less than 3.8 kg by ultrasound scan and spontaneous onset of labor.

Data was retrieved from medical records on maternal characteristics of nationality, age, height, parity, primary and repeat CS, previous vaginal delivery, and the indications for CS in the two previous cesarean deliveries. The primary CS is defined as delivery of a neonate by CS in mothers with no previous history of a CS and repeat CS is delivery of a neonate by CS following a previous CS. Other data included presentation of the fetus in labor, the use of analgesia and syntocinon during labor, gestational age at delivery, duration of labor and type of vaginal delivery. Neonatal characteristics such as baby weight, Apgar score at 1 and 5 minutes, admission to neonatal intensive care unit (NICU) and baby outcome were also retrieved.

Statistical Analysis

Data was analyzed using STATPAC Gold statistical analysis package and is presented as percentages and means (± SD).

RESULTS

During the study period, a total of 30,378 deliveries were conducted at KKUH, including 3877 (12.8 %) by CS. Primary CS comprised of 1959 cases (6.5%), and repeat CS (> 2 CS) comprised of 1918 (6.3%) cases out of the total deliveries. Repeat CS included 498 women (1.6%) who had two CS. Of the 498 women with two CS, forty women (8 %) underwent a voluntary trial of labor after obtaining informed consent. The characteristics of this cohort of women are presented in Table 1.

Table 1: Demographic and obstetric characteristics of 40 women with history of previous CSs delivered vaginally in the index pregnancy

Characteristics	No.	%
Nationality		
Saudi	39	97.5
Non-Saudi	1	2.5
Age (yrs)		
< 35	24	60
>35	16	40
Height (cms)		
<150	12	30
>150	28	70
Primary CS	20	50
Repeat cesarean in 2nd pregnancy	10	25
History of vaginal delivery	32	80
Intervening vaginal delivery	16	40
Spontaneous onset of labour	38	95
Epidural analgesia	9	22.5
Syntocinon augmentation	18	45
Gestation at delivery (weeks)		
<37	7	17.5
37-40	30	75
>40	3	7.5
Type of delivery		
SVD	34	85
Assisted breech	6	15
	Mean ± SD	**Range**
Age (years)	33.6 ± 4.26	24 - 42
Parity	4.6 ± 1.95	2 - 9
Height (cms)	151.9 ± 5.34	140 - 165
Gestation at delivery (weeks)	37 ± 4.0	26 - 42
Duration of labor (hours and minutes)		
First stage	6.1 ± 4.01	1.15 - 19.21
Second stage	0.15 ± 0.12	0.03 - 0.47

All women were Saudi except one who was a Pakistani. 40% out of these were > 35 years and parity ranged from 2 to 9, were short statured (< 150 cm), half of them had CS in their first pregnancy (primary CS) and 25% had a repeat CS in their second pregnancy. More than two third (80%) had a history of vaginal delivery and 40% had had intervening vaginal delivery (vaginal delivery between the 2 CS). Thirty eight women (95%) went into labor spontaneously at a mean gestational age of 37 + 4.0 weeks (range 26 - 42 weeks) and labor was induced in two women who had mid-trimester intrauterine fetal deaths with prostaglandin intravenous (IV) Nalador infusion. Forty-five percent of the women needed labor augmentation by syntocinon infusion and epidural analgesia. Thirty-four (85%) of the laboring women had spontaneous vaginal deliveries and the remaining were assisted breech. Regarding mean duration of labor, the first stage was 6.1 + 4.01 hrs (range 1.15 - 19.21) and the second stage was 0.15 + 0.12 hrs (range 0.03 - 0.47).

Table 2: Neonatal characteristics of babies born to 40 women with history of previous 2 CSs delivered vaginally

Characteristics	n	%
Presentation of fetus		
Breech	6	15
Cephalic	34	85
Neonatal weight (gms)		
< 2500	14	35
2500 - 3500	22	55
> 3500	4	10
NICU admission	6	15
Neonatal outcome		
Alive	35	87.5
IUFD	5	12.5
Apgar score (n = 35)		
At 1 min		
4 - 6	2	5.7
7 - 9	33	94.3
At 5 min		
5 - 7	2	5.7
8 - 10	33	94.3

NICU = Neonatal intensive care unit, IUFD = Intrauterine fetal death

Neonatal characteristics depicted in Table 2 shows that four babies weighed more than 3.5 kg and the mean birth weight was 2590 + 737.31 gm (range 950 - 3650 gm). Out of the 40 women, five had intrauterine fetal deaths (IUFD), four were diagnosed prior to labor and one presented with an abruptio placenta at 37 weeks. Only two (5.7%) babies had low Apgar scores at 1 and 5 minutes. In six women (15%) the presentation of fetus was breech in labor (Table 3). Four of them were preterm (gestational age 26 - 27 weeks), one had IUFD at 37 weeks gestation, and the sixth one was 38 weeks pregnant. All the six had assisted vaginal breech deliveries.

There were six (15%) admissions to the NICU in the entire study group (Table 4). Four out of these admissions were breech deliveries, admitted mainly due to prematurity. The other two cephalic presentations delivered at 35 and 36 weeks of gestation with birth weights of 2130 and 2600 grams respectively and were admitted for grunting. The two grunting babies were kept under observation for two days while the four premature babies delivered by assisted breech were in the NICU for an average period of four weeks.

The indications for the two previous CS in the study group are depicted as pie diagrams in Fig. 1 and 2. Five cases of special interest have been presented in detail, in which vaginal delivery was accomplished after two prior CS in spite of the presence of such features as cephalo-pelvic disproportion (CPD), breech presentation, big baby, short stature, obesity, diabetes, unknown scar and high blood pressure.

Case I: A 32-year-old woman who had two previous CS for CPD was booked at 19 weeks in her third pregnancy. Lateral pelvimetry revealed a pelvic inlet of 8.3 cm and an outlet of 9.5 cm. At 37 weeks, she presented in labor with lack of fetal movements for one day. The fundal height corresponded to 32 weeks, with breech presentation. There was no fetal heart activity. On pelvic examination, the cervix was soft, fully effaced and 6 cm dilated with intact membranes and a frank breech at minus-2 station. Ultrasound fetal weight was estimated to be 1.9 kg. Four hours later she progressed to spontaneous delivery of the breech following an episiotomy. The outcome was a male fresh still-born, normal macroscopically and weighing 1.7 kg. The post-partum period was uneventful.

Case II: This was a 28-year-old woman, para 2 + 0, who had had two CS previously at different hospitals for failure to progress. She was booked in this hospital for the current pregnancy. Her height was 148 cm but the radiological pelvimetry was adequate. At 39 weeks of gestation she presented in labor, the fundal height corresponding with her weeks of gestation, and the fetus was a cephalic presentation and the head was $2/5^{th}$ palpable per abdomen. Clinical examination was normal and the cervix was found to be 6 cm dilated. The membranes ruptured spontaneously, and following an episiotomy she had spontaneous vertex delivery of a normal healthy baby boy weighing 3.6 kilogram. The third stage was uneventful.

Case III: A 34-year-old woman, para 4 + 0, with two previous CS for breech presentation and with

Table 3: Characteristics of fetuses presenting as breech in six women with history of previous two CS who delivered vaginally

Fetus no.	Gestational age in weeks	Weight in grams	Apgar score	NICU admission
1	26	950	4 - 7	Yes
2	26+	950	5 - 7	Yes
3	27	1440	7 - 9	Yes
4	27	1310	7 - 9	Yes
5	37	1700	0 - 0	-
6	38	3060	7 - 9	No

Table 4: Characteristics of babies admitted in NICU of six women with history of previous two CS who delivered vaginally

Baby no.	Gestational age in weeks	Weight in grams	Mode of delivery	Apgar score
1	26	950	Assisted breech.	4 - 7
2	26+	950	Assisted breech.	5 - 7
3	27	1440	Assisted breech.	7 - 9
4	27	1310	Assisted breech.	7 - 9
5	35	2130	Vertex	7 - 8
6	36	2600	Vertex	7 - 9

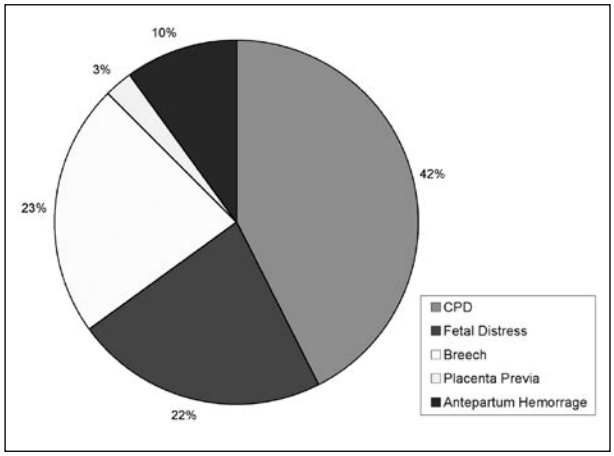

Fig. 1: Shows percentage of the indications for the first cesarean section (CS) in women with two CS (CPD = cephalo-pelvic disproportion)

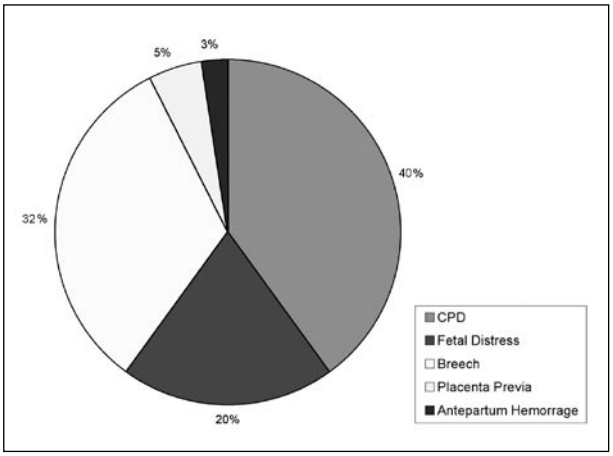

Fig. 2: Shows percentage of the indications for the second cesarean section (CS) in women with two CS (CPD = cephalo- pelvic disproportion)

two intervening vaginal vertex deliveries, was booked at 24 weeks of gestation in this hospital. She was a case of unknown scar status. At 40 weeks, the fundal height corresponded with the period of gestation. The presentation was cephalic and the head was 5 / 5 palpable per abdomen. She was allowed to await spontaneous onset of labor. Four days later, she presented in labor with partially effaced cervix which was 4 cm dilated. The membranes were intact and the presenting part was at minus-2 station. She was cross-matched for blood, an intravenous fluid was instituted, and the mother and the fetus were monitored.

Three hours later, the cervix was fully effaced and 6 cm dilated, an artificial rupture of membranes was performed, and clear liquor drained. The vertex was at the ischial spines. The fetal heart had remained reactive with good variability. The cervix had reached full dilatation in two hours and within 30 minutes, she delivered spontaneously of a healthy baby girl weighing 3.3 kilograms. The placenta and membranes were delivered by the Brandt Andrews method. She had uneventful post-natal period.

Case IV: A 29-year-old Pakistani woman had two previous CS after a failure to progress in labor. Her first delivery was vaginal. This fourth pregnancy has been uncomplicated apart from gestational diabetes managed by diet. She was 140 cm tall and weighed 82.3 kg at 38 weeks. At this gestation, she presented in advanced labor to the labor ward with a breech at plus-2 station. She managed to have an assisted vaginal breech delivery of a healthy male infant weighing 3.06 kg. The cord was twisted five times around the neck and the Apgar score was 7 and 9 at 1 and 5 minutes respectively. The third stage was uneventful.

Case V: A 37-year-old woman, para 8 + 0, had a history of two previous CS (4th and 6th pregnancies) for breech presentation and failure to progress. She had personal and family history of hypertension. At booking in this hospital, she was 18 weeks gestation, her BP was 160/100 mmHg despite using alpha methyldopa 250 mg twice daily. This was increased to 1 gm a day in divided doses. She had no symptoms or proteinuria, her renal function test, uric acid, random blood sugar and urine analysis were reportedly normal. Her hypertension was satisfactorily managed with drugs. At 37-weeks gestation, she presented to the labor ward with slight vaginal bleeding. The blood pressure was 167/100 mmHg with a pulse of 90 beats per minute. She looked rather pale. However, the abdomen was not tender and corresponded with her dates, and palpable contractions were felt.

The fetus presented by the head which was 5 / 5 palpable per abdomen. The fetal heart could not be heard. The cervix was 1 cm long and 2 cm dilated, soft and the membranes were intact. Ultrasound had confirmed death in utero. She remained well clinically. Artificial rupture of the membranes was performed four hours later, and blood stained liquor drained. Syntocinon augmentation was initiated. She progressed within two hours into spontaneous vertex delivery of a macerated male baby weighing 3.480 kg. There was a large retro-placental clot measuring 330 ml. The third stage was uneventful.

One year later, she managed to get pregnant and had gestational diabetes which needed insulin treatment. She went into spontaneous labour at 39 weeks and had spontaneous vertex delivery of a male infant weighing 3.6 kg. Mother and baby were discharged in good condition.

DISCUSSION

The rise in cesarean birth has occurred in spite of the growing acceptance of VBAC[11,14,19-25,29]. Numerous reports support the contention that a trial of labor is

an appropriate option for women with a previous low transverse CS[19-24]. A meta-analysis of 29 studies found that the success rates for VBAC ranged form 67% for patients with a prior failure to progress in labor, to 85% where the indication for the primary operation was breech presentation, with all indication for previous CS being associated with success rates of vaginal delivery that would make trial of labor appropriate[30].

A history of multiple CS may not exclude the woman from the alternative of CS; the more widespread use of trial of labor in such women could lead to significant reduction in the national CS rate with its inherent morbidity and mortality. The available data strongly suggest that such trials appear to be justified, appropriate and of reasonable consideration[19-26,28]. These pregnant women should not be treated differently from those who had one CS. Riva and Teich[31] were the first to systematically study VBAC in uteri with multiple scars including four previous CS. Their success rate was 66% with no uterine dehiscence or rupture.

Since then, there have been more than 900 such trials after two CS, most of which concluded that, the vaginal delivery rate of 80 percent in women with two previous sections was no different from women with only one previous CS[21-23,32]. A fairly large study of 115 women with two previous CS, done in Riyadh, Saudi Arabia, showed a success rate of 90 percent, which was higher than that after one previous CS[23]. This was explained by the fact that there was more rigorous selection of pregnant women for trial of labor.

Several studies found a significantly greater success rate of VBAC in women who had their previous CS for breech presentation or had previous vaginal delivery[32-33]. However, Chattopadhyay found no significant difference in the rate of vaginal delivery in women who previously had vaginal delivery compared with women who had not previously delivered vaginally[23]. In the present study group, majority of the women (80%) had experienced vaginal delivery previously and most of the indications for prior CS in this group were non-recurring.

The present study reports the use of syntocinon (oxytocin) augmentation in 45% of the cases with no adverse effects such as uterine dehiscence / rupture. The use of oxytocin augmentation in these women however, remains a controversial issue as in women with one previous CS, even though there were a large number of trials that used oxytocin. Most of these trials however, were consistent with the finding that oxytocin augmentation was not related to significantly increased incidence of uterine dehiscence[32-34]. However, previous reports showed an increasing rate of uterine dehiscence / rupture as the number of previous uterine incisions increased[35]. In contrast, Phelan[21] had the largest trial of 501 parturient with more than one previous CS who had trial of labor. The incidence of uterine dehiscence in his study was higher in the non-trial group; 4.6 % as compared with1.8 % in the trial group. This was also reported in the study by Chattopadhyay[23].

Documentation of the type of prior uterine incision has previously been a pre-requisite to allow the woman to undergo a trial of labor, because low vertical or classical incision has a higher likelihood of uterine rupture[36]. However, different studies had demonstrated that, the incidence of uterine dehiscence was not statistically increased with an unknown scar compared to that seen in women with prior low transverse incisions[37]. The present study included women with unknown scars. However, there was no case of uterine dehiscence in this group of women. Nevertheless, knowledge that the woman's scar is of the classical type will help the management in such cases. Fortunately, classical incision is seldom utilized today.

Epidural analgesia was used in almost two thirds of women in several studies. This did not affect the course of labor and did not prevent the recognition of early signs of uterine rupture[38-39]. In this study epidural analgesia was used in only 22.5% of the cases with no adverse effects on labor outcome. The small percentage of epidural usage was because it is not widely acceptable by the laboring women in general, and epidural was not advocated by the local obstetricians. Febrile morbidity has significantly been found to be lower in the VBAC group compared with those undergoing elective repeat CS in previous studies. Moreover, hospital stay was also reduced by half as in previous studies[24,40].

Recently, an increasing number of expectant Saudi women prefer to have vaginal delivery after two CS. From the literature, vaginal delivery in such women appears to be justified and very appealing in a community like Saudi Arabia where there is an increased demand from the consumers favoring large healthy family. The mode of delivery, therefore, should be based on the specific clinical scenarios and the woman's choice, but after appropriate selection and counseling. Otherwise, such women might hide information such as the number of their previous CS, or they opt to labor at home, and then they will be faced with increased serious delivery hazards[40-41].

There is no doubt that there may be risks associated with VBAC, but in a hospital setting with appropriate resources, these risks are low, even if they would still seem unacceptable. Labor should occur in a setting that permits timely intervention for the rare instance in which intervention becomes necessary. A woman planning VBAC may need extra understanding and support as she rebuilds her belief in herself in preparation for another birth. Most women do not voluntarily submit themselves and their babies to risks

of CS. It is recommended that every woman who is planning a birth after two previous CS, is encouraged and supported to plan a vaginal birth in a hospital setting.

CONCLUSION

The findings of this study are similar to those of previous studies suggesting that a trial of vaginal delivery after prior two CS is a reasonable option in women in whom it is not obstetrically contraindicated and who are appropriately counseled and managed. The high success rate of vaginal deliveries (95%) achieved in this study group could be attributed to its selective nature. However, the sample size may be too small to draw any firm conclusions. Therefore, larger trials would need to be undertaken in our community to support the results achieved.

As much as possible, women with previous two CS should be involved in the decision-making regarding the mode of their delivery to reduce the rise in repeat CS rate. Unless something is done about the rise in the CS rate, our obstetrics' future may end in peril of repeated CS. It is advisable therefore, that every obstetric unit should have ongoing CS reduction initiatives, with emphasis laid on the importance of careful selection of such women.

ACKNOWLEDGMENT

I am grateful to Ms Najma Khalil for her assistance in statistics and would wish to thank Ms Denden Ponsaran for her secretarial work. I would also like to offer my sincere appreciation to Professor Babatunde Adelusi for editorial advice.

REFERENCES

1. Obstetricians and Gynaecologists' Clinical Effectiveness Support Unit: National Sentinel Caesarean Section Audit Report: London (UK): Royal College of Obstetricians and Gynaecologists: 2001.
2. Khashoggi T, Sultan MH, Al-Nuaim L, Addar M, Chowdhury N, Adelusi B. Primary CS in King Khalid University Hospital: Indications and obstetric outcome. Ann Saudi Med 1995; 15:585-588.
3. ACOG practice bulletins: Vaginal birth after previous cesarean delivery. Int J Gynecol Obstet 1999; 66:197-204.
4. Hamilton BE , Martin JA , Sutton PD. Births: preliminary data for 2003. Natl Vital Stat Rep 2004; 53 (9).
5. Menacker F. Trends in cesarean rates for first births and repeat cesarean rates for low risk women: United States, 1990-2003. Natl Vital Stat Rep 2005; 54:1-8.
6. Jakobi P, Weissman A, Paldi E. Reversing the upward trend in the caesarian section rate. Eur J Obstet Gynecol Reprod Biol 1987; 25:105.
7. Shiono PH, McNellis D, Rhoads GC. Reasons for the rising cesarean delivery rates: 1978 - 1984. Obstet Gynecol 1987; 69:696 - 700.
8. Sultan MH, Al-Nuaim L, Khashoggi T, Chowdhury N, Kangave D, Adelusi B. Sequelae of repeat caesarean sections. Int J Gynecol Obstet 1996; 52:126-132.
9. Gillian M, Rosenberg D, Davis F. The likelihood of placenta previa with greater number of caesarean deliveries and higher parity. Obstet Gynecol 2002; 99:976-980.
10 Kastner E, Figueroa R, Garry D. Emergency peripartum hysterectomy: Experience in a community teaching hospital. Obstet Gynecol 2002; 99:971-975.
11. Paul RH, Phelan JP, Yeh S. Trial of labor in patients with a prior cesarean birth. Am J Obstet Gynecol 1985; 151:297-304.
12. Gibbs CE. Planned vaginal delivery following caesarean section. Clin Obstet Gynecol 1980; 23:507-515.
13. Flamm BL, Lim OW, Jones C, Fallon D, Newman LA, Mantis JK. Vaginal birth after CS: Results of a multicentre study. Am J Obstet Gynecol 1988; 158:1079-1084.
14. Weinstein D, Benshushan Y, Ezra N, Rojonsky. Vaginal birth after CS: Current opinion. Int J Gynecol Obstet 1996; 53: 1-10.
15. Coltart TM, Davies JA, Katesmark M. Outcome of second pregnancy after a previous CS. Br J Obstet Gynaecol 1990; 97:1140-1143.
16. Muylder X DE, Thiery M. The cesarean delivery rate can be safely reduced in a developing country. Obstet Gynecol 1990; 75:360-364.
17. McMahon M, Luther E, Bowes W, *et al*. Comparison of a trial of labor with an elective second caesarean section. N Eng J Med 1996; 335:689-695.
18. Flamm BL, Newman L, Thomas S, *et al*. Vaginal birth after caesarean delivery; Results of a 5 year multicentre collaborative study. Obstet Gynaecol 1990; 76:750-754.
19. Porreco RP, Meier PR. Trial of labour in patients with multiple previous caesarean sections. J Reprod Medicine 1983; 28:770-772.
20. Farmakides G, Duvivien R, Schulman H, Schneider E, Biordi J. Vaginal birth after two or more previous CS. Am J Obstet Gynecol 1987; 156:565-566.
21. Phelan JP, Ahn MO, Diaz F, Brar HS, Rodriguez MH. Twice a caesarean section, always a cesarean? Obstet Gynecol 1989; 73: 161-165.
22. Jeannes N, Stephens A, Myer DO, Gleicher N. Obstetric outcome of patients with more than one prior CS. Am J Obstet Gynecol 1989; 16:364-367.
23. Chattopadhyay SK, Sherbeeni MM, Anokute CC. Planned vaginal delivery after previous caesarean section. Br J Obstet Gynecol 1994; 101:498-500.
24. Bretelle F, Cravello L, Shojai R, Roger V, D'Ercole C, Blanc B. Vaginal birth following two previous caesarean sections. Eur J Obstet Gynecol Reprod Biol 2001; 94:23-26.
25. Spaans WA , van der Vliet LME, Roell -Schorer EAM, Bleker OP, van Roosmalen J. Trial of labor after two or three previous CS. Eur J Obstet Gynecol Reprod Biol 2003; 110:16-19.
26. Landon MB, Spong CY , Thom E, Hauth JC , Bloom SL, Varner MW. Risk of uterine rupture with a trial of labor in women with multiple and single prior cesarean delivery. Obstet Gynecol 2006; 108:12-20.
27. Cragin EB. Conservatism in Obstetrics. NY Med J 1916; 104:1-3.

28. Cahill A, Tuuli M, Odibo A, Stamilio D, Macones G. Vaginal birth after caesarean for women with three or more prior caesareans: assessing safety and success. BJOG 2010; 117:422-428.
29. Rosen MG, Dickinson JC, Westhoff CL. Vaginal birth after caesarean: a meta-analysis of morbidity and mortality. Obstet Gynecol 1991; 77:465-470.
30. Brody CZ, Kosasa TS, Nakayama RT, Hale RW. Vaginal birth after caesarean section in Hawaii. Experience at Kapiolani medical center for women and children. Hawaii Med J 1993; 52:38-42.
31. Riva HL, Teich SC. Vaginal delivery after CS. Am J Obstet Gynecol 1961; 81:501-510.
32. Pruett KM, Kirshon B, Cotton DB, Poindexter AN. Is vaginal birth after two or more caesarean section safe? Obstet Gynecol 1988; 72:163-165.
33. Clark SL, Eglinton GS, Beall M, Phelan JP. The effect of indication for previous caesarean section on subsequent delivery outcome in patient undergoing trial of labor. Reprod Med 1984; 29:22-25.
34. Flamm BL, Goings JR, Fuelberth NJ, Fishermann E, Jones C, Hersh E. Oxytocin during labor after previous caesarean section: results of multicenter study. Obstet Gynecol 1987; 70:709-712.
35. Lao TT, Leung BF. Rupture of the gravid uterus. Eur J Obstet Gynecol Reprod Biol 1987; 25:175-180.
36. Pedowitz P, Schwartz RM. The true incidence of silent rupture of CS scars: A prospective analysis of 403 cases. Am J Obstet Gynecol 1957; 74:1071-1081.
37. Halperin ME, Moore DC, Hannah WJ. Classical versus low-segment transverse incision for preterm caesarean section: Maternal complications and outcome of subsequent pregnancies. Br J Obstet Gynecol 1988; 95:990-996.
38. ArunKumaran S, Chua S, Ratnam SS. Symptoms and signs with scar rupture - value of uterine activity measurements. Aust NZ J Obstet Gynecol 1992; 32:208-212.
39. Cheek T, Gutsche B. Epidural analgesia for labor and vaginal delivery. Clin Obstet Gynecol 1987; 30:515-532.
40. Jukelevics N. Women in the crossfire: Forced repeat caesarean. Birth 2002; 29:149-150.
41. Flamm BL. Vaginal birth after caesarean: What's new in the new millenium? Curr Opin Obstet Gynaecol 2002; 14:595-599.

Original Article

Characterization of Acrylamide Mediated Testicular Toxicity in Rat: Light and Electron Microscopic Study

Nesreen Rajeh[1,2], Samar Al Saggaf [1], Nasra Ayuob[1], Sufian ElAssouli[3]
[1]Department of Anatomy, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[2]Department of Histology and Cytology, Faculty of Medicine, Mansoura University, Egypt
[3]King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia

Kuwait Medical Journal 2011; 43 (3): 196-205

ABSTRACT

Objectives: Acrylamide (AA) has been shown to be a reproductive toxicant in animals and is associated with risk of cancer. The objective of this study was to evaluate the dose-dependent acute testicular toxicity of AA in rats.
Design: Experimental study
Setting: King Fahd Medical Research Center, King Abdulaziz University, Jeddah, Saudi Arabia
Subjects: Forty-eight rats
Intervention: Animals were loaded with AA orally at doses (5, 15, 30, 45, 60 mg/kg/day) for five consecutive days
Main Outcome Measures: Histopathological effects of AA on testis and epididymis
Results: AA induced a significant body weight reduction, increase in testis / body weight ratio and a significant reduction in sperm count, in the two groups treated with 45 mg and 60 mg/kg/day. Abnormal sperm shapes were detected in all groups. Histopathological signs of AA toxicity on testes and epididymis included; degeneration of spermatogonia, widening of intercellular junctions and degeneration of peritubular myoid cell. Sertoli cells showed darkening of its nuclei, detachment from the basement membrane, increase in the number and size of lipid droplets in their cytoplasm, failure of sperm release and phagocytosis of some sperms. Leydig cell atrophy was observed which contributed to sperm defects and various abnormal histopathological lesions including apoptosis in rat testis. A possible cause of tail intersegmentation seen in mature sperm tails was clarified by electron microscope (EM) examination.
Conclusion: AA induced harmful effects on the testis evidenced by degeneration of spermatogenic and Sertoli cells and Leydig cells atrophy in addition to reducing sperm count and appearance of abnormal sperms.

KEY WORDS: acrylamide, acute-toxicity, epididymis, histology, testis

INTRODUCTION

Acrylamide (AA) is an important compound in the production of polyacrylamide which is used in a variety of industries. It is well-known as a neurotoxicant after human and animal exposure and it also has been shown to elicit genotoxic, reproductive and carcinogenic effects in laboratory animals. Following the announcement of Swedish National Food Administration[1] that AA could be formed in carbohydrate rich foods when cooked at a high temperature, researchers worldwide have been energized to study AA and its implication on human health.

Although the underlying mechanism of AA formation in cooked foods has not been fully established to date, one possible mechanism is that AA is formed due to a heat-catalyzed chemical reaction between the amino acid asparagine and certain sugars (*e.g.*, glucose), both of which occur naturally in foods[2,3].

The investigators found that the content of AA in chips began to increase after three days of storage of potatoes at 2 ºC and that was correlated with the increase in reducing sugars in the tubers. This indicated that the reducing sugar content of the potato tubers determined the degree of AA formation and that, as a result, storage of potatoes at low temperature should be avoided to prevent increased AA formation[4].

A large number of studies have been reported on AA neurotoxicity, because it was first identified as a neurotoxicant in laboratory animals and industrial workers a long time ago[5]. However, many recent investigations of AA have been conducted to evaluate its other toxic effects, including reproductive toxicity[6-8], genotoxicity[7, 9] and carcinogenicity[10 - 12].

AA stimulates axonapathies. A primary target for neuronal damage is the medium to large diameter axons. Within the axonopathy reaction, the myelin sheath becomes degenerated and retreats away from the cell body. On a biochemical level, the AA acts as a "chemical transectant" which interferes with the axon along some point in the myelin sheath, thus

Address correspondence to:
Nasra Ayuob, Faculty of Medicine, King Abdulaziz University, Medical Education Department, Jeddah, Saudi Arabia. Tel: 00966/530112205, E-mail: nasra_ayuob@yahoo.com

biologically separating it from the remaining healthy neuron but disturbing the myelin and consequently, axon potential transmission[13].

Several studies have been conducted to evaluate the reproductive toxicity of AA, both in mice and rats, with single or multiple doses and with different routes of administration. In the early studies conducted by Mccollister *et al*, Burek *et al*. and Zenick *et al*[14-16] on rats, AA was shown to have reproductive toxicity. The major aim of the study was to determine the dose-response characteristics of AA testicular toxicity, by using different AA doses to induce testicular damage.

MATERIALS AND METHODS

General materials

Plus OneTM Acrylamide (PAGE grade, purity > 99.95%, < 0.05% impurities of acrylic acid), was obtained from Pharmacia Biotech (Upsala, Sweden) and Wright Stain from Merck (Darmstadt, Germany). Rose Bengal, Sodium Salt and Hematoxylin solution gill No. 2 were obtained from Sigma-Aldrich (Steinheim, Germany). All other chemicals and materials were purchased from BHD laboratory supplies (Analar®, England) and were of molecular biology grade.

Animals and dosage formulation

This was an experimental study in which a total of 48 virgin male Sprague-Dawley rats were used and allowed to acclimatize in the experimental environment for three days before dosing initiation. The rats were 60 days old and weighed 250 - 300 gm. They were divided into 5 AA treatment groups and one vehicle control group with eight randomly chosen animals in each group (n = 8). Acrylamide was given at doses 5, 15, 30, 45, 60 mg/kg/day for five consecutive days, because this is the dose range which has previously been reported in the literature to produce adverse effects on the testis[7]. Dosing solutions were freshly prepared daily using distilled water, based on the initial body weight of the rats at day zero. Control group was gavaged with 1 ml of distilled water. Animals were dosed with acrylamide, once per day for five consecutive days by oral gavage. All animals were weighed and observed for mortality or any behavioral changes once per day during the dosing and recovery period. Seventy two hours after the last AA dose, the rats were killed by cervical dislocation under ether anesthesia. The right testis and right epididymis of all animals were isolated and weighed for further experimental evaluation. All experiments were undertaken with the consent of the animal ethics committee in accordance with the guidelines set out by the Canadian Council on Animal Care.

Caudal sperm count

Two microlitre (2 μl) from each caudal tissue suspension (diluted 1:20) was taken, and sperm number was manually counted using a Makler Counting Chamber, Sefi-medical instruments (Haifa) in a strip of ten squares. Counting was undertaken using a LEICA, DM 1000 light microscopy at x 20 magnification.

Evaluation of sperms shape abnormality

Smear samples (of caudal tissue suspension) were prepared on slides after staining the slides with 10% rose Bengal ($C_{20}H_2Cl_4I_4Na_2O_5$) sodium salt solution for 15 minutes. In addition, Wright stain was also used for staining of smear suspensions.

Histopathological evaluation

Organs were fixed by one of two fixatives (Bouin's solution and formaldehyde) dependent upon the end use for these tissues. Tissues were then processed using standard laboratory procedures for histology and were examined using light microscopy at the indicated magnifications and representative images photographed with a Leica DC -180 camera.

Electron microscopy

To evaluate the toxicological effects of AA on the ultrastructural components of the rat testis, a pilot study of four rats; two for test and two for control was conducted. Rats were gavaged with 45 mg/kg of AA for five consecutive days, and then they were killed by cervical dislocation. Testicular tissue processing, embedding, sectioning and staining for electron microscopy was done in the electron microscopy unit at KFMRC. The slides were examined using an electron microscope (CM100 Philips, Holland).

Statistical analysis

Body weight, testis/body weight, and epididymal (caudal) sperm count were measured. These data were statistically analyzed by one-way analysis of variance (ANOVA) using SPSS software for Windows 15. A value of $p < 0.05$ was used as the criterion for statistical significance.

Ethics committee approval

The research was approved by the Biomedical Ethics Research Committee in The Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

RESULTS

Gross observational changes

The group that was treated with 60 mg/kg AA, showed signs of aggression starting on day-three and reaching its maximum level on day-five of dosing. In addition, rough coat features and loss of weight were observed in this group. The testis of rats of this group and those treated with 45 mg/kg AA were prominent and appeared enlarged. Finally, these rats developed severe hind limb weakness and unsteady movement

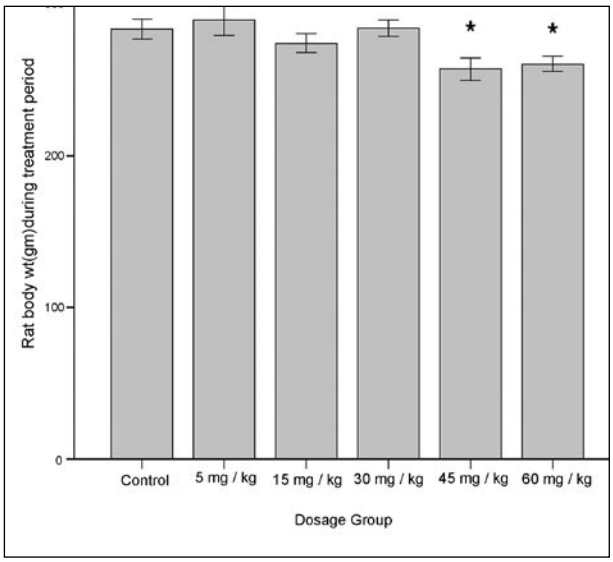

Fig. 1: Shows the effects of different doses of AA on rats' body weight during the treatment period (day 1 - 5). There is a statistically significant decrease in body weight (★ = $p < 0.05$) of the groups treated with 45 and 60 mg/kg AA.

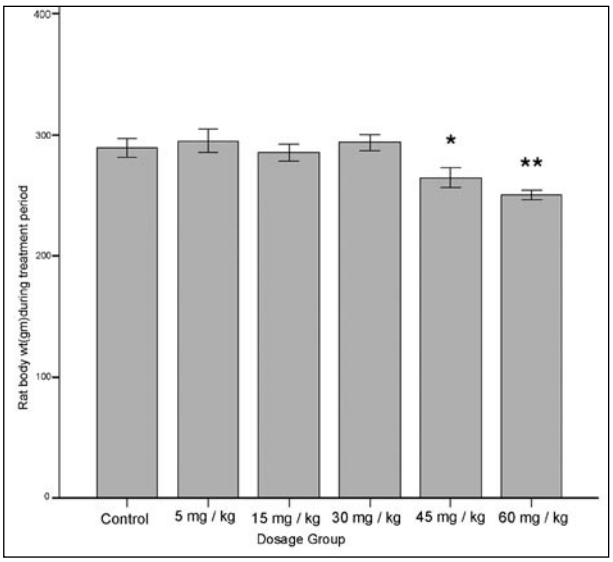

Fig. 2: Shows the effects of different doses of AA on rats' body weight during the recovery period (day 5 - 8), after cessation of AA treatment. There is a statistically significant decrease in body weight at AA doses of 45 and 60 mg/kg, (★ = $p < 0.05$) and (★★ = $p < 0.01$) respectively, as compared to the control group.

that varied in its severity along with lethargy and reduction in activity. None of these potential markers of toxicity were present in the other treatment groups.

Effect of AA on rats' body weight

During the treatment period (day 1 - 5) there was a statistically significant drop in body weight ($p < 0.05$) in the groups of rats treated with 45 and 60 mg/kg AA. (Fig.1). During the recovery period, (5 - 8 days) after cessation of AA treatment, the loss of body weight became less pronounced with slight weight gain occurring in some animals of all groups. However, there was still a statistically significant decrease in body weight at AA doses of 45 and 60 mg/kg, ($p < 0.05$) and ($p < 0.01$) respectively, as compared to the control group (Fig. 2).

Effect of AA on testis / body weight ratio

This study revealed a significant increase ($p < 0.05$) of the testis / body weight ratio in the group treated

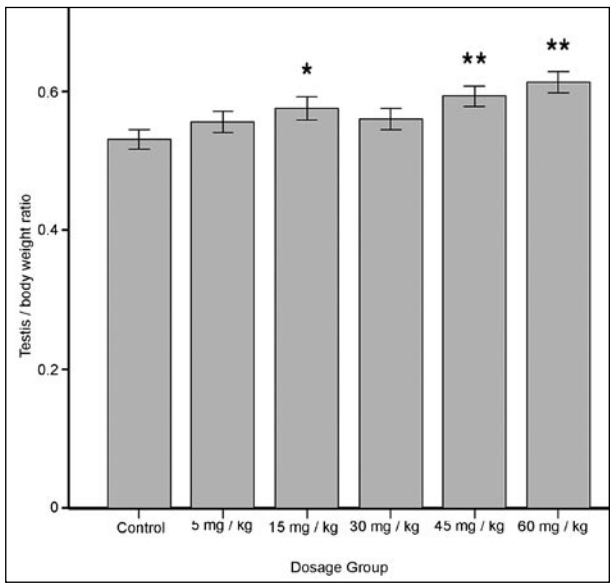

Fig. 3: Shows effects of different doses of AA on rats' testis / body weight ratio at the end of the experiment. There is a significant increase (★ = $p < 0.05$) in testis weight in relation to the body weight of the rats in the group treated with 15 mg/kg AA. Moreover, a very significant increase (★★ = $p < 0.01$) in testis / body weight ratio was detected in the two groups treated with 45 and 60 mg/kg.

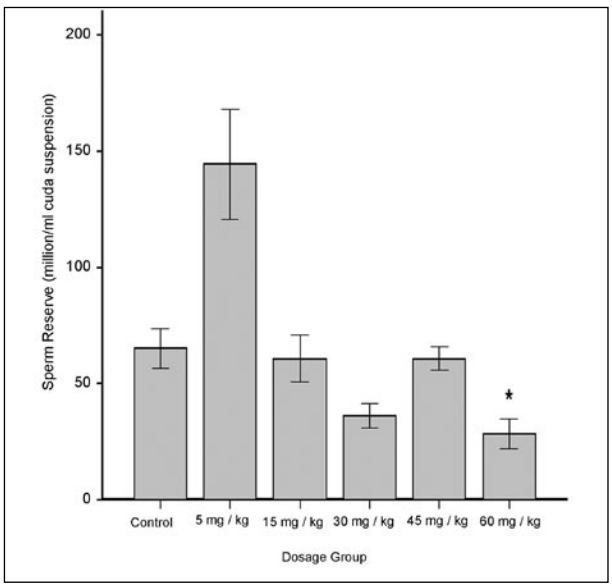

Fig: 4: Shows the effects of different doses of AA on caudal sperm count. There is significant reduction (★ = $p < 0.05$) in sperm count of the group treated with 60 mg/kg AA. Other groups showed no difference in relation to control group.

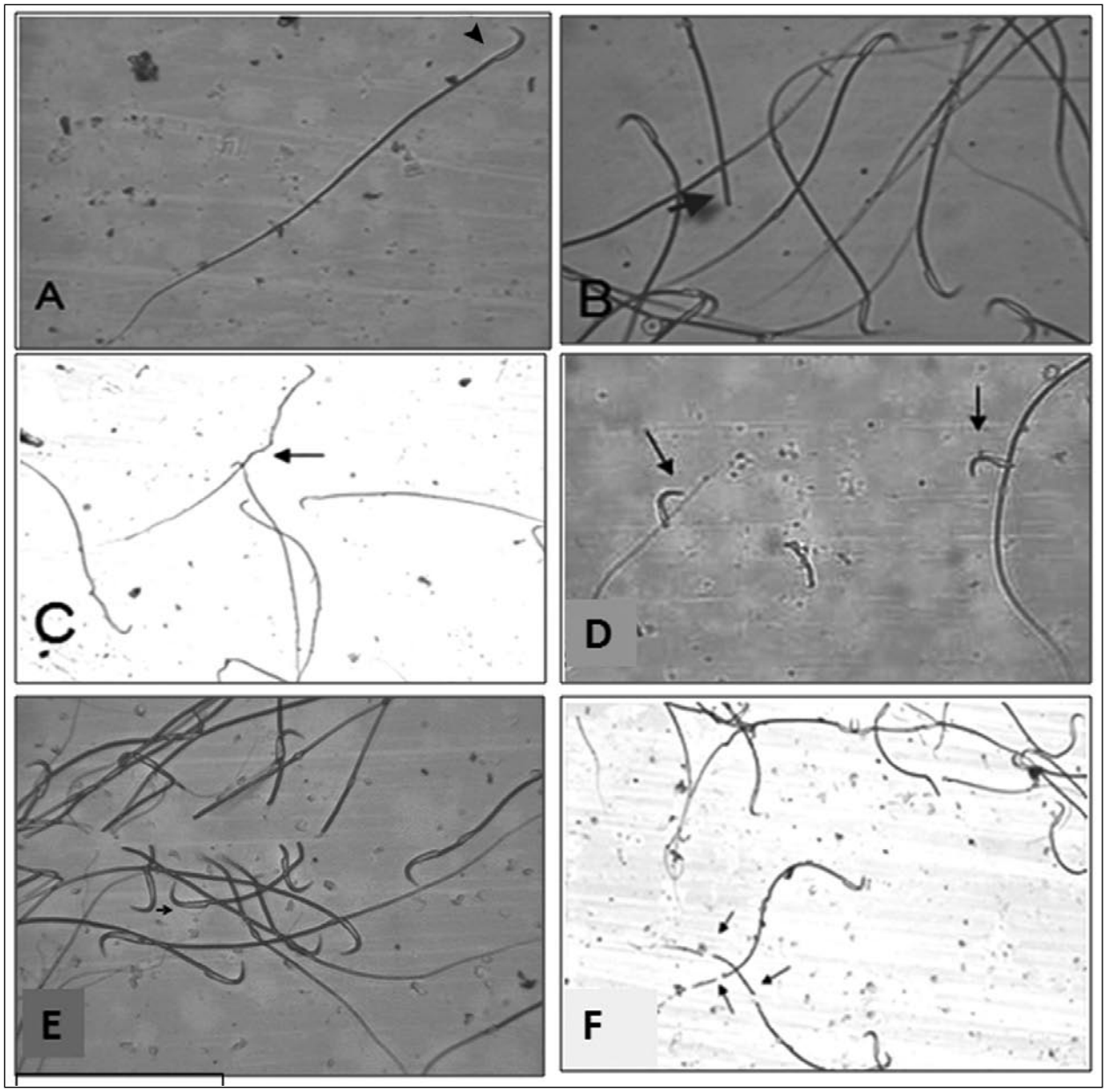

Fig. 5: Shows caudal sperm morphology of (A) control rat with normal head (black head arrow) (B) rat treated with 5 mg/kg AA showing detached tail (black arrow) (C) rat treated with 5 mg/kg AA showing twisted middle piece (black arrow) (x 40). (D) rat treated with 15 mg/kg AA showing cleaved heads(black arrow) (x 100). (E) rat treated with 45 mg/kg AA showing cleaved heads (arrow) (x 40). (F) rat treated with 60 mg/kg AA showing typical tail intersegmentation (small arrows) (x 40). Smears stained with Wright stain.

with 15 mg/kg AA. Moreover, a highly significant increase ($p < 0.01$) in testis / body weight ratio was detected in the two groups treated with 45 and 60 mg/kg of AA (Fig. 3).

Effect of AA on epididymal (cauda) sperm count

AA induced a significant reduction ($p < 0.05$) of sperm count in the group treated with 60 mg/kg AA (Fig. 4). Other groups showed no difference when compared to control group.

Effect of Acrylamide on epididymal (Caudal) sperm morphology

Abnormal sperm shapes have been detected in all used doses of AA. However, marked increase in the number of head / tail-cleaved sperms was noted maximally in those rats treated with 45 and 60 mg/kg AA (Fig. 5). Moreover, an abnormality named tail intersegmentation, that was not detected during previous studies on AA was markedly observed among these groups (Fig. 5F). Tail intersegmentation was also observed to a lesser extent among control rats.

Effect of AA on histological appearance of rat testes and epididymis

At a dose of 5 mg/kg AA, the testes showed disruptions of its appearance. Some germ cells appeared degenerated and many basal vacuolization was

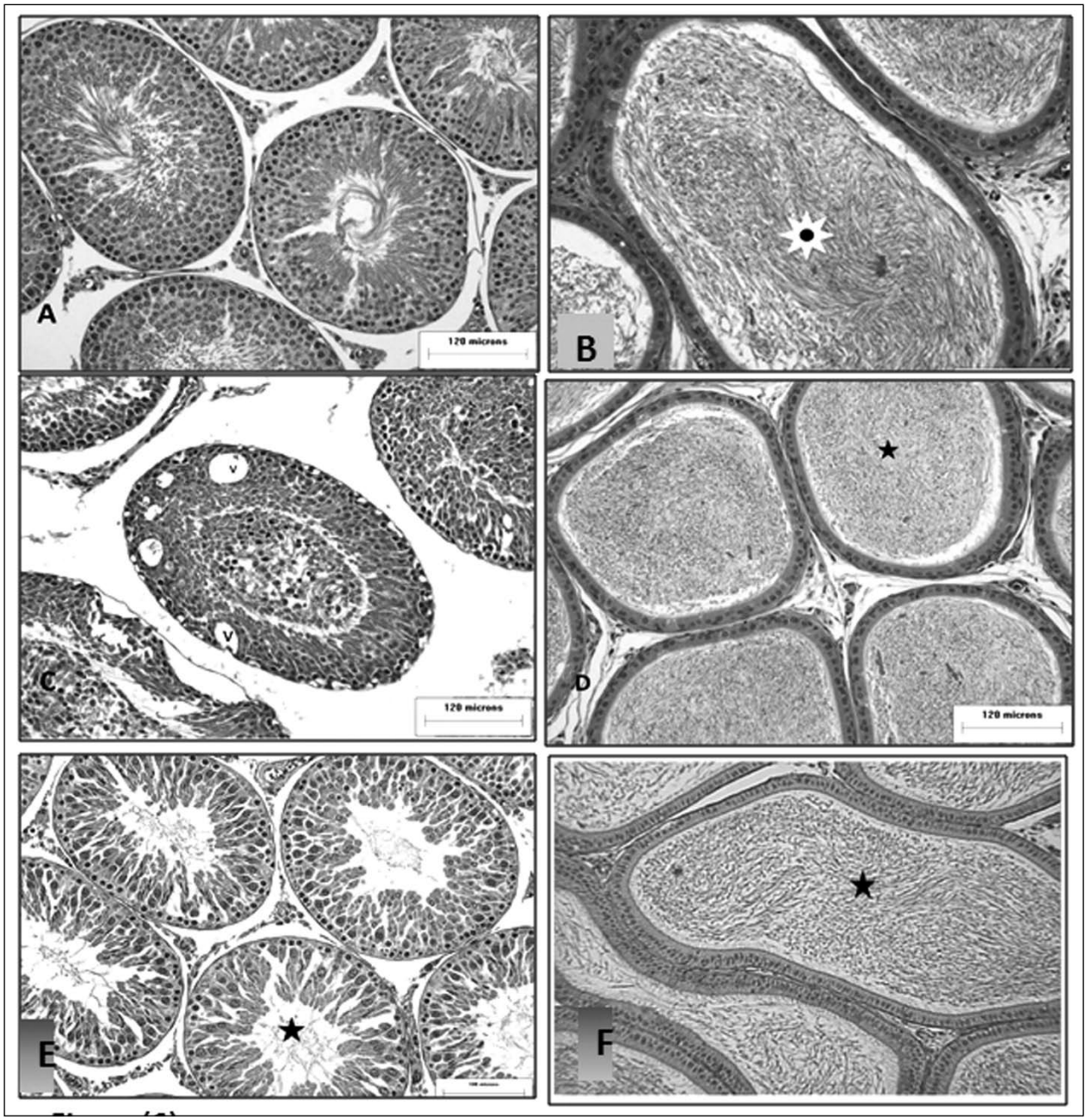

Fig. 6: (A) Control rat testis showing multiple cross sections in seminiferous tubules and normal Leydig cell, (B) control rat epididymis showing apparent sperm reserve in its lumen (★) x 40, (C) Testis of rat treated with 5 mg/kg AA showing multiple vacuoles (v), sloughing of germinal epithelium into lumen x 20, (D) Epididymis of rat treated with 5 mg/kg AA, appears normal x 20, (E) Testis of rat treated with 15 mg/kg AA showing degeneration of spermatogonia, hypospermatogenesis, widening of intercellular spaces and reduction in the mature spermatozoa in the lumen x 20, (F) Epididymis of rat treated with 15 mg/kg AA, showing reduction in sperm reserve (★) x 40. Sections stained with H&E stain.

observed between the inner cells of the seminiferous tubules. However, the epididymis appeared normal (Fig. 6, C and D). At a dose of 15 mg/kg AA, the testes showed increased debris, widening of the intercellular spaces and reduction of the mature spermatozoa in the lumen of the tubule. The epididymis appeared normal with good sperm reserve (Fig. 6, E and F).

At a dose of 45 mg/kg AA, the testes showed sloughed seminiferous epithelium and multinucleated giant (MNG) cells in tubular lumen. Further, Leydig cells appeared atrophied while epididymis was apparently normal (Fig. 7 A, B and C). At the higher dose of AA (60 mg/kg), the histopathological changes observed were similar to those of the lower dose (45 mg/kg) but with a more pronounced degree. The MNG cells increased in number and size and some of them had cytoplasmic vacuolization. They appeared in both ST and epididymis. The mature spermatozoa were significantly reduced in the lumen of the tubules (Fig. 7, D, E and F)

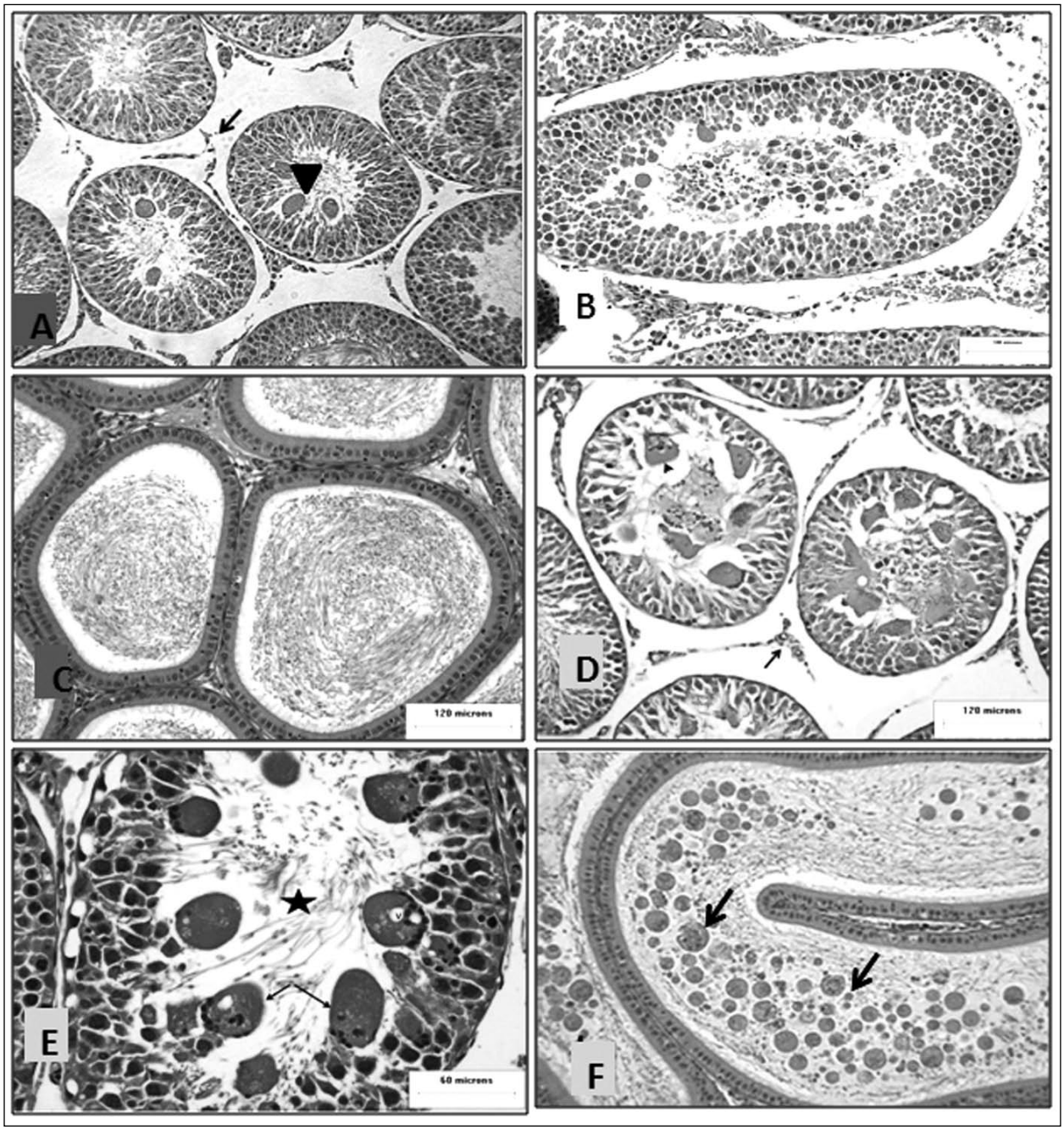

Fig. 7: (A) Testis of rat treated with 45 mg/kg AA showing small multinucleated giant cells (MNG) in their lumen (arrow head) and atrophy of Leydig cells (arrow) x 20, (B) Testis of same group showing shedding of germinal epithelium in the lumen x 40, (C) Epididymis of same group appears normal x 20, (D) Testis of rat treated with 60 mg/kg AA showing multiple (MNG) cells in the lumen (small arrow head), scanty mature spermatozoa and atrophy of Leydig cells (arrow) x 20, (E) Testis of same group showing ST with multiple MNG (small arrow) with vacuolated cytoplasm, degenerated spermatogonia and reduction in mature spermatozoa (star) x 40, (F) Epididymis of same group showing multiple MNG (arrows) of different size in and clear reduction in sperm reserve x 40. Sections stained with H&E stain.

Electron microscopy (EM) on rat testes

The testes of rat treated with 45mg/kg AA showed degeneration of spermatogonia with large basal vacuolization, widening of intercellular junctions and degeneration of peritubular myoid cell (Fig. 8 C). While Sertoli cells of the control testis showed normal histological features (Fig. 8 B), those of the AA treated rat showed numerous histological abnormalities. These abnormalities included darkening of Sertoli cell nucleus, detachment of the cell from the basement membrane and increase in the number and size of lipid droplets in its cytoplasm. Further, failure of sperm release and phagocytosis of some sperms by Sertoli cell were also detected (Fig. 8 D).

The transverse and longitudinal sections in the axoneme of developing spermatids from control rat appeared normal apart from dissolution of one circumferential rib in the principal piece of few spermatids (intersegmentation of fibrous sheath). (Fig. 9 C). As regards the AA treated group, the developing

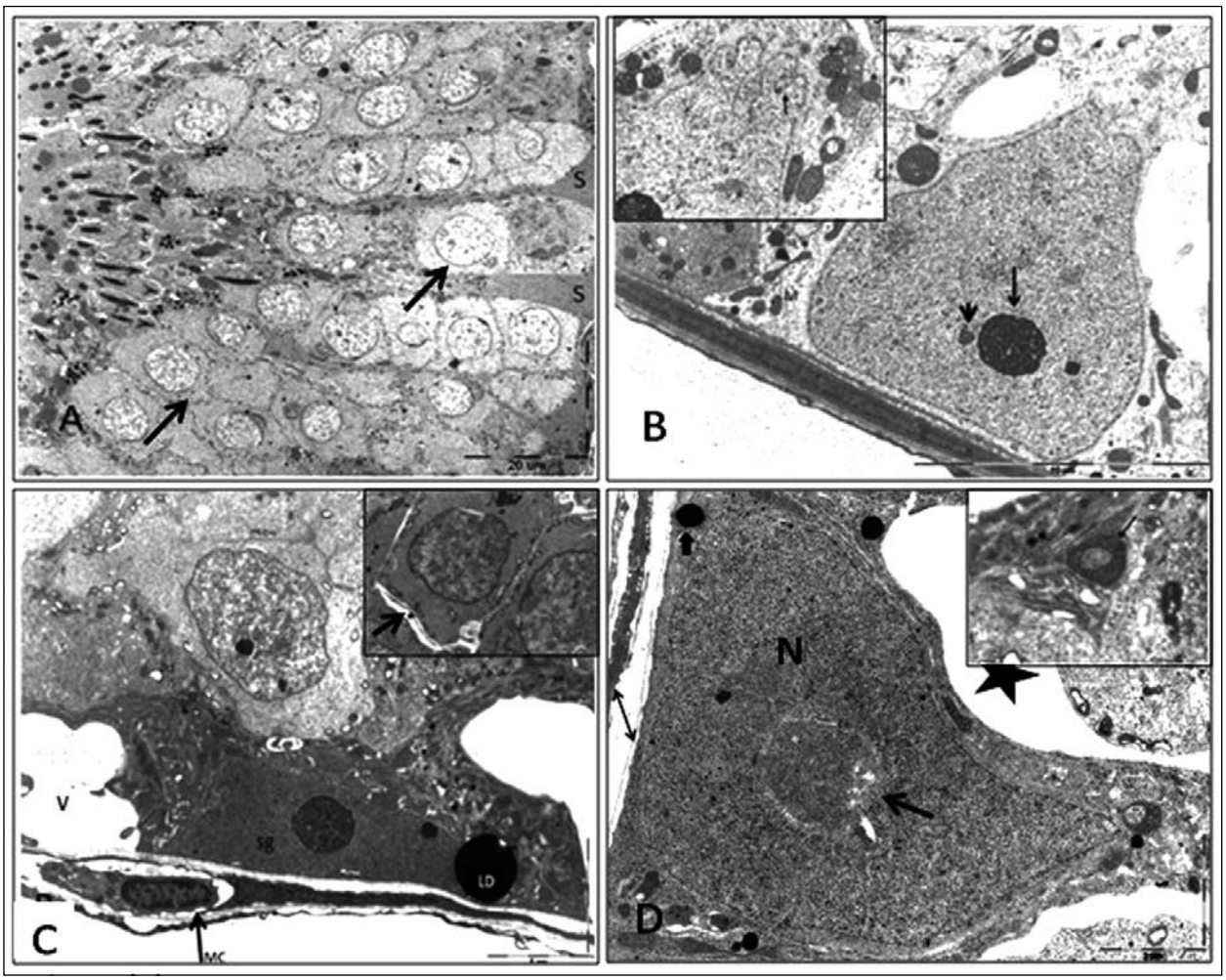

Fig. 8: (A) Part of seminiferous tubule from control rat testis showing many normal spermatogenetic (arrows) and Sertoli cells (S) x 1100, (B) Control rat testis showing Sertoli cell with prominent nucleolus (long arrow) and two characteristic bodies near it (small arrow) x 4600, Insert showing apical cleft of the nucleus (arrow) and mitochondria (M) in the cytoplasm x 10,500, (C) rat testes treated with 45 mg/kg AA showing degenerated spermatogonia (sg) with large lipid droplet (LD),degenerated peritubular myoid cell (MC) and vacuole (V) at the basal part of the tubule x 3400. The insert showing widening of the intercellular junctions (arrow) of the two adjacent germ cells x 5800, (D) rat testes treated with 45 mg/kg AA showing degenerated Sertoli cell nucleus (N) with condensed chromatin and shrunken nucleolus (arrow). Cytoplasmic lipid droplets (small arrow), widening of tight junctions between Sertoli cell and the surrounding spermatocytes (star) were observed. Detachment of Sertoli cell from the basal lamina (double head arrow) was also observed x 7900. The insert showing spermatid (arrow) phagocytozed by the Sertoli cell x 7900. Transmission electron microscope

spermatid showed normal shape, number and arrangements of outer dense fibers (ODF) through the middle and principal piece of its tail. However, partial dissolution of fibrous sheath in the principal piece was frequently observed (Fig. 9 D). Leydig cells showed clear atrophy after AA treatment (Fig. 9 A and B).

DISCUSSION

In this study, testicular toxicity of AA was investigated by examining the influence of this compound on body weight changes, testis and epididymal weight, sperm count and morphology and histopathological changes in rat testis and epididymis. Rats gavaged with AA at doses of 45 or 60 mg/kg/day for five days showed a significant reduction in body weight. A reduction in epididymal sperm count was observed in the group treated with 60 mg/kg AA. Abnormal epididymal sperm morphology and abnormal histopathological findings were noted in the testis of all treated rats. These dose response changes provided the initial characterization of AA induced testicular toxicity in rats.

Gross observational and behavioural changes and neurotoxicity observed on rats treated with AA at doses of 45 and 60 mg/kg were entirely consistent with the previous study conducted by Hashimoto *et al*[8] who treated mice with 0.2 to 0.5 of the LD50 of AA (1.5 mmol/kg equivalent to 106.6 mg/kg) twice weekly by oral gavage for 8-10 weeks. Tyl *et al* and Lopachin[17,18] have also reported this phenomenon in rats. It must be highlighted that no clear mechanism underlying AA neurotoxicity has yet been uncovered, although several possible mechanisms have been suggested. These include inhibition of kinesin-based

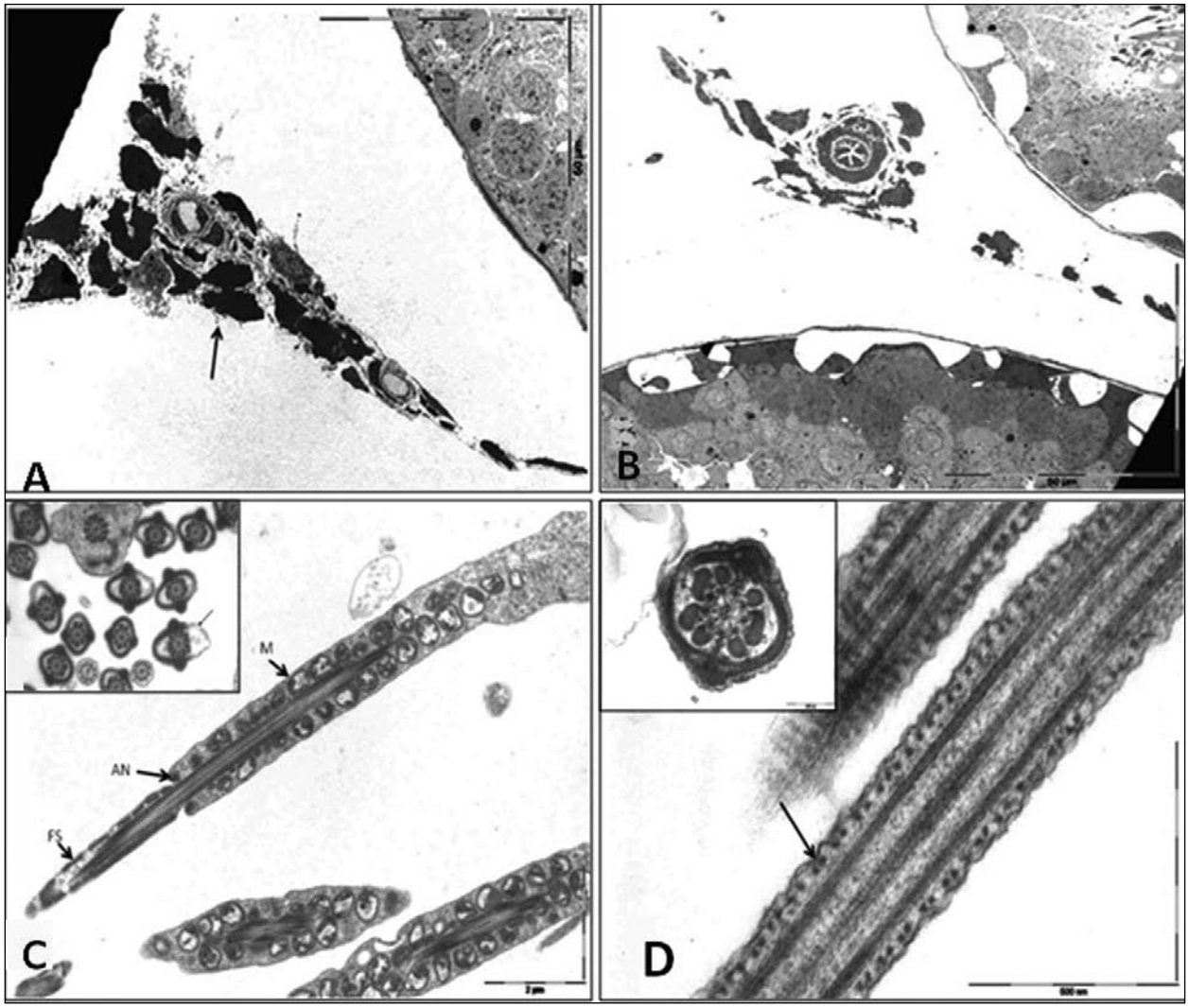

Fig. 9: (A) Leydig cells of the control rat testis appear normal x 620. (B) Leydig cell of 45 mg/kg AA treated rat appear atrophied and few in number x 620, (C) transverse and longitudinal sections in the axoneme of developing spermatids from control rat showing mitochondria (M) surrounding the middle piece of the tail, also the annulus (AN) between middle and principal piece x 7900. The insert showing transverse sections through the principal piece of spermatids. Note complete dissolution (arrow) of one circumferential rib in the principal piece x 34,000. (D) spermatid of rat treated with 45 mg/kg AA showing longitudinal section of the principal piece of a spermatid. Note the fibrous sheath (arrow) x 64,000. The insert showing transverse section of the principal piece of spermatid, with normal shape ODF. Note partial dissolution started to occur above ODF number one x 92,000. Transmission electron microscope

fast axonal transport by AA[19], induction of synaptic dysfunction by AA[20], or a central mechanism operating through inhibition of brain GST and a decrease in brain dopamine receptors[21]. Additionally, it should be noted that hind limb dysfunction is one of the factors that negatively influences or disrupts the copulatory behavior of male rats[14].

Similarly, in a study conducted by Yang *et al*[6], there was a significant reduction in rat body weights at doses of 45 and 60 mg/kg/day compared to the control group, following the oral gavage of AA for five consecutive days. In a study reported by Sakamoto *et al*[24], in which prepubertal and adult male mice received a single oral dose of 100 or 150 mg/kg of AA, the mice showed a significant reduction in body weight for three and five days, respectively, following the treatment. In contrast to the above studies, many other investigators have reported that AA has no influence on the body weight of treated animals[8,22,23]. It is unclear at present why these differences should exist in the influence of AA on body weight. However, it might be a function of the dose or the rat strain used. The interpretation for this body weight loss following AA treatment may be due to loss of appetite by the treated animals, leading to decreased food intake and consequent decline in weight.

In the current study, a significant increase in testis to body weight ratio was detected among groups treated with 15 mg, 45 mg and 60 mg/kg. This result is in agreement with finding of Sakamoto *et al*[24] in adult mice following a single oral dose of AA (150 mg/kg). In that case, the absolute testicular weight was not affected, but the testes to body weight ratio was increased significantly. This was in contrast to several previous

studies that reported a significant decrease in testis weight following AA treatment. These decreases were most likely due to severe atrophy of the testes[6, 8, 25].

The findings of this study as regards the epididymal sperm count and morphology tend to support results reported in a previous study by Yang *et al*[6,7]. The results of the current study were also consistent with the observations made by Sakamoto and Hashimoto[25] conducted on male mice, which showed a significant reduction in sperm count and an increase in abnormal sperm morphology following the administration of the highest dose of AA (1.2 mM) in the drinking water. The results of present study are in agreement with these previous findings of Yang *et al*[7]. Although the percentage of abnormal sperm was not calculated in the current study, it was observed that all of the AA treated groups showed an abnormal sperm morphology, characterized by (i) detached heads, (ii) coiled and fragile tails and (iii) cleaved tails. The most striking AA induced morphological change was the appearance of intersegmented tails, a response to AA that has not been previously reported to the best of our knowledge, and requires further substantiation and investigation.

The histopathological findings of this study were similar to the reports of other investigators[6, 7] in rat studies and[8] in a mouse study. Hashimoto *et al* reported a normal histological appearance of the epididymis (although there was slight reduction in relative weights of the epididymis) following AA treatment of male mice at 1.5 mmol/kg (106.6 mg/kg, twice weekly by oral gavage for 8 - 10 weeks)[8]. An attempt has been made by Rotter *et al*[26] to explain the mechanism underlying the appearance of MNG cells in the lumen of the seminiferous tubules of treated mice. They postulated that primary 4N spermatocytes were unable to undergo meiotic division to generate haploid sperm cells and instead underwent DNA replication only, giving rise to MNG cells.

The consequence of Sertoli cell injury, which has been detected as Sertoli cell vacuolations in this study, is evident in the form of sloughing and shedding of germinal epithelium, leading to the appearance of aggregates of cellular material in the lumen[27]. Most Sertoli cell toxicants alter germ cell attachment to the Sertoli cell, resulting in loss of germ cell attachment to the seminiferous epithelium and hence, the presence of germ cells in the lumen.

The results of the pilot EM study were highly consistent with the detected histopathological changes observed by light microscopy. All changes, including some that had not been detected previously, were consistent with acute cell injury. Excessive lipid droplets in the Sertoli cell cytoplasm are indicative of germ cell degeneration[28].

One of the atypical forms of the principal piece detected in control sperm appeared to be an intersegmented tail when viewed with EM. There was a partial or complete dissolution of the circumferential ribs of the fibrous sheath, which probably, led to the inability of Wright or Rose Bengal stains to colorize the internal structure of the axoneme. This gave the appearance of an intersegmented tail under light microscopy. This abnormality was detected in this study to some extent in control rats; however, its frequency increased with AA treatment. Possibly, the genotoxic effect of AA is exerted mainly on stages of late spermatid and early spermatozoa formation[17] and hence results in abnormal sperm morphology. Several mechanisms of toxicity were proposed and one of these is mediated by an AA metabolite (glycidamide) as it induces significant levels of DNA damage as per Hansen *et al*[29] who have shown that human lymphocytes are more susceptible to glycidamide-induced lesions than mouse cells.

Although the histological examination of testis by light microscopy hinted at Leydig cell toxicity, with the aid of EM, Leydig cell atrophy was clearly detected. Furthermore, the signs of insult to Sertoli cells after AA treatment were signs of Sertoli cell death. This might be due to a direct influence of AA on Sertoli cells or may be due to testosterone reduction resulting from Leydig cell atrophy, or both.

Abnormal spermatogenesis due to a reduction in testosterone hormone resulting from Leydig cell atrophy might be another factor for these abnormal sperms. Another consequence of testosterone reduction would be abnormal Sertoli cells, because testosterone influences the Sertoli cell to undergo normal spermatogenesis[30]. Consequently, this abnormality in Sertoli cell structure and function results in abnormal spermatogenesis, while impairment of intercellular junctions leads to sloughing of germ cells and the formation of large vacuoles that occupy the basal and adluminal compartments. In severe cases, Sertoli cells might be released from epithelium after death, leaving large basal vacuoles.

Regarding the effect of AA on the widening of intercellular spaces, Cheville[31] reported dissociations of desmosomes-like structures (present normally between cells), and of hemidesmosomes (present between the cells and the basement membrane), with subsequent detachment of cells from the basement membrane and widening of intercellular spaces, usually signs of acute cell injury. Widening of spaces surrounding the seminiferous tubules in histological examinations were believed to be due to Leydig cell atrophy, and with the aid of EM, Leydig cell atrophy was clearly detected. This pilot EM study of the AA treated group (45 mg/kg for five days) needs to be replicated and validated with additional studies using larger numbers of exposed and control rats.

ACKNOWLEDGMENT

Conflict of interest:

The authors declare that no conflict of interest exists.

REFERENCES

1. SNAFA. Swedish National Food Administration, 2002. Swedish National Food Administration, 24 April 2002. Information About Acrylamide in Food. Available: http://www.slv.se/engdefault.asp.
2. Blank I. Current status of Acrylamide research in food: Measurement, safety assessment, and formation. Ann N Y Acad Sci 2005; 1043:30-40.
3. Tareke E, Rydberg P, Karlsson P. Analysis of acrylamide, a carcinogen formed in heated food stuffs. J Agric Food Chem 2002; 50:4998-5006.
4. Ohara-Takada A, Matsuura-Endo C, Yoshihiro C, *et al*. Change in content of sugars and free amino acids in potato tubers under short-term storage at low temperature and the effect on Acrylamide level after frying. Biosci Biotechnol Biochem 2005; 69:1232-1238.
5. Dearfield KL, Abernathy CO, Ottley MS, Brantner JH. Acrylamide: its metabolism, development and reproductive effects, genotoxicity and carcinogenicity. Mutat Res 1988; 195:45-77.
6. Yang HJ, Lee SH, Jin Y, Choi JH, Han CH, Lee MH. Genotoxicity and toxicological effects of acrylamide on reproductive system in male rat. J Vet Sci 2005; 6:103-109.
7. Yang HJ, Lee SH, Jin Y, *et al*. Toxicological effects of acrylamide on rat testicular gene expression profile. Reprod Toxicol 2005; 19:527-534.
8. Hashimoto K, Sakamoto J, Tanii H. Neurotoxicity of acrylamide and related compounds and their effects on male gonads in mice. Arch Toxicol 1981; 47:179-189.
9. Sega GA, Valdiviaalcota RP, Tancongco CP, Brimer PA. Acrylamide binding to the DNA and protamine of spermiogenic stages in the mouse and its relationship to genetic damage. Mutat Res 1989; 216:221-230
10. Rice JM. The carcinogenicity of Acrylamide. Mutat Res 2005, 580:3-20.
11. Friedman MA, Dulak LH , Stedham MA. A life time oncogenicity study in rats with acrylamide. Fund Appl Toxicol 1995; 27:95-105.
12. Johnson KA, Gorzinski SJ, Bodner KM. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. Toxicol Appl Pharmcol 1986; 85:154-168.
13. Klaassen CD, Cassarett G and Doull's H. Toxicology, The basic science of poisons. 6th Ed. McGraw Hill Publishing Co. 2001.
14. Zenick H, Hope E, Smith MK. Reproductive toxicity associated with acrylamide treatment in male and female rats. Toxicol Environ Health 1986; 17:457-472.
15. Burek JD, Albee RR, Beyer JE, Bell TJ, Carreon RM, Morden D C. Sub chronic toxicity of acrylamide administration to rats in the drinking water followed by up to 144 days of recovery. Environ Pathol Toxicol 1980; 4:157-182.
16. Mccollister D, Oyen F, Rowe V. Toxicology of acrylamide. Toxicol Appl Pharmcol 1964; 6:172-181.
17. Tyl RW, Marr MC, Myers CB, Ross WP. Relationship between acrylamide reproductive and neurotoxicity in male rats. Reprod Toxicol 2000; 14:147-157.
18. Lopachin RM. The changing view of acrylamide neurotoxicity. Neurotoxicology 2004; 25:617-630.
19. Srivastava SP, Sabri MI, Agrawal AK, Seth PK. Effect of single and repeated doses of acrylamide and bis-acrylamide on glutathione-S-transferase and dopamine receptors in rat brain. Brain Res 1986; 37:319-323.
20. Lopachin RM, Schwarcz AI, Gaughan CL, Mansukhani S, Das S. *In vivo* and *in vitro* effects of acrylamide on synaptosomal neurotransmitter uptake and release. Neurotoxicology 2004; 25:349-363.
21. Lehning EJ, Balaban CD, Ross JF, Lopachin RM. Acrylamide neuropathy. III. Spatiotemporal characteristics of nerve cell damage in forebrain. Neurotoxicology 2003; 24:125-136.
22. Smith MK, Zenick H, Preston RJ, George EL, Long RE. Dominant lethal effects of sub-chronic acrylamide administration in the male Long -Evans rat. Mutat Res 1986; 173:273-277.
23. Lafferty JS, Kamendulis LM, Kaster J, Jiang J, Klaunig JE. Sub chronic acrylamide treatment induces a tissue-specific increase in DNA synthesis in the rat. Toxicol Letters 2004; 154:95-103.
24. Sakamoto J, Kurosaka Y, Hashimoto K. Histological changes of acrylamide-induced testicular lesions in mice. Exp Mol Pathol 1988; 48:324-334.
25. Sakamoto J, Hashimoto K. Reproductive toxicity of acrylamide and related compounds in mice - effects on fertility and sperm morphology. Arch Toxicol 1986; 59:201-205.
26. Rotter V, Schwartz D, Almon E, *et al*. Mice with reduced levels of p53 protein exhibit the testicular giant-cell degenerative syndrome. Proc Natl Acad Sci 1993; 90:9075-9079.
27. Boekelheide K. Sertoli cell toxicants . In: The Sertoli Cell. Russell LD, Griswold MD, editors. Cache River Press, Clearwater, Florida 1993; pp 551-575.
28. Schulze C, Holstein AF. Human Sertoli cells under pathological conditions. In: The Sertoli cell. Russell LD, Griswold MD, editors. USA, Cache River Press, Clear Water 1993, pp 597-610.
29. Hansen SH, Olsen AK, Soderlund EJ, Brumborg G, *et al*. In vitro investigations of glycidamide-induced DNA lesions in mouse male germ cells and in mouse and human lymphocytes. Mutat Res 2010; 696:55-61.
30. Johnson MH, Everitt BJ. Essential reproduction. 5th edition. Blackwell Science; 2000:196-197.
31. Cheville NF. Ultra structural Pathology: An introduction to interpretation. Cheville NF, editor. Iowa State University Press, Ames, IA, 1994, pp. 51-76.

Original Article

Complications of Brucellosis in Adults: An Experience from a State Hospital in Southeastern Anatolia Region of Turkey

Mehmet Ulug, Nuray Can-Ulug
Department of Infectious Diseases and Clinical Microbiology, Özel Ümit Hospital, Eskişehir, Turkey
Department of Neurology, Özel Ümit Hospital, Eskişehir, Turkey

Kuwait Medical Journal 2011; 43 (3): 206-212

ABSTRACT

Objective: To evaluate the complications and systems involvement of acute *Brucella* infection in adults
Design: Retrospective study
Setting: Midyat State Hospital, Mardin, Turkey
Subjects: Seventy-eight patients with acute brucellosis
Interventions: Brucellosis treatment
Main Outcome Measures: The frequency of complications and systems involvements
Methods: This retrospective study was carried out at the Infectious Diseases and Neurology clinics between April 2007 and August 2008. The diagnosis of brucellosis was made with compatible clinical findings, positive Brucella agglutination 1/160 titers, and / or the isolation of *Brucella* species. Complication was defined as the presence of symptoms or physical signs of infection at a particular anatomic site in a patient with active brucellosis.
Results: This study focuses on the frequency of complications in cases with brucellosis. Out of 78 patients, 46 (59%) were female and 32 (41%) were male. The mean age of patients was 36.4 ± 14.2 years. Skeletal complications were the most frequent, found in 26 (33.8%) cases, followed by hematological (n = 25, 32.1%), cutaneous (n = 3, 3.9%), nervous (n = 2, 2.6%), genitourinary (n = 2, 2.6%), respiratory (n = 1, 1.3%) and gastrointestinal system (n = 1, 1.3%).
Conclusion: Brucellosis, whether in an endemic region or not, remains a diagnostic puzzle due to occasional misleading unusual presentations and non-specific symptoms. It is a systemic infection in which any organ or system of the body can be involved. Our data showed that brucellosis is a preventable disease. Knowledge and early diagnoses of the complications are especially important.

KEY WORDS: adult, *Brucella melitensis*, Brucellosis, complication, osteoarticular, Turkey

INTRODUCTION

Brucella species are small, non-motile, non-spore-forming, encapsulated Gram-negative coccobacilli. There are seven species, of which only four can cause human brucellosis: *Brucella aboruts*, *Brucella melitensis*, *Brucella suis*, and *Brucella canis*[1,2]. Brucellosis is a systemic infectious disease and it is still an important public health problem throughout the world, but especially in the Mediterranean region, including Turkey[3,4]. Disease incidence and prevalence rates vary widely among nations. Due to variable reporting, true estimates in endemic areas are unknown. According to reports from the Turkish Ministry of Health, 37 cases were reported in 1970, with numbers rising to 18,408 cases in 2004 (incidence rate 25.67/100,000). It is frequent especially in the rural areas of the middle and southeastern regions, and *B. melitensis* is the most prevalent strain[5,6]. It is thought that this increase is a result of improvements in diagnosis and increased reporting, rather than a real increase in the prevalence of the disease.

Humans are infected by direct contact with infected animals or their products or, indirectly, by ingesting infected milk or dairy products[1]. Following infection, the bacteria initially localize in the regional lymph nodes, and then disseminate hematogeneously to the organs of the reticuloendothelial system to multiply within phagocytic cells. The release of bacterial endotoxin from phagocytic cells produces the constitutional symptoms and signs of the disease[7].

Brucellosis can be an acute or chronic febrile illness and presents with a variety of manifestations after an incubation period, which can vary from one to six weeks or several months[8]. The most frequent symptoms are fever, chills or rigors, malaise, generalized ache, headache and fatigue. Gastrointestinal, skeletal,

Address correspondence to:
Dr. Mehmet Uluğ, Department of Infectious Diseases and Clinical Microbiology, Özel Ümit Hospital, Eskişehir, Turkey. Tel: (0532) 4475756, Fax: 0222 3350170 (Hospital), E-mail: mehmetulug21@yahoo.com

cardiovascular, genitourinary and hematological manifestations are well-known. Neurobrucellosis, peritonitis, pericarditis, pancytopenia are unusual manifestations of brucellosis[6]. If the disease is not well recognized and not included in the differential diagnosis, a treatable disease will be missed[3]. In this study, all patients were investigated in more detail with respect to complications in adult cases in southeastern Anatolia region of Turkey.

SUBJECTS AND METHODS

This study was retrospectively carried out at Midyat State Hospital, Departments of Infectious Disease and Neurology, between April 2007 and August 2008. For its size, Midyat, a small and mostly rural county of approximately 75,000 inhabitants, had an unusually high annual incidence of brucellosis due to poor preventive measures and inadequate public health policies.

Brucellosis was diagnosed according to the case definition and treatment guidelines of the Turkish Ministry of Health[9]; isolation of microorganisms in blood, other body fluids or tissue samples, or the presence of compatible clinical symptoms such as arthralgia, fever, sweating, chills, headache, myalgia and malaise combined with a serum antibody titer 1/160 or at least a fourfold increase in this titer by the standard tube agglutination (STA) test in a two or three weeks interval. *B. abortus* S99 antigens (Seromed Laboratory Products, Turkey) were used for the STA. The BACTEC 9240 system (Becton-Dickinson, Maryland, USA) for initial blood and other body fluids cultures with subculturing onto chocolate blood agar at 37 ºC in CO_2 was used. All of the cultures were done in Biosafety Class II cabinets. Smears from colonies that grew were stained with Gram stain. The isolates of Gram-negative cocco-bacilli were identified with use of conventional biochemical tests (*e.g.*, motility; oxidase, catalase and urease tests; effect to glucose and production of H_2S), and Sceptor system (Becton-Dickinson, Maryland, USA). Patients who were known to have any chronic or acute systemic disease other than brucellosis, or were younger than 15 years of age were excluded from the study.

Focal form or complication was defined as the presence of symptoms or physical signs of infection at a particular anatomic site in a patient with active brucellosis. Osteoarticular involvement was diagnosed in instances of tenderness, restriction of movement and swelling in any peripheral joint, or by unrelieved pain at rest together with radiological alterations. However, swelling was not essential for the diagnosis of hip, spine or sacroiliac arthritis. Diagnoses of spondylitis and sacroiliitis were confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI). Neurobrucellosis was defined as: isolation of *Brucella* spp. from cerebrospinal fluid (CSF) of patients with suspected findings for brucellosis or isolation of *Brucella* spp. from bone marrow or blood cultures of patients with abnormal CSF findings with or without STA positivity of any titer in CSF with abnormal findings. Hematologic involvement was defined as hematologic abnormalities in laboratory and clinical findings (epistaxis, bleeding, petechiae, purpura, disseminated intravascular coagulation, and thrombophlebitis), excluding asymptomatic or poorly symptomatic cytopenias or coagulation disturbances. Anemia, thrombocytopenia and leucopenia were defined as hemoglobin level < 120 g/dl in females, < 135 g/dl in males, a platelet count of < 142,000/mm^3 and leukocyte count of < 4600/mm^3, respectively. Hepatic complications were defined as the presence of a five-fold or greater rise in normal levels of aspartate aminotransferase or alanine aminotransferase, or jaundice.

In addition, completed history and physical examination of all patients were reviewed: tests for complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor and blood chemistry profile were performed in all patients. In suspected cases the following tests were performed: lumbar puncture, CT and / or MRI for meningitis, routine chest X-ray and thorax CT for pneumonia, scrotal doopler ultrasonography (USG) for epididymo-orchitis and abdominal USG for hepatitis.

Patients were treated with various combinations of antibiotics. The regimens included the following: oral doxycycline (100 mg every 12 h), oral rifampin (300 or 600 mg every 24 h), intramuscular streptomycin (1 g every 24 h), and co-trimoxazole (80/400 or 160/800 every 12 h). The choice depended on several conditions: clinical presentation, pregnancy, drug side effects, tolerability and co-morbidity; in addition, in regions with scarce resources, therapeutic decisions are also determined by treatment costs and drug availability. In neurobrucellosis, pregnant women and patients with relapses and drug side effects intravenous ceftriaxone (2 g per day) was added to the regimen initially for two to four weeks and other antimicrobials were given for at least six weeks. When required, the duration of therapy was extended.

Patients were followed up fortnightly until the end of the treatment period, monthly for three months, and thereafter every three months for one year. Relapse was assessed by a recurrence of symptoms and signs of the disease, a positive blood culture or rising antibody titer after treatment, in the absence of re-exposure to infection.

RESULTS

In this study, 78 patients (46 female and 32 male) with brucellosis were analyzed. The female / male

Table 1: Clinical characteristics in 78 patients with brucellosis

Symptoms	n (%)	Signs	n (%)
Fever	74 (95)	Fever	64 (82)
Malaise/ Weakness	72 (92)	Hepatomegaly	22 (28)
Arthralgia	70 (90)	Splenomegaly	18 (23)
Myalgia	64 (82)	Lymphadenopathy	5 (6.5)
Sweating	61 (78)	Rash	3 (3.9)
Lack of appetite	58 (74)		
Lumbar pain	54 (69)		
Chills	46 (59)		
Headache	44 (56)		
Vomiting	19 (24)		

ratio was 1.43, and the mean age was 36.4 ± 14.2 years (range: 17-73). Signs and symptoms of brucellosis in this series reflected a combination of systemic illness with certain manifestations. Table 1 lists the main symptoms and signs noted on presentation. The severity of symptoms varied from mild illness to severe painful localized disease. Fever, malaise, arthralgia, myalgia and sweating were the main presenting symptoms overall. The most common abnormalities on physical examination were fever, hepatomegaly and splenomegaly.

The most common laboratory findings were high CRP levels (88%), high ESR (56%), and anemia (21.8%). While 63 patients (80%) had normal leukocyte counts, leucopenia was found in 11 cases (14%) and leukocytosis in four cases (5.2%). Thrombocytopenia was seen in six patients (7.8%). The STA test was positive in all patients, with titers ranging from 1/160 to 1/1280. *Brucella* growth was achieved in eight of 78 patients from whom appropriate cultures were taken. Of these, six (7.8%) were from blood, one (1.3%) from bone marrow and one (1.3%) from synovial fluid. All microorganisms isolated were *B. melitensis*. The rest of the laboratory results are shown in Table 2.

Osteoarticular complications were the most frequent focal forms, being present in 26 cases, representing 33.8% of all patients. Out of 78 patients, 70 had arthralgia in joints other than the joints affected

Table 2: Laboratory findings in our study

Variables	n (%)
WBCc /mm^3	
< 4600	11 (14.1)
4600 – 10200	63(80.7)
> 10200	4 (5.2)
Hemoglobin	
Female < 120 gram/dl	28 (36.4)
Male < 135 gram/dl	6 (7.8)
Platelet < 142,000 mm^3	26 (33.8)
ALT > 35 IU/l	28 (36)
AST > 40 IU/l	32 (41)
GGT > 50 IU/l	10 (13)
ALP > 128 IU/l	17 (22)
Total bilirubin > 1.2 mg/dl	14 (18)
ESR > 20 mm/h	44 (56)
CRP > 8 mg/dl	69 (88)
Positive RF	1 (1.3)

WBCc: White blood cell count, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, GGT: γ-glutamyl transpeptidase, ALP: Alkaline phosphatase, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, RF: Rheumatoid factor

Table 3: The complications, STA titers and culture results of patients

Complications	n (%)	STA titers				Culture	
		1/160 n (%)	1/320 n (%)	1/640 n (%)	1/1280 n (%)	Blood n (%)	Others n (%)
Skeletal system							
Sacroiliitis	11 (14.3)	2 (2.6)	6 (7.8)	2 (2.6)	1 (1.3)	3 (3.9)	-
Peripheral monoarthritis	7 (9.1)	1 (1.3)	3 (3.9)	2 (2.6)	1 (1.3)	-	1 (1.3)
Spondylitis	6 (7.8)	-	4 (5.2)	2 (2.6)	-	-	-
Peripheral polyarthritis	2 (2.6)	-	1 (1.3)	-	1 (1.3)	1 (1.3)	-
Hematologic system							
Anemia	34 (44.2)	9 (11.7)	18 (23.4)	4 (5.2)	3 (3.9)	5 (6.5)	2 (2.6)
Thrombocytopenia	26 (33.8)	3 (3.9)	20 (26)	2 (2.6)	1 (1.3)	2 (2.6)	1 (1.3)
Pancytopenia	2 (2.6)	-	-	-	2 (2.6)	1 (1.3)	1 (1.3)
Cutaneous system							
Rash	3 (3.9)	1 (1.3)	1 (1.3)	1 (1.3)	-	-	-
Genitourinary system							
Epididymo-orchitis	1 (1.3)	-	-	1 (1.3)	-	-	-
Abortion	1 (1.3)	-	1 (1.3)	-	-	-	-
Nervous system							
Meningitis	1 (1.3)	-	-	-	1 (1.3)	1 (1.3)	1 (1.3)
Depression	1 (1.3)	1 (1.3)	-	-	-	-	-
Gastrointestinal system							
Hepatitis	1 (1.3)	-	1 (1.3)	-	-	-	-
Respiratory system							
Pneumonia	1 (1.3)	-	1 (1.3)	-	-	-	-
More than one complication	16 (20.5)	1 (1.3)	8 (10.4)	4 (5.2)	3 (3.9)	6 (7.8)	2 (2.6)

STA: Serum tube agglutination test, *Cerebrospinal and synovial fluid

Table 4: Treatment and outcome of patients with complications

Complications	n	Treatment						Outcome		
		Dox + Rif n (%)	Dox + S n (%)	Dox + Rif + S n (%)	Dox + Rif + CRO n (%)	CRO + TMP - SXT n (%)	Dox + CRO + TMP - SXT* n (%)	Recovery n (%)	Relapse n (%)	DSE n (%)
Skeletal system										
Sacroiliitis	11	-	11 (14.3)	-	-	-	2 (2.6)	10 (13)	1 (1.3)	-
Peripheral monoarthritis	7	6 (7.8)	-	-	1 (1.3)	-	3 (3.9)	6 (7.8)	1 (1.3)	2 (2.6)
Spondylitis	6	-	-	6 (7.8)	-	-	2 (2.6)	6 (7.8)	-	3 (3.9)
Peripheral polyarthritis	2	2 (2.6)	-	-	-	-	1 (1.3)	1 (1.3)	1 (1.3)	-
Hematologic system										
Anemia	34	11 (14.3)	18 (23.4)	3 (3.9)	1 (1.3)	1 (1.3)	7 (9.1)	14 (18.2)	3 (3.9)	6 (7.8)
Thrombocytopenia	26	20 (26)	5 (6.5)	-	1 (1.3)	-	1 (1.3)	5 (6.5)	1 (1.3)	1 (1.3)
Pancytopenia	2	-	1 (1.3)	1 (1.3)	-	-	-	2 (2.6)	-	-
Cutaneous system										
Rash	3	1 (1.3)	1 (1.3)	1 (1.3)	-	-	2 (2.6)	2 (2.6)	1 (1.3)	3 (3.9)
Genitourinary system										
Epididymo-orchitis	1	-	1 (1.3)	-	-	-	-	1 (1.3)	-	-
Abortion	1	-	-	-	-	1 (1.3)	-	1 (1.3)	-	-
Nervous system										
Meningitis	1	-	-	-	1 (1.3)	-	-	1 (1.3)	-	-
Depression	1	-	1 (1.3)	-	-	-	1 (1.3)	1 (1.3)	-	1 (1.3)
Gastrointestinal system										
Hepatitis	1	-	1 (1.3)	-	-	-	-	1 (1.3)	-	-
Respiratory system										
Pneumonia	1	-	-	-	1 (1.3)	-	-	1 (1.3)	-	-

(Dox = Doxycycline, Rif = Rifampin, S = Streptomycin, CRO = Ceftriaxone, TMP-SXT = Co-trimoxazole, DSE = Drug side-effects)

* This regimen was only used for patients with relapse and drug side-effects

by arthritis. The arhralgia manifested as intermittent or migratory pain of large or small joints, or both, with or without limitation of movements. The most commonly affected joint was the sacroiliac joint (11 patients, 14.3%), with predominantly unilateral involvement. The second most affected joint type in patients with musculoskeletal involvement were peripheral joints (11.7%), with the hip (n = 4, 5.2%) and knee (n = 2, 2.6%) being the most commonly affected.

Hematologic complications were most common, followed by cutaneous, genitourinary and the nervous system. Gastrointestinal and respiratory complications were rare and no case of cardiovascular complication was seen (Table 3).

Various initial regimens were administered to the 78 patients with brucellosis. All the patients were followed up for one year. Ceftriaxone and co-trimoxazole were added to the regimen of patients diagnosed with neurobrucellosis or pregnancy. Patients having no nervous system involvement were given various regimens (Table 4). The treatment duration was 6 - 12 weeks in osteoarticular involvement, 12 - 24 weeks in neurobrucellosis, and 6 - 12 weeks for the other clinical forms. Treatment failed in nine patients (11.7%); owing to true relapse in three and to non-compliance and drug side-effects in the other six. These nine patients recovered after a new regimen (doxycycline plus co-trimoxazole plus ceftriaxone) was used. No mortality was registered in our patients. Seventy-six patients received medical treatment alone and two (spondylitis) required medical and surgical treatment as well.

DISCUSSION

Brucella is one of the world's main zoonotic pathogens, and is responsible for enormous economic losses, as well as considerable human morbidity in endemic areas[10]. *B. melitensis* is the most common and virulent cause of the disease worldwide[11].

As the symptoms of brucellosis are not specific, confirmation can be reached by serological tests, with significantly raised or rising titer, in the presence or absence of blood culture. However, antibody detection is not always sufficient to indicate the existence of active infection, especially in endemic areas[12]. Therefore, diagnosis of brucellosis should be performed according to international or national case definitions. In this study, our national case definition for the diagnosis of brucellosis was applied.

Brucellosis can occur at any age but is most common in adolescents and young adults[3,6]. In this study, the mean age of patients was 36.4 ± 14.2 years. According to the results of several studies, brucellosis affected males and females equally[1, 3] or affected more males than females[13]. But the results of our study show that more females were affected than males. Women mostly carry out the livestock maintenance and processing of milk and its products in Midyat. This is, most probably, the reason why most of our patients were women.

The clinical manifestation of brucellosis is very great, ranging from asymptomatic infection to serious debilitating disease. Organ involvement can be assigned as focal involvement or as a complication. For the most part, brucellosis is a systemic infection that can involve any organ of the body[1]. The most common systems affected are the locomotor, gastrointestinal, genitourinary, hematologic, cardiovascular, respiratory, and central nervous systems[5,6]. Symptoms are non-specific and may include fever, arthralgia, myalgia, chills, sweats, headache, and fatigue[14]. However, routine laboratory data reported in most studies have been of little diagnostic value[3,12].

Complications of brucellosis are a major medical problem in countries where brucellosis is still endemic, as in our region of southeastern Anatolia in Turkey. Osteoarticular involvement with a prevalence varying from 5.2 to 69% is the most common frequent complication of brucellosis[3,4,10,11,15-18]. The enormous range between reports in the literature may be due to characteristics of the study populations, the radio-diagnostic methods used, and the different diagnostic criteria employed. Brucellosis may also affect the musculoskeletal system at any site[4,14]. We observed osteoarticular involvement in 33.8% of 78 patients. As can be seen in Table 3, we found that the most commonly affected site was the sacroiliac joint, a finding in agreement with those recently reported by some authors[10, 11,18,19]. In this study, unilateral sacroiliitis (n = 8, 72%) was very common and it is similar to that reported by Geyik *et al*[14] and Calmenero *et al*[20]. However, Tasova *et al*[21] found a high rate of bilateral sacroiliitis (60%). Peripheral arthritis, especially presenting as monoarthritis, is the predominant involvement in some brucellosis series, and large joints such as the hips, knees and ankles are the most frequently affected[3,19,20]. In this study, peripheral arthritis was the second most frequent type of osteoarticular involvement, although the rate (34.6%) was higher than the Calmenero *et al* study(12%)[20]. On the other hand, the incidence of spondylitis reported in the literature varies significantly, ranging from 6% to greater than 50%[3,20,21]. In the present study, the rate of spondylitis was 7.8%.

Hematological alterations in brucellosis are common, but they rarely constitute a true complication and resolve promptly with treatment[3]. The hematological manifestations of brucellosis include anemia, leucopenia, thrombocytopenia and clotting disorders[8]. Anemia in patients with brucellosis results from alteration in iron metabolism secondary to infection, hypersplenism, bleeding, and bone marrow suppression or autoimmune hemolysis[22]. The incidence of anemia has been reported as 44 to 74% in adult series in brucellosis[8,23]. This ratio was 55%, 56% and 54.6% cases in studies by Akdeniz *et al*[24], Dilek *et al*[8] and Aygen *et al*[23] respectively. In our group, incidence of anemia was 44.2% and it is similar to the other studies. Earlier literature has emphasized the characteristic picture of a normal or reduced leukocyte count with relative or absolute lymphocytosis in patients with brucellosis[8, 22]. Leukopenia has been found to occur in 30 - 68% of the reported cases[22]. In this study, 80% of the patients had a normal leukocyte count and 14.3% has leucopenia. Leucopenia was detected 7.7%, 16% and 52% cases in the Aygen *et al*[23], Gur *et al*[3] and Dilek *et al*[8] studies, respectively. The cause of leucopenia seems to be multifactorial. Thrombocytopenia is less common, having been reported in only 1 - 8% of cases, and it is rarely severe enough to cause bleeding[18]. Although the mechanism of the thrombocytopenia in brucellosis is not yet entirely known, it may be hypersplenism, bone marrow suppression due to septicemia, hemophagocytosis, granulomas and peripheral immune destruction of thrombocytes[8]. Thrombocytopenia was detected in 33.8% of patients in this study and it is higher than reported by Akdeniz *et al*[24] (26%) and Dilek *et al*[8] (14%). Pancytopenia has been described as between 3 - 21% in patients with brucellosis in the published series[8,22]. In this study, the incidence of pancytopenia was 2.6% and it is similar to that reported by Ertek *et al*[18] and Gur *et al*[3]. On the other hand, Sarı *et al*[25] reported the rate as 14.9%.

In the present study, cutaneous complications were the third most frequent (3.9%). Cutaneous lesions occur in approximately 1 - 17% of patients with brucellosis[3,4,10,11,15-18]. Patients exhibit non-specific skin symptoms, such as erythema, papules, petechiae, urticaria, impetigo, eczematous rash, erythema nodosum, subcutaneous abscess, and cutaneous vasculitis[5]. Cutaneous findings in this study were similar to other reported studies[18,26,27]. It is important to emphasize that cutaneous lesions are not specific to brucellosis and may be seen in a variety of other dermatologic diseases caused by many agents.

Genitourinary involvement occurs in 2 - 40% of patients with brucellosis[3]. In this study, 2.6% (n = 2, epididymo-orchitis and abortion) out of 78 patients had genitourinary complications. In men, various genitourinary infections including epididymo-orchitis, prostatitis, cystitis, pyelonephritis, interstitial nephritis, exudative glomerulonephritis, renal and testicular abscess, and seminal vasculitis have been attributed to brucellosis[6]. The most frequent genitourinary complication of brucellosis is epididymo-orchitis, affecting 2 - 20% of males with brucellosis[6, 28]. Although the prognosis of brucellar epididymo-orchitis, as in our patient, is usually good, delay in diagnosis or inappropriate management may result in serious complication, such as testicular abscess, which may require orchiectomy[29]. It is well known that the effect of Brucella infection on pregnancy is no

more than those of other bacterial infections[19]. While abortion was seen in 5% (n = 8) of our patients, a lower rate was reported by Memish *et al*[7], Bukharie *et al*[10] and Kochar *et al*[16] studies. However, Kahn *et al*[30] reported that the incidence of spontaneous abortion in the first and second trimesters was 43%, and that of intrauterine fetal death in the third trimester was 2%, but this result needs to be evaluated with a prospective and controlled clinical study.

Nervous system complications include meningitis, encephalitis, myelitis, radiculoneuritis, brain abscess, epidural abscess, demyelination syndromes and meningovascular syndromes[31]. These may occur at any stage of the disease[19]. The reported incidence of neurological complications ranges from zero to19.4%[3,4,10,11,15-18]. In the present study, the incidence was 1.3%, after a case with depression was excluded. Meningitis is the most frequent neurological complication, and it can be the presenting finding or it can occur late in the course of the disease[4]. A high cure rate can be achieved by treatment with triple combination in these diseases (tubercular meningitis, viral encephalitis, aseptic meningitis), which may otherwise have a high mortality and morbidity[3]. The prognosis of meningitis, as in our patient, is usually good. The most common disturbance in patients with brucellosis is depression. Although depression and mental inattention are common complaints in brucellosis, direct invasion of the central nervous system occurs in less than 5% of cases[3]. In the present study, the frequency of depression was low (1.3%). On the other hand, the frequency was 37.8% in the study by Savas *et al*[1].

Gastrointestinal symptoms, including anorexia, nausea, vomiting, diarrhea, abdominal pain, and gastrointestinal bleeding were reported[23]. Liver and spleen enlargement with mild non-specific elevation of liver enzyme levels can be detected in approximately 50% of all patients with brucellosis[32]. On the other hand, all cases with elevated liver enzymes should not be evaluated as liver involvement. Hepatic involvement has been reported in the literature at around 2 - 3%[3,5,18]. While hepatitis is common, it is usually subclinical, and jaundice is rare[10]. Lulu *et al*[33] reported 40% hepatic involvement in their study, namely 1% clinical hepatitis and 38.5% anicteric hepatitis. In our study, liver enzyme elevation was observed in 28 - 32% of cases and a diagnosis of clinical hepatitis was made in only 1.3% cases. *Brucella* is also a rare cause of liver abscess, acute cholecystitis, pancreatitis and spontaneous peritonitis[31].

Respiratory involvement in brucellosis may occur following inhalation of infectious aerosols, and possibly *via* bacteremic spread of the organisms to the lungs[34]. A variety of pulmonary manifestations have been documented in the literature, including bronchopneumonia, lung abscess, empyema, pleural effusion, granulomas, solitary nodules, hilar and paratracheal lymphadenopathy[35]. Pulmonary involvement was detected in < 1 - 5% cases[34] and pneumonia may sometimes be the sole presentation of brucellosis[35]. There was a patient with pneumonia in this study group, who was cured by standard antibiotic therapy.

In brucellosis, the aim of the treatment regimen is to control the acute illness and to prevent both complications and relapses[14]. The successful treatment of brucellosis requires prolonged chemotherapy regimen with a combination of antibiotics[3]. Despite treatment including several antibiotic regimens, relapse is estimated to occur in 5 - 40% of patients with acute brucellosis in the following year, depending on antibiotic use, duration of treatment, and drug combination[5]. In this study, the patients were given various regimens. The treatment duration was based on organ involvement, CRP and ESR normalization. We did not treat with a single agent and thus our relapse rate was low (3.9%) during the one-year follow-up.

CONCLUSION

Brucellosis will continue to be a public health problem in countries where consumption of raw milk and / or its products and stockbreeding are widespread. The most frequent complication of brucellosis is osteoarticular, followed by hematological, cutaneous, genitourinary, nervous and other system complications. Since brucellosis is a preventable disease, knowledge and early diagnosis of the complications are especially important. Consequently, primary health care physicians in endemic regions must recognize that brucellosis is an infection which may involve almost any organ system and which may vary markedly in its clinical presentation.

REFERENCES

1. Savas L, Onlen Y, Savas N, Yapar AF, Aydın M, Tugal O. Prospective evaluation of 140 patients with brucellosis in the southern region of Turkey. Infect Dis Clin Pract 2007; 15:83-88.
2. Mantur BG, Amarnath SK. Brucellosis in India-a review. J Biosci 2008; 33:539-547.
3. Gur A, Geyik MF, Dikici B, *et al*. Complications of brucellosis in different age groups: a study of 283 cases in southeastern Anatolia of Turkey. Yonsei Med J 2003; 44:33-44.
4. Kokoglu OF, Hosoglu S, Geyik MF, *et al*. Clinical and laboratory features of brucellosis in two university hospital in southeast Turkey. Trop Doct 2006; 36:49-51.
5. Buzgan T, Karahocagil MK, Irmak H, *et al*. Clinical manifestations and complications in 1028 cases of brucellosis: a retrospective evaluation and review of the literature. Int J Infect Dis 2010; 14:e469-478.

6. Celen MK, Ulug M, Ayaz C, Geyik MF, Hosoglu S. Brucellar epididymo-orchitis in southeastern part of Turkey: an 8 year experience. Braz J Infect Dis 2010; 14:109-115.
7. Memish Z, Mah MW, Al Mahmoud S, Al Shaalan M, Khan MY. Brucella bacteraemia: Clinical and laboratory observations in 160 patients. J Infect 2000; 40:59-63.
8. Dilek I, Durmus A, Karahocagil MK, *et al*. Hematological complications in 787 cases of acute brucellosis in eastern Turkey. Turk J Med Sci 2008; 38:421-424.
9. Case definition and treatment guideline. Turkish Republic Ministry of Health. Ankara: Gökçe Ofset; 2003, p. 177.
10. Bukharie HA. Clinical features, complications and treatment outcome of *Brucella* infection: Ten years' experience in an endemic area. Trop J Pharm Res 2009; 8:303-310.
11. Andriopoulos P, Tsironi M, Deftereos S, Aessopos A, Assimakopoulos G. Acute brucellosis: presentation, diagnosis,and treatment of 144 cases. Int J Infect Dis 2007; 11:52-57.
12. Hizel K, Guzel O, Dizbay M, *et al*. Age and duration of disease as factors affecting clinical findings and sacroiliitis in brucellosis. Infection 2007; 35:434-437.
13. Gonzalez-Gay MA, Garcia-Porrua C, Ibanez D, Garcia-Pais MJ. Osteoarticular complications of brucellosis in an Atlantic area of Spain. J Rheumatol 1999; 26:141-145.
14. Geyik MF, Gur A, Nas K, *et al*. Musculoskeletal involvement of brucellosis in different age groups: a study of 195 cases. Swiss Med Wkly 2002; 132:98-105.
15. Mantur BG, Biradar MS, Bidri RC, *et al*. Protean clinical manifestations and diagnostic challenges of human brucellosis in adults: 16 years' experience in an endemic area. J Med Microbiol 2006; 55:897-903.
16. Kochar DK, Gupta BK, Gupta A, Kalla A, Nayak KC, Purohit SK. Hospital-based case series of 175 cases of serologically confirmed brucellosis in Bikaner. J Assoc Physicians India 2007; 55:271-275.
17. Shehata A, Adib SM, Al-Anzi AA. Risk factors and clinical presentation of brucellosis in Al Jahra Hospital (1997-1999). Kuwait Med J 2001; 33:44-47.
18. Ertek M, Yazgi H, Kadanali A, Ozden K, Tasyaran MA. Complications of Brucella infection among adults: An 18 year retrospective evaluation. Turk J Med Sci 2006; 36:377-381.
19. Doganay M, Aygen B. Human brucellosis: an overview. Int J Infect Dis 2003; 7:173-182.
20. Colmenero JD, Reguera JM, Fernandez-Nebro A, Cabrera- Franquelo F. Osteoarticular complications of brucellosis. Ann Rheum Diseases 1991; 50:23-26.
21. Tasova Y, Saltoglu N, Sahin G, Aksu HSZ. Osteoarticular involvement of brucellosis in Turkey. Clin Rheumatol 1999; 18:214-219.
22. Al-Eissa Y, Al-Nasser M. Hematological manifestation of childhood brucellosis. Infection 1993; 21:29-32.
23. Aygen B, Doganay M, Sumerkan B, Yildiz O, Kayabas U. Clinical manifestations, complications and treatment of brucellosis: a retrospective evaluation of 480 patients. Med Mal Infect 2002; 32: 485-493.
24. Akdeniz H, Irmak H, Anlar O, Demiroz AP. Central nervous system brucellosis: presentations, diagnosis and treatment. J Infect 1998; 36:297-301.
25. Sari I, Altuntas F, Hacioglu S, *et al*. A multicenter retrospective study defining the clinical and hematological manifestations of brucellosis and pancytopenia in a large series: Hematological malignancies, the unusual cause of pancytopenia in patients with brucellosis. Am J Hematol 2008; 83:334-339.
26. Metin A, Akdeniz H, Buzgan T, Delice I. Cutaneous findings encountered in brucellosis and review of the literature. Int J Dermatol 2001; 40:434-438.
27. Milionis H, Christou L, Elisaf M. Cutaneous manifestations in brucellosis: a case report and review of the literature. Infection 2000; 28:124-126.
28. Navarro-Martinez A, Solera J, Corredoira J, *et al*. Epididymoorchitis due to Brucella melitensis: A retrospective study of 59 patients. Clin Infect Dis 2001; 33:2017-2022.
29. Yurdakul T, Sert U, Acar A, Karalezli G, Akcetin Z. Epididymoorchitis as a complication of brucellosis. Urol Int 1995; 55:141-142.
30. Kahn MY, Mah MW, Memish ZA. Brucellosis in pregnant woman. Clin Infect Dis 2001; 32:1172-1177.
31. Young EJ. Brucella species. In: Mandell GL, Bennett JE, Dolin R editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 6th ed. Philadelphia: Churchill Livingstone; 2005, p. 2669-2674.
32. Kadanali A, Ozden K, Altoparlak U, Erturk A, Parlak M. Bacteremic and nonbacteremic brucellosis: clinical and laboratory observations. Infection 2009; 37:67-69.
33. Lulu AR, Araj GF, Khateeb MI, Mustafa MY, Yusuf AR, Fenech FF. Human brucellosis in Kuwait: a prospective study of 400 cases. Q J Med 1988; 66:39-54.
34. Pappas G, Basilkovski M, Akritidis N, Mastora M, Krteva L, Tsianos E. Brucellosis and respiratory system. Clin Infect Dis 2003; 37:e95-99.
35. Ataman-Hatipoglu C, Bilgin G, Tulek N, Kosar U. Pulmonary involvement in brucellosis. J Infect 2005; 51:116-119.

Original Article

Combination of Ballistic Lithotripsy and Transurethral Plasmakinetic Resection for Treating 200 Men with Bladder Calculi and Benign Prostatic Hyperplasia: A Trial with Two-Year Follow-Up

Jiansong Wang, Haifeng Wang, Yigang Zuo, Delin Yang, Mingxia Ding, Ruping Yan
Department of Urology, The Second Affiliated Hospital of Kunming Medical University, Kunming 650101, China

Kuwait Medical Journal 2011; 43 (3): 213-215

ABSTRACT

Objective: To assess the outcome of 200 men with bladder calculi (BC) and benign prostatic hyperplasia (BPH) who underwent transurethral ballistic lithotripsy (BL) as well as transurethral plasmakinetic resection of prostate (PKRP).
Design: Retrospective study
Setting: Department of Urology, The Second Affiliated Hospital of Kunming Medical University, Kunming, China
Subjects: In a trial at our department, we performed a retrospective analysis of the results of 200 patients who underwent endoscopic removal of BC and PKRP.
Intervention: BL and PKRP
Main Outcome Measure(s): International Prostate symptom score (IPSS), Quality of life scores (QOL), Maximum flow rate (Qmax), Residual urine volume (RUV) and postoperative complications
Results: At two years, the results showed that IPSS, QOL, Qmax and RUV were all significantly different between preoperative and postoperative data. Urethral stricture, short-term urinary incontinence, recurrent calculi, and BPH recurrence developed in 3.5% (n = 7), 5.0% (n = 10), 1.0% (n = 2), and 1.5% (n = 3) of the 200 patients, respectively. Overall, 178 (89.0%) cases did not have any complications.
Conclusion: Combined BL and PKRP is an effective, safe, and economical way of treating patients with BC and BPH simultaneously.

KEY WORDS: ballistic lithotripsy, bladder calculi, BPH, follow-up, PKRP

INTRODUCTION

Open surgical removal of bladder calculi (BC) used to be the mainstay of treatment. But this method is very traumatic. After 1980, extracorporeal shockwave lithotripsy (ESWL) and endourologic procedures have revolutionized the treatment of most lithiases[1]. Since then, ballistic lithotripsy (BL) became the spare wheel and was widely used when ESWL was likely to fail as in patients with a large stone burden. Meanwhile, BC are usually associated with benign prostatic hyperplasia (BPH). Endoscopic treatment of BPH, the method of transurethral plasmakinetic resection of prostate (PKRP) is a new technology, which has advantages of being non- traumatic and leads to quick recovery. Treatment of patients with both BC and BPH in a single procedure under the same anesthesia is a practical solution.

From August 2002 to April 2008, nearly 300 patients with BC and BPH underwent BL as well as transurethral PKRP. We randomly selected 200 patients who had been followed up for two years, and performed a retrospective analysis.

SUBJECTS AND METHODS

Clinical data

This study complies with the current ethical considerations. The age of 200 patients in this cohort ranged from 51 to 92 (mean 68 ± 8.5) years. The duration of their disease ranged from two months to 22 (mean 5.1 ± 4.6) years. All patients had dysuria and bladder irritation before surgery. All patients were diagnosed as BPH and BC, and not prostate cancer, by preoperative digital rectal examination, PSA, ultrasound, KUB + IVU and other tests. According to Rous (1985), BPH is divided into four grades. They are: grade I prostatic hyperplasia (20 – 25 g), grade II (25 – 50 g), grade III (50 – 70 g) and grade IV (> 70 g). There were 16 cases of grade I, 69 cases of grade II, 91

Address correspondence to:
Jiansong Wang, Department of Urology, The Second Affiliated Hospital of Kunming Medical University, Kunming 650101, China. Tel: +86-13888256716, E-mail: wanghaifeng0871@gmail.com

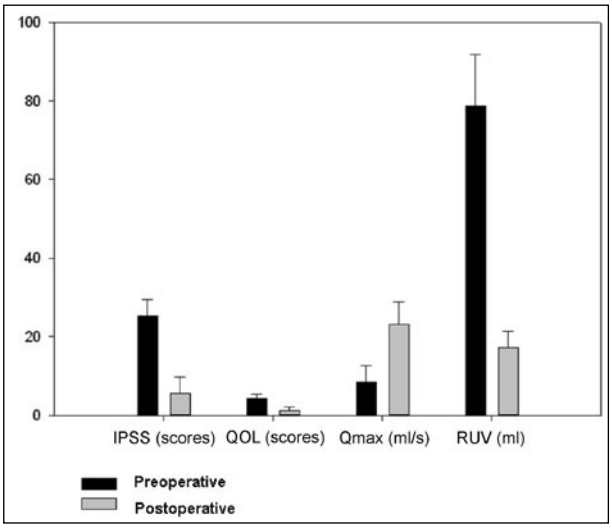

Fig. 1: Bar diagram showing IPSS, QOL, Qmax and RUV scores before and after surgery

cases of grade III and 24 cases of grade IV, respectively. The size of BC was from 0.7 cm × 0.3 cm × 0.4 cm to 5.5 cm × 6.4 cm × 6.9 cm. There were 68 patients with single calculus and 132 patients with multiple calculi (2 - 31). International prostate symptom score (IPSS) was (25.4 ± 4.1). Quality of life scores (QOL) was (4.2 ± 1.1). Maximum flow rate (Qmax) was (8.5 ± 4.2) ml / s. Residual urine volume (RUV) was (78.6 ± 13.3) ml. Out of the 200 cases, there were 43 cases of hypertension, 11 cases of diabetes, six cases of hemiplegia caused by infarction or hemorrhage of urethral canal and three cases of cardiac pacemaker.

Treatment

Before surgery, physicians, surgeons or anesthesiologists would correct patients' disorders of heart, brain, lung, kidney or other important organs in order to make patients fit for anesthesia. We installed temporary or permanent pacemakers into patients with grade II atrioventricular block, controlled arterial oxygen partial pressure > 50 mmHg in pulmonary insufficiency patients, gave one week of preoperative withdrawal for patients on anticoagulant therapy.

The simultaneous BL and PKRP were performed under spinal or general anesthesia in 186 cases (93%). General anesthesia and tracheal intubation were used in 14 cases (7%). Using a probe passed through a 27F rigid resectoscope (Gyrus), the pneumatic lithotripter was used for the management of BC. We passed the ureteric catheters probe through the working channel, and carried out the fragmentation using short bursts of the probe. We broke the stone (s) sequentially until the size of the stone(s) was less than 0.6 cm in diameter. The litholapaxy was performed by Ellik washer. After this operation, PKRP surgery was performed. Depending on the volume of the hyperplastic prostate and whether the prostate was adherent with the capsule or not, PKRP was performed by the methods of simple anterograde resection, divided anterograde resection, divided retrograde enucleation and total retrograde enucleation of the prostate, respectively.

Table 1: Clinical data before and after surgery

Period	IPSS (scores)	QOL (scores)	Qmax (ml/s)	RUV (ml)
Preoperative	25.4 ± 4.1 (17 - 34)	4.2 ± 1.1 (3 - 6)	8.5 ± 4.2 (4.3 - 14.2)	78.6 ± 13.3 (12 - 410)
Postoperative	5.5 ± 4.3* (0 - 13)	1.3 ± 0.8* (0 - 2)	23.1 ± 5.7* (17.2 - 27.1)	17.2 ± 4.1* (0 - 26)

* Statistically significant; $p < 0.01$

Statistical analysis

SPSS 17.0 statistical package was used for analysis of all data. The results were reported as means ± standard deviation and a p-value of < 0.05 was considered statistically significant.

RESULTS

Out of 200 patients, the transurethral BL was performed within 16 - 195 (mean 65.3 ± 21.6) min, and stone fragmentation was complete. PKRP operation time was 31 - 195 (mean 72.3 ± 23.2) min. The weight of the removed gland tissue was 19 - 200 g (mean 63.4 ± 23.7). There was no transurethral resection syndrome, no rectal perforation and no bladder perforation during surgery. Blood transfusion was required in two cases during surgery and in one case after surgery. No deaths occured in this group. After surgery, IPSS was (5.5 ± 4.3), QOL was (1.3 ± 0.8), Qmax was (23.1 ± 5.7) ml / s. and RUV was (17.2 ± 4.1) ml. These were statistically significant improvements over preoperative scores ($p < 0.01$).

During the two-year follow-up, urethral stenosis occured in 12 cases, out of which 10 cases were treated by urethral dilation and two cases were treated by internal urethrotomy. There were four cases of short-term incontinence of urine that spontaneously resolved within four weeks. Permanent urinary incontinence and secondary bleeding did not occur. Clinical improvements after surgical treatment are shown in Table 1 and Fig. 1.

DISCUSSION

BC associated with BPH is fairly common. The reported formation rate of BPH inducing BC was about 2 - 10%, and BC inducing BPH was nearly 80%[2]. In China, BC occurs usually in men over 50 years of age and is associated with BPH. Removal of stones and correction of the causes are advocated by most experts in urology[3,4].

A variety of mechanical and shockwave devices have become available to accomplish endoscopic stone fragmentation. Laser lithotripsy has become

increasingly attractive in endoscopic stone therapy[5-7]. Although the operation time of holmium laser is shorter than BL treatment, it is also the most expensive method for stone fragmentation. Compared to laser lithotripsy, BL is the most common and the most economical method for the treatment of BC in the clinical practice. The choice of modality when deciding on BL is based on many factors, including urinary level, stone type, available lithotriptor unit, the presence or absence of infection in a potentially obstructed system, as well as the overall patient condition. In this study, from a cost, safety, and efficacy point of view, we chose the best method of lithotripsy for stone fragmentation.

Transurethral resection of prostate (TURP) is still known as the "gold standard" for the treatment of benign prostatic hyperplasia (BPH). However, problems of TURP include absorption of the irrigation fluid, bleeding, transurethral resection syndrome, the incidence of bladder neck contracture and others[8]. Endoscopic treatment of BPH using PKRP is a new technology. The basic principle of PKRP is the current loop through the RF electrode and the formation of the bipolar loop electrode. RF energy will convert conducting media (NS) ionization into an ion beam, and this ion beam plays the role of cutting the target tissue. The changed principle of power cutting, and the lower temperature of power cutting (40-70 °C) contribute to an increase in surgical safety.

Despite the limitation of our work (the follow-up time of patients with BPH is not long enough), the results of this study are as good as those previously reported in the literature[9,10]. All scores (IPSS, QOL, Qmax and RUV) showed significant improvement and achieved the better prognosis in comparison to preoperative scores. The incidence of stricture, short-term urinary incontinence, recurrent calculi, and BPH recurrence was low, and 89.0% cases did not have any complications. Consequently, combined BL and PKRP is an effective, safe, and economical way of treating patients with BC and BPH simultaneously, and is suitable for patients who have a good overall condition, better urinary level, not very hard stones and belong to a poor economic class.

CONCLUSION

Our study demonstrated that the combination of BL and transurethral PKRP has a satisfactory outcome and is an effective, safe, and economical method of treating patients with BC associated with BPH.

ACKNOWLEDGMENT

The authors would like to thank Prof. Changxing Ke and Dr. Hui Zhan for their encouraging support and valuable technical discussion.

REFERENCES

1. Omur Elcioglu, Hilmi Ozden, Gul Guven, Sahin Kabay. Urinary bladder stone extraction and instruments compared in textbooks of Abul-Qasim Khalaf Ibn Abbas Alzahrawi (Albucasis) (930–1013) and Serefeddin Sabuncuoglu (1385–1470). J Endourol 2010; 24:1463-1468.
2. Shah HN, Hegde SS, Shah JN, Mahajan AP, Bansal MB. Simultaneous transurethral cystolithotripsy with holmium laser enucleation of the prostate: a prospective feasibility study and review of literature. BJU Int 2007; 99:595-600.
3. Meissner A, Mamoulakis C, Laube N. Urinary tract infections and Urolithiasis. Urologe A 2010; 49:623-628.
4. O'Connor RC, Laven BA, Bales GT, Gerber GS. Nonsurgical management of benign prostatic hyperplasia in men with bladder calculi. Urology 2002; 60:288-291
5. Healy K, Chamsuddin A, Spivey J, Martin L, Nieh P, Ogan K. Percutaneous endoscopic holmium laser lithotripsy for management of complicated biliary calculi. JSLS 2009; 13:184-189.
6. Maghsoudi R, Amjadi M, Norizadeh D, Hassanzadeh H. Treatment of ureteral stones: A prospective randomized controlled trial on comparison of Ho:YAG laser and pneumatic lithotripsy. Indian J Urol 2008; 24:352-354.
7. Kara C, Resorlu B, Cicekbilek I, Unsal A. Transurethral cystolithotripsy with holmium laser under local anesthesia in selected patients. Urology 2009; 74:1000-1003.
8. Yang Kun, Zhang Feng , Liu Si-kuan , Yu Jiang. TURS during transurethral vaporization of the prostate (report of 19 cases). Chinese Journal of Urology 2004; 25:121-123.
9. Rahman MH, Islam MA, Joarder AI. Uroflowmetry before and after transurethral resection of prostate for bladder outlet obstruction. Mymensingh Med J 2010; 19:601-607.
10. Woo HH, Hossack TA. Photoselective vaporization for prostatic obstruction with the 120-W lithium triborate laser: 1-year clinical outcomes. Int J Urol 2011; 18:162-165.

Original Article

Correlation of Fine Needle Aspiration Cytological Features of Extra-pulmonary Tuberculous Lesions with detection of Acid Fast Bacilli – Mubarak Al-Kabeer Hospital, Kuwait Experience

Kusum Kapila[1,2], Bahiyah E Haji[1], Sara S George[1], Mohammad Jaragh[1],Taiba A Alansary[1], Eiman E Mokaddas[3].
[1]Department of Pathology, Faculty of Medicine, Kuwait University, Jabriya, Kuwait
[2]Cytology Laboratory, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait
[3]Department of Microbiology, Faculty of Medicine, Kuwait University, Jabriya, Kuwait

Kuwait Medical Journal 2011; 43 (3): 216-219

ABSTRACT

Objective: To correlate the spectrum of cytomorphological changes in fine needle aspirates (FNA) of extra pulmonary tuberculous lesions with the demonstration of acid fast bacilli (AFB) by Ziehl-Neelsen (ZN) staining and culture of the mycobacterial organism
Design: Prospective, from January 2008 to August 2009
Setting: Mubarak Al-Kabeer Hospital, Kuwait
Subjects: Three hundred and eighty-one patients with suspected tuberculosis
Intervention: FNA was done on lymph nodes (313 cases, 82%), soft tissue (37 cases, 10%), breast (24 cases, 6%), thyroid (3 cases, 1%) and epididymis (4 cases, 1%). Papanicolaou and / or May-Grunwald-Giemsa (MGG) stained smears were classified into: Group A: granulomas with necrosis (n = 202, 53%), Group B: granulomas alone (n = 59, 15.5%), Group C: acellular necrosis alone (n = 53, 13.9%) and Group D: acute inflammatory exudate (n = 67, 17.6%).
Main Outcome Measure(s): The cytomorphological features of extra-pulmonary tuberculosis in FNA were correlated with AFB demonstration by ZN staining and mycobacterial culture.
Results: The AFB positivity by ZN stain was 46.6, 7.9, 58.1 and 22% in groups A, B, C and D respectively. Culture was positive in 53.1, 6.7, 56 and 15.4% in groups A, B, C and D respectively. In 32 out of 109 cases both ZN staining and culture were positive. In 77 cases negative for AFB the culture was positive in 31.2% and negative in 68.8%.
Conclusion: Evaluation of all FNA from suspected cases of tuberculosis should include staining for AFB and culture for mycobacteria.

KEY WORDS: acid fast bacilli, cytomorphological spectrum, extra-pulmonary tuberculosis

INTRODUCTION

Tuberculosis (TB) is on the rise globally, with an estimated one-third of the world's population being infected with *Mycobacterium tuberculosis* and approximately 3 - 4 million new cases every year[1]. Pulmonary TB is most common but isolated extra-pulmonary organ involvement is well-known, the common sites being lymph nodes, kidney, long bones, genital tract, brain and meninges[2]. Studies from developed countries have reported that extra pulmonary TB is on the rise due to human immunodeficiency virus (HIV) epidemic. High burden countries with low prevalence of HIV have also reported an increase[3,4]. Demonstration of acid fast bacilli (AFB) in smears and culture of sputum is widely employed for diagnosis of pulmonary TB. However, biopsy with histopathological examination and demonstration of AFB has been the gold standard for diagnosis of extra-pulmonary lesions. With the advent of fine needle aspiration cytology (FNAC) the scenario has changed. FNAC, a simple, cost effective, non-invasive technique is readily performed in the out-patient setting and has proved to be useful in the diagnosis of TB from practically any site in the body. Palpable masses anywhere in the body are easily amenable to FNAC and the technique has assumed an important role in the evaluation of peripheral adenopathy as a possible non-invasive alternative to excisional biopsy[5-7].

Very few reports document the use of FNAC in the diagnosis of extra-pulmonary TB in palpable masses in the Middle East[3,6,7]. The purpose of this study was to identify the spectrum of cytomorphological changes seen in aspirates from palpable masses from patients suspected to have extra-pulmonary TB. We also tried

Address correspondence to:
Kusum Kapila, MD, FAMS, FIAC, FRCPath, Professor & Head, Cytology Unit, Department of Pathology, Faculty of Medicine, Kuwait University P O Box 24923, Safat 13110, Kuwait. Tel: 2531 9476 or 2498 6247, Fax: +965-2533 8905, E-mail: kkapila@hsc.edu.kw

Table 1: Correlation of age distribution and nationality with cytomorphological spectrum in FNA smears from extra-pulmonary tuberculous lesions

Age group (years)	Total	Nationality		Cytological diagnosis			
		Kuwaiti n (%)	Non- Kuwaiti n (%)	G -with N n (%)	G -alone n (%)	N- alone n (%)	AIE n (%)
0 - < 15	13	9 (69.2)	4 (30.8)	8 (61.5	2 (15.4)	1 (7.7)	2 (15.4)
15 - < 25	52	16 (30.8)	36 (69.2)	29 (55.8)	8 (15.4)	6 (11.5)	9 (17.3)
25 - < 35	155	14 (9)	141 (91)	91 (58.7)	20 (12.9)	22 (14.2)	22 (14.2)
35 - < 45	92	10 (10.9)	82 (89.1)	49 (53.3)	16 (17.4)	10 (10.8)	17 (18.5)
45 - < 55	34	7 (20.6)	27 (79.4)	13 (38.2)	8 (23.5)	5 (14.7)	8 (23.5)
55 - < 65	24	11 (45.8)	13 (54.2)	7 (29.2)	4 (16.7)	7 (29.2)	6 (25.0)
> 65	7	7 (100)	0	2 (28.6)	1 (14.3)	2 (28.6)	2 (28.6)
Age & Nationality NA	4	-	-	3 (1.5)	-	-	1 (1.5)
Total	381	74 (19.4)	303 (79.5)	202 (53.0)	59 (15.5)	53 (13.9)	67 (17.6)

G-with N: Granulomas with necrosis; G-alone: granulomas alone; N - alone: Necrosis alone; AIE: Acute inflammatory exudate; NA - Not available

to correlate the detection of acid-fast bacilli (AFB) by the Ziehl-Neelsen (ZN) method and by culture of the organism with the cytomorphological features.

SUBJECTS AND METHODS

FNA smears from palpable masses from 381 cases with suspected tuberculosis over a period of 20 months (January 2008 – August 2009) in Mubarak Al-Kabeer Hospital, Kuwait were studied. Aspiration was performed using a 23 gauge needle fitted to a 10 ml syringe. Alcohol fixed and air dried smears were stained by Papanicolaou stain and May-Grunwald-Giemsa (MGG) stain for the evaluation of cytomorphological features. Extra smears were fixed in alcohol for demonstration of AFB by the ZN stain. A portion of the pus - like material aspirated or the needle rinses in saline were sent for mycobacterial culture using MGIT 960, (Becton Dickinson, USA).

Based on the cytomorphologic features, the smears were classified into the following four groups: Group A: epithelioid cell collection with a variable amount of granular necrotic material. Giant cells may or may not be identified; Group B: only epithelioid cell collections identified; Group C: only granular necrotic material seen and Group D: only an acute inflammatory exudate.

ZN stained smears were screened under x 100 (oil immersion) objective. AFB was seen as red beaded rod-like structures against a blue background. Known positive smears were used with each batch of staining as positive controls.

The cytomorphological findings were correlated with AFB positivity on ZN smears as well as culture results. An attempt was also made to document the nationality of the study group where possible.

RESULTS

Table 1 shows the distribution of the cytomorphological feature in the various age groups and nationalities. Out of 381 cases, 74 (19.4%) were Kuwaiti and in four the nationality was not known. There were 170 male and 211 female. The commonest cytomorphological feature seen was granuloma with necrosis (n = 202, 53%) followed by granulomas alone (n = 59, 15.5%) and necrotic material alone (n = 53, 13.9%). In 67 (17.6%) patients an acute inflammatory exudate was aspirated in which AFB were demonstrated by ZN stain or culture.

Table 2 shows the distribution of the various sites aspirated – lymph nodes (n = 313, 82.2%) were the most common followed by soft tissues (n = 37, 9.7%), breast (n = 24, 6.3%), epididymis (n = 4, 1%), and thyroid (n = 3, 1%). Necrotizing granulomas were the most common cytomorphological findings in lymph nodes (59.4%) and thyroid (66.7%), while necrosis alone or an acute inflammatory exudate was predominantly seen in FNA from soft tissue swellings, breast and epididymis (Table 2). ZN stain was available in 292 cases and

Table 2: Correlation of cytomorphological spectrum with site of fine needle aspiration cytology

Cytological spectrum	Total n (%)	Site of fine needle aspiration cytology				
		Lymph node n (%)	Soft tissue n (%)	Breast n (%)	Epididymis n (%)	Thyroid n (%)
Granulomas with necrosis	202 (53.0)	186 (59.4)	8 (21.6)	5 (20.8)	1 (25)	2 (66.7)
Granulomas alone	59 (15.5)	54 (17.3)	3 (8.1)	0	1 (25)	1 (33.3)
Necrosis alone	53 (13.9)	42 (13.4)	9 (24.3)	2 (8.4)	0	0
Acute inflammatory exudate	67 (17.6)	31 (9.9)	17 (45.9)	17 (70.8)	2 (50)	0
Total	381	313 (82.2)	37 (9.7)	24 (6.3)	4 (1)	3 (0.8)

Table 3: Correlation of cytomorphological spectrum with AFB positivity in smears and culture

Cytological spectrum	Total cases n (%)	Cases with ZN stain n	AFB positive (ZN Stain) n (%)	Cases with mycobacterial culture done n	Mycobacterial culture positive n (%)
Granulomas with necrosis	202 (53.0)	161	75 (46.6)	98	52 (53.1)
Granulomas alone	59 (15.5)	38	3 (7.9)	30	2 (6.7)
Necrosis alone	53 (13.9)	43	25 (58.1)	25	14 (56)
Acute inflammatory exudate	67 (17.6)	50	11 (22)	26	4 (15.4)
Total	381	292	114 (39)	179	72 (40.2)

ZN-Ziehl Neelsen, AFB- acid fast bacilli

culture in 179 cases. The frequency of mycobacterial positivity by the two methods correlated with the cytomorphological features is highlighted in Table 3. AFB were readily identified by ZN stain and culture in 25 of 43 (58.1%) of Group C (necrosis alone) and 11 of 50 (22%) of Group D (acute inflammatory exudates) cases. In 109 cases, both ZN stain and mycobacterial culture were available. In 32 of those cases both methods were positive for AFB. In the 77 cases negative for AFB by ZN stain, the mycobacterial culture was positive in 24 (31.2%) and negative in 53 (68.8%).

DISCUSSION

TB remains a major public health problem worldwide. A definitive and accurate diagnosis of TB is important because satisfactory results can be achieved with chemotherapy alone, obviating surgery[9]. FNA has provided an alternative and easy procedure for collection of material for cytomorphological and bacteriologic examination[2,5,8]. In smears with necrotizing granulomas, the diagnosis of TB can be suggested irrespective of AFB positivity. However, any acellular necrotic or inflammatory material must be subjected to AFB staining and culture so as not to miss the diagnosis of TB[2]. Few reports are available from the Middle East to document these findings[3,6,7,9-11]. We have tried to correlate the cytomorphological findings and AFB positivity in FNAC samples of palpable masses.

The highest rate of AFB positivity was found in necrotic material (58.1%) and a previous study from Kuwait also reported maximum positivity (63%) in TB lymphadenitis[6]. In granulomatous lesions we detected AFB in 7.9% of cases by ZN stain and 6.7% by culture. However, Gupta *et al*[6] found 20% and 40% of granulomatous lymphadenitis to be positive for AFB by ZN stain and culture respectively in their study.

In aspirates with acute inflammatory exudate, AFB was found in 11 of 59 cases by ZN stain and 15.4% by culture. In the absence of ZN staining, these cases would have been reported as suppurative lesions. In the negative smears on ZN staining, mycobacterial culture was positive in 24 of 77 cases (31.2%). Eighteen percent of 157 aspirates from suspected lymph nodes were positive by ZN smear and 45% by culture[12] and in this study[12], culture identified AFB in 12 aspirates with an inflammatory exudate alone. Culture positivity has been reported to be significantly higher than smear positivity[6,13].

Table 4 correlates the AFB positivity by ZN stain and the cytomorphological spectrum in fine needle aspirates reported in various series[5,6,9,16-18]. The AFB positivity in FNA with granulomas with necrosis ranged from 14.3[18] to 75.6%[9], while in our study, it was 46.9%. However, the detection of bacilli when granulomas alone were identified, ranged from 1.9 [17] to 28.5%[9]. In our study, we could demonstrate AFB in 7.9% of the FNA with granulomas alone. The AFB positivity was high 58.1% in our study, when necrosis alone was seen in aspirates and literature review shows it to range from 17.8[17] to 68.7%[9]. In many studies, details on AFB staining of FNAC showing an acute inflammatory exudate alone are not available. Two studies report AFB positivity in 35.8[18] and 42.9%[16] of

Table 4: AFB positivity and cytomorphologic spectrum in FNA smears from tuberculous lesions

Cytological spectrum	Authors reference (% positivity of ZN Stain)						
	Kumar *et al*[18]	Das *et al*[5]	Kakkar *et al*[16]	Prasoon[17]	Gupta *et al*[6]	Ergete & Bekel[9]	Present study
Granulomas with necrosis	14.3	31.9	21.4	19.1	32	75.6	46.6
Granulomas alone	-	-	-	1.9	20	28.5	7.9
Necrosis alone	26.2	36.6	88.8	17.8	32.2	68.7	58.1
Acute inflammatory exudate alone	35.8	-	42.9	-	-		22
All cases	33.5	-	38.6	-		71.7	39

AFB - Acid Fast Bacilli, ZN - Ziehl-Neelsen

their cases with an acute inflammatory exudate while we observed them in 22% of our cases. Our study is comparable with an overall positivity of 39%. Culture of the aspirated material and molecular biology techniques like PCR are known to further increase the sensitivity and specificity[1,8].

In the palpable masses, lymph node has been reported to be the most common extra-pulmonary site (81.3%) of TB, other extranodal sites being epididymis, parotid, breast, thyroid and skin sinuses[2]. We found a similar distribution (Table 2). Thyroid tuberculosis is rare and may be primary or result from contiguous or hematogenous spread from pulmonary TB. In his review of thyroid TB Simkus quoted the range in the literature being from 0.1 to 1%[14]. In our study, thyroid tuberculosis was detected in 0.8% of cases. Epdidymis is reported as a common extra-pulmonary site but in our study only four cases presented with an epididymal swelling. Tuberculous mastitis has been reported with varying frequency (0.66-1.6% of all mammary lesions in non-endemic countries to as high as 3.4% of all mammary lesions from countries where TB is endemic)[15,16], the hall mark of the diagnosis being necrotizing granulomas. We also found TB mastitis in our study and it comprised only 6.3% of the extra-pulmonary sites examined.

CONCLUSION

FNAC coupled with ZN staining is a very useful diagnostic tool in the diagnosis of TB. Culture examination is of further help in the characterization of mycobacteria and in determining drug sensitivity.

REFERENCES

1. Pahwa R, Hedan S, Jain S, *et al*. Assessment of possible tuberculous lymphadenopathy by PCR compared to non-molecular methods. J Med Microbiol 2005; 54:873-878.
2. Rajwanshi A, Bhambhani S, Das DK. Fine-needle aspiration cytology diagnosis of tuberculosis. Diagn Cytopathol 1987; 3:13-16.
3. Hasibi M, Rezaii J, Kermani ZM, Asadollahi M, Rashidi A, Abouzari M. The need to reassess the value of fine needle aspiration in the diagnosis of tuberculous cervical lymphadenitis in Iran. Scand J Infect Dis 2007; 39:750-751.
4. Al-Otaibi F, El Hazmi MM. Extra pulmonary tuberculosis in Saudi Arabia. Indian J Pathol Microbiol 2010; 53:227-231.
5. Das DK, Bhambhani S, Pant JN, *et al*. Superficial and deep-seated tuberculous lesions: fine-needle aspiration cytology diagnosis of 574 cases. Diagn Cytopathol 1992; 8:211-215.
6. Gupta SK, Chugh TD, Sheikh ZA, Al-Rubah NA. Cytodiagnosis of tuberculous lymphadenitis: a correlative study with microbiological examination. Acta Cytol 1993; 37:329-332.
7. Khan FY. Clinical pattern of tuberculous lymphadenitis in Qatar: Experience with 35 patients. Scand J Infect Dis 2009; 41:128-134.
8. Verma K, Kapila K. Aspiration cytology for diagnosis of tuberculosis – perspectives in India. J Pediatr 2002; 69:39-43.
9. Ergete W, Bekele A. Acid fast bacilli in aspiration smears from tuberculous patients. Ethiop J Health Dev 2000; 14:99-104.
10. Francis IM, Das DK, Luthra UK, Sheikh Z, Sheikh M, Bashir M. Value of radiologically guided fine needle aspiration cytology (FNAC) in the diagnosis of spinal tuberculosis: a study of 29 cases. Cytopathology 1999; 10:390-401.
11. Qari FA. The spectrum of tuberculosis among patients of The King Abdul Aziz University Hospital, Jeddah, Saudi Arabia. Southeast Asian J Trop Med Public Health 2002; 33:331-337.
12. Reddy KVC, Aparna S, Prasad CE, *et al* Mycobacterial culture of fine needle aspirate – A useful tool in diagnosing tuberculous lymphadenitis. Indian J Med Microbiol 2008; 26:259-261.
13. Nataraj G, Kurup S, Pandit A, Metha P. Correlation of fine needle aspiration cytology, smear and culture in tuberculous lymphadenitis: a prospective study. J Postgrad Med 2002; 48:113-116.
14. Simkus A. Thyroid tuberculosis. Medicina 2004; 40:201-204.
15. Das DK, Sodhani P, Kashyap V, Parkash S, Pant JN. Inflammatory lesions of the breast: diagnosis by fine needle aspiration. Cytopathology 1992; 3:281-289.
16. Kakkar S, Kapila K, Singh MK, Verma K. Tuberculosis of the breast: A cytomorphological study. Acta Cytol 2000; 44:292-296.
17. Prasoon D. Acid fast bacilli in fine needle aspiration smears from tuberculous lymphnodes - where to look for them. Acta Cytol 2000; 44:297-300.
18. Kumar N, Tiwari MC, Verma K. AFB staining in cytodiagnosis of tuberculosis without classical features: a comparison of Ziehl-Neelsen and fluorescent methods. Cytopathology 1998; 9:208-214.

Original Article

Evaluation of Insulin Resistance by the Homeostasis Model Assessment in Female Patients with Primary Sjogren's Syndrome

Gonca Karabulut[1], Fulden Sarac[2], Gul Kitapcioglu[3], Candeger Yılmaz[2], Yasemin Kabasakal[1]
[1]Department of Rheumatology, Ege University Faculty of Medicine, Izmir, Turkey
[2]Department of Endocrinology and Metabolism, Ege University Faculty of Medicine, Izmir, Turkey
[3]Department of Biostatistics and Medical Informatics, Ege University Faculty of Medicine, Izmir, Turkey

Kuwait Medical Journal 2011; 43 (3): 220-223

ABSTRACT

Objective: To evaluate insulin resistance in Primary Sjogren's Syndrome (pSS) using homeostasis model assessment (HOMA) method
Design: Cross-sectional study conducted between January 2006 and December 2008
Setting: Ege University Faculty of Medicine, Izmir, Turkey
Subjects: Thirty-five female patients with pSS fulfilling the US-European Consensus Criteria
Interventions: A brief clinical history, demographic, anthropometric, clinical and laboratory profiles were recorded
Main Outcome Measures: HOMA-IR and serum lipid levels
Results: Mean level of HOMA-IR was 1.8 ± 0.7 in patients with pSS. Mean levels of plasma fasting glucose and insulin were 90.6 ± 7.1 mg/dl, 7.8 ± 2.5 microU/l, respectively. A statistically significant difference was detected between ANA positivity and HOMA-IR values (p = 0.016). Four patients with pSS had high HOMA values (> 2.7) and all these patients had ANA positivity. A statistically significant positive correlation was detected between HOMA-IR values and HDL-C levels (R = 0,450 p = 0.009). However, a statistically significant difference was detected between extraglandular involvement and LDL-C (p = 0.01) and total cholesterol levels (p = 0.01). Patients who had no extraglandular involvement had higher levels of total cholesterol and LDL-C levels. Lower triglyceride levels were seen in patients with anti-La antibodies (p = 0.01) but not other antibodies (p > 0.05). Patients with ANA positivity and pSS had lower LDL-C levels (p = 0.009).
Conclusion: Autoimmune mechanisms may play a role in insulin resistance in pSS. Metabolic alterations should be taken into account in their management.

KEY WORDS: HOMA, insulin resistance, Sjogren's syndrome

INTRODUCTION

Insulin resistance is a common metabolic state defined as a subnormal biologic response to given physiological levels of insulin, and plays an important role in the pathogenesis of several metabolic diseases such as obesity and diabetes mellitus (DM)[1].

There are several mechanisms that could contribute to altered insulin sensitivity that may be important in patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE), and they provide insights into pathogenesis of insulin resistance associated with inflammation. These include obesity, the medications used to treat inflammatory diseases, and inflammatory mediators. The adipose tissue functions as an endocrine organ and produces several inflammatory mediators, thus contributing to a proinflammatory state and increased cardiovascular risk[2].

There are two types of insulin resistance syndrome; type A results from genetic defects in the insulin signaling mechanism and type B is caused by an autoimmune phenomenon associated with insulin receptor autoantibody formation[3].

Sjogren's syndrome (SS) is a slowly progressive, inflammatory autoimmune disease affecting primarily the exocrine glands which then leads to clinical features of dry eyes and dry mouth. Extraglandular involvement including arthritis, pulmonary disease, renal disease and vasculitis may also occur in SS. In isolation, SS is termed as "primary" and when in combination with another autoimmune disease, it is termed as "secondary"[4-5].

Address correspondence to:
Gonca Karabulut, MD, Division of Rheumatology, Department of Internal Medicine, Ege University School of Medicine, Izmir, Turkey. Tel: +90 232 3904235; Fax: +90 232 3423289, E-mail: gonca4us@yahoo.com

Primary Sjogren's syndrome (pSS) can occur at all ages, but it affects primarily females during fourth and fifth decades of life, with a female / male ratio of 9 : 1, and its prevalence estimates range from approximately 0.5 to 2%[6,7].

There are a number of tests available for evaluating insulin sensitivity or resistance. Homeostasis model assessment (HOMA), the most commonly used method in clinical practice is used to assess insulin resistance using the fasting glucose and insulin concentrations[8].

There are a few studies up to date investigating the relationship of insulin resistance with systemic inflammatory rheumatic diseases such as RA and SLE[9-11].

There are a few studies up to date investigating the clinical significance of metabolic alterations in patients with pSS[12-14]. However, there is no study related to insulin resistance in pSS. Therefore, the aim of the study was to evaluate the insulin resistance in pSS by using the HOMA method.

SUBJECTS AND METHODS

This cross-sectional study was conducted by enrollment of 35 female patients with pSS who fulfilled the US-European Consensus Criteria[15] and were followed up by the Department of Rheumatology of Ege University. They were fully examined clinically.

Patients with renal dysfunction (serum creatinine ≥ 1.2 mg/dl), DM or known glucose metabolism disturbances, hypothyroidism or any other inflammatory or malignant diseases were excluded. There were no patients on glucocorticoid, metformin, acorbose and antihypertensive treatment. Twenty of the patients with pSS were taking hydroxychloroquine (54.3%).

This study was performed according to the principles of the Declaration of Helsinki and an informed consent was obtained from all patients.

A brief clinical history, demographic, anthropometric and clinical profiles were recorded in all patients. Serum concentrations of glucose, triglyceride, total cholesterol, and high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) were determined by enzymatic procedures and insulin was measured by chemiluminance. Insulin resistance (IR) was estimated using the HOMA formula from fasting glucose and insulin concentrations as follows:

HOMA - IR = (fasting plasma insulin [μU/ml] x fasting plasma glucose [mmol/l]) / 22.50

HOMA – IR values < 2.7 were considered normal.

Statistical analysis

The statistical analysis was performed using the statistical package program (SPSS 18.0). Mann–Whitney U test and correlation analysis were used for statistical analysis and a p-value less than 0.05 was accepted as significant.

RESULTS

Thirty-five pSS female patients were included this study. The mean age of the participants was 53.5 ± 9.2 years. Mean disease duration time was 8.0 ± 4.2 years.

The clinical and laboratory features of the patients are shown in Table 1 and Table 2.

Table 1: Characteristics of pSS patients

Clinical and Laboratory Features	n	%
Subjective Symptoms		
Dry mouth	32	91.4
Dry eyes	30	85.7
Extraglandular Manifestations	17	48.6
Eye Findings		
Positive Schirmer-I test	20	57.1
Immunological Features		
ANA positivity	32	91.4
Anti Ro/SS-A positivity	29	82.9
Anti La/SS-B positivity	16	45.7
RF positivity	17	51.5
Minor Salivary Gland Biopsy		
Chisholm III	15	42.9
Chisholm IV	20	57.1

Table 2: Laboratory and physical examination characteristics of pSS patients

Characteristics	Mean ± SD
Laboratory Characteristics	
HOMA-IR	1.8 ± 0.7
Fasting insulin (pmol/l)	54.17 ± 17.37
Fasting glucose (mmol/l)	5.03 ±4.22
HbA1c (%)	5.2 ± 0.4
Total Cholesterol (mmol/l)	5.28 ± 0.95
LDL-C (mmol/l)	3.16 ± 0.76
HDL-C (mmol/l)	1.58 ± 0.41
Triglyceride (mmol/l)	1.23 ± 0.38
Physical Examination	
Weight (kg)	73.44 ± 12.44
Waist circumference (cm)	93.82 ± 14.29
Body Mass Index (kg/m2)	26.41 ± 2.97
Systolic blood pressure (mmHg)	127.49 ± 18.24
Diastolic blood pressure (mmHg)	69.58 ± 17.24

Mean levels of plasma fasting glucose and insulin were 5.03 ± 4.22 mmol/l, 54.17 ± 17.37 pmol/l respectively. Only one person had impaired glucose tolerance test by OGTT in pSS group (Table 2).

In the pSS patient group, the extraglandular involvement rate was 48.6% (17 / 35). There was no association between the presence of extraglandular involvement and HOMA-IR values in patients with pSS (p = 0.523).

There were no statistically significant differences between SS related symptoms such as dry eyes (p = 0.925), dry mouth (p = 0.860), parotid swelling (p = 0.525), Schirmer test (p = 0.881) results and minor

salivary gland biopsy (p = 0.790) and HOMA-IR values.

There were no statistically significant differences between the HOMA-IR values and autoantibodies such as rheumatoid factor (p = 0.241), anti-Ro (p = 0.710) and anti-La autoantibody (p = 0.476) positivity.

However, a statistically significant difference was detected between ANA positivity and HOMA-IR values (p = 0.016). Four patients with pSS had high HOMA values (> 2.7) and all these patients had ANA positivity.

There was a positive correlation between HOMA values and insulin levels as expected (p < 0.0001) and also, there were no statistically significant differences between the HOMA-IR values and fasting glucose, triglyceride, HDL-C, LDL-C, Body Mass Index (BMI), systolic and diastolic blood pressure. However, a statistically significant positive correlation was detected between HOMA-IR values and HDL-C levels (R = 0.450 p = 0.009) (Table 3).

Table 3: Correlation between HOMA and laboratory tests

HOMA	R	p-value
Fasting glucose (mmol/l)	0,069	0,693
Fasting insulin (microU/l)	0.857	<0.0001
HbA1c (%)	0,146	0,402
Triglyceride (mmol/l)	-0,093	0,607
Total Cholesterol(mmol/l)	0,041	0,819
HDL-C (mmol/l)	0,450	0,009
LDL-C (mmol/l)	-0,168	0,35

However a statistically significant difference was detected between extraglandular involvement and LDL-C (p = 0.01) and total cholesterol levels (p = 0.01). Patients with no extraglandular involvement had higher levels of total and LDL-C .

Lower triglyceride levels were seen in patients with anti-La antibodies positivity (p = 0.01) but not other antibodies (p > 0.05). pSS patients with ANA positivity had lower LDL-C levels (p = 0.009).

In this study, patients who had not received antimalarials showed higher levels of total cholesterol (p = 0.042) and HDL-C (p = 0.01). There were no statistically significant difference between antimalarial therapy and the other biochemical parameters such as HOMA values, insulin, LDL-C and triglyceride levels (p > 0.05).

DISCUSSION

To the best of our knowledge, this is the first study about insulin resistance in pSS. This study evaluated insulin resistance by using HOMA method in a total of 35 pSS patients. The major finding was that pSS patients with ANA had significantly higher HOMA values than ANA negative patients.

Also, lipid profile alterations were seen in patients with pSS[14]. In this study, a statistically significant positive correlation was detected between HOMA-IR values and HDL-C levels. The patients with no extraglandular involvement had higher levels of total and LDL-C. Patients who had not received antimalarial drugs showed higher levels of total and HDL-C. Lower triglyceride levels were seen in only anti-La antibodies positive patients. pSS patients with ANA positivity had lower LDL-C levels.

There are a few studies about the clinical significance of metabolic alterations in patient with pSS. Experimental and clinical studies showed that there are an association between pSS and diabetes[6,12]. Binder *et al* studied 102 type-1 diabetic patients and found anti-Ro antibody among 32% of the patients[12]. The non-obese diabetic (NOD) mouse is a murine model of diabetes that develops an exocrine disease similar to human pSS[16].

In our study, a statistically significant difference was detected between ANA positivity and HOMA-IR values (p = 0.016). Four patients with pSS had high HOMA values (> 2.7) and all these patients had ANA positivity. Islet cell auto antigen 69 is present in salivary and lachrymal glands and pancreatic beta cell and tissue of the nervous system[17]. Winer *et al* reported that elevated levels of autoantibodies to this protein were frequently found in serum of patients with pSS[18]. These autoantibodies may be responsible for the HOMA-IR and ANA association.

In addition to diabetes, in a previous study, Lodde *et al* described a differentiated serum lipid profile in patients with pSS. They found that total cholesterol levels were significantly lower in pSS patients with anti-Ro and lower HDL-C levels were seen in patients with anti-La[14]. Ramos-Casals *et al* stated that patients with pSS showed negative correlation between autoantibody production and cholesterol/HDL-C levels[13].

However, in our study, lower triglyceride levels were seen in patients with anti-La antibodies positivity but not other antibodies, and lower LDL-C levels in pSS patients with ANA positivity (p = 0.009). Adipose tissue has a pivotal role in inflammation, releases several inflammatory and immune mediators termed adipokines[9]. We can speculate that the role of adipokines in inflammatory rheumatic diseases may explain the lipid profile alteration in patients with pSS.

As regards insulin resistance data in other rheumatic diseases such as SLE, Zeng *et al* reported that SLE patients with hyperglycemia were characterized by insulin resistance and reduced pancreatic beta cell function[9] Likewise, Tso *et al* and Parker *et al* suggested that SLE is associated with an increased prevalence of the metabolic syndrome and patients also show evidence of increased insulin resistance[3,10]. Likewise Shahin *et al* showed that early untreated RA patients are characterized by a severe insulin resistant

state that is driven primarily by disease activity and systemic inflammation[11]. The etiopathogenic role of insulin resistance in the development of metabolic alterations in patients with pSS may be an important factor similar to other autoimmune diseases such as SLE or RA.

In this study, insulin resistance is higher in pSS with ANA positivity and also, ANA positive pSS patients had higher mean level of HOMA-IR. These findings suggest that autoimmune mechanisms may play a pivotal role for insulin resistance in pSS. However, we readily admit that these findings should be confirmed in larger series of patients in the future.

CONCLUSİON

Autoimmune mechanisms may play a role for insulin resistance in pSS. We suggest that metabolic alterations should be taken into account in the management of patients with pSS.

REFERENCES

1. Moller DE, Flier JS. Insulin resistance: mechanisms, syndromes, and implications. N Engl J Med 1991; 325:938-948.
2. Chung CP, Oeser A, Solus JP, *et al*. Inflammation-associated insulin resisitance, differential effects in rheumatoid arthritis and systemic lupus erythematosus define potential mechanisms. Arthritis Rheum 2008; 58:2105-2112.
3. Tso TK, Huang HY, Chang CK, *et al*. Clinical evaluation of insulin resistance and beta-cell function by the homeostasis model assessment in patients with systemic lupus erythematosus. Clin Rheumatol 2004; 23:416-420.
4. Tzioufas AG, Mitsias ID, Mouthsopoulos HM. Sjögren's Syndrome. In Rheumatology. Hochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH, editors. 4th edition, Vol. II, Mosby Elsevier, 2008; 1341-1352.
5. Fox RI. Sjogren's syndrome. Lancet 2005; 366:321-331.
6. Kabasakal Y, Kitapcioglu G, Turk T, *et al*. The prevalence of Sjogren's syndrome in adult women. Scand J Rheumatol 2006; 35:379-383.
7. Thomas E, Hay EM, Hajeer A, Silman J. Sjögren's syndrome: A community –based study of prevalence and impact. Br J Rheumatol 1998; 37:1069-1076.
8. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assesment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28:412-419.
9. Zeng YJ, Zeng FQ, Dai L, *et al*. Characteristics and risk factors for hyperglycemia in Chinese female patients with systemic lupus erythematosus. Lupus 2010; 19:1344-1350.
10. Parker B, Bruce IN. The metabolic syndrome in systemic lupus erythematosus. Rheum Dis Clin North Am 2010; 36:81-97.
11. Shahin D, Eltoraby E, Mesbah A, Houssen M. Insulin resistance in early untreated rheumatoid arthritis patients. Clin Biochem 2010; 43:661-665.
12. Binder A, Maddison PJ, Skinner P, Kurtz A, Isenberg DA. Sjogren's syndrome: association with type-1 diabetes mellitus. Br J Rheumatol 1989; 28:518-520
13. Ramos-Casals M, Brito-Zerón P, Sisó A, *et al*. High prevalence of serum metabolic alterations in primary Sjogren's syndrome: influence on clinical and immunological expression. J Rheumatol 2007; 34:754-761.
14. Lodde BM, Sankar V, Kok MR, *et al*. Serum lipid levels in Sjogren's syndrome. Rheumatology (Oxford) 2006; 45:481-484.
15. Vitali C, Bombardieri S, Jonsson R, *et al*. European Study Group on Classification Criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61:554-558.
16. Tran SD, Kodama S, Lodde BM, *et al*. Reversal of Sjogren's-like syndrome in non-obese diabetic mice. Ann Rheum Dis 2007; 66:812-814.
17. Routsias JG, Tzioufas AG. Sjogren's syndrome--study of autoantigens and autoantibodies. Clin Rev Allergy Immunol 2007; 32:238-251.
18. Winer S, Astsaturov I, Cheung R, *et al*. Primary Sjögren's syndrome and deficiency of ICA69. Lancet 2002; 360:1063-1069.
19. Santos MJ, Fonseca JE. Metabolic syndrome, inflammation and atherosclerosis - the role of adipokines in health and in systemic inflammatory rheumatic diseases. Acta Reumatol Port 2009; 34:590-598.

Case Report

Duodenal Diverticulum Mimicking Pancreatic Abscess

Khaleda Dashti, Ammar Aljumah, Sarah Almutawa
Department of Clinical Radiology, Mubarak Al-Kabeer Hospital, Kuwait

Kuwait Medical Journal 2011; 43 (3): 224-226

ABSTRACT

A 73-year-old lady presented with abdominal pain. On initial radiological workup the case mimicked pancreatic abscess but on further investigation, proved to be duodenal diverticulum, thus avoiding unnecessary surgical intervention. The clinical and radiological features are presented in order to avoid misinterpretation of duodenal diverticulum as pancreatic abscess.

KEY WORDS: abdominal pain, cystic tumor, pancreatic lesion

INTRODUCTION

The duodenum is a common location for gastrointestinal diverticula. These diverticula typically occur in the periampullary region[1]. In 90% of cases it is asymptomatic and is detected incidentally. However, in about 10% of cases, patients with duodenal diverticula undergo cross-sectional imaging, owing to the onset of biliopancreatic disease symptoms or other complications of duodenal diverticula[2].

Duodenal diverticula are usually easily recognized on CT scan (computed tomography) when completely filled with gas or a combination of fluid and gas[2]. However, the radiologist can potentially misinterpret a duodenal diverticulum as a cystic tumor of the pancreas due to their proximity to the pancreas.

We report a case in which the presenting clinical and imaging findings of initial CT scan were misinterpreted as pancreatic abscess which later on follow up CT scan proved to be a duodenal diverticulum.

CASE REPORT

A 73-year-old Iranian lady with previous medical history of coronary artery bypass grafts (CABG) 12 years ago and hypercholesterolemia, presented to emergency department with epigastric pain radiating to the back, rigors and non-bilious vomiting of one day duration. On clinical examination she had fever of 39 ºC, stable blood pressure and pulse and right upper quadrant tenderness. Her white blood count was 20.5 and serum urea and electrolytes were normal. The cholesterol was elevated measuring 4.25 mg/dl. Her liver enzymes were also elevated (ALT 183, AST 263, TBIL 101). The serum amylase was 856 and two hour urinary amylase was elevated measuring 715 IU/ml.

Admission ultrasound examination showed sludge within the gallbladder with normal wall thickness and bulky pancreas. CT pancreas was done and showed a small round lesion with air / fluid level and wall enhancement within the region of the head of pancreas which was reported as pancreatic abscess (Fig 1). Patient underwent conservative management with antibiotic, had an uneventful hospital stay and was discharged.

Follow-up CT examination of the pancreas showed the cystic lesion to contain oral contrast material and connected to duodenum. Thus, it was diagnosed as duodenal diverticulum (Fig. 2) which was later proved by barium meal examination (Fig. 3).

Patient is now doing fine and under follow-up in surgical outpatient clinic.

DISCUSSION

Radiologists should be familiar with the anatomic variants and disease entities that can mimic primary pancreatic lesion to avoid unnecessary tests and procedures as well as to initiate the required work-up and treatment[3].

After the colon, the duodenum is the second most common location for diverticulae. Duodenal diverticula may be of either the congenital intraluminal or, more commonly, the acquired extrinsic pulsion type. These are actually pseudo-diverticula resulting from

Address correspondence to:
Dr. Khaleda Dashti, Department of Clinical Radiology, Mubarak Al-Kabeer Hospital, Jabriya, Kuwait. Tel: 25312700, ext 6001, Mob: 00965-66091119, E-mail: dashtikh@hotmail.com

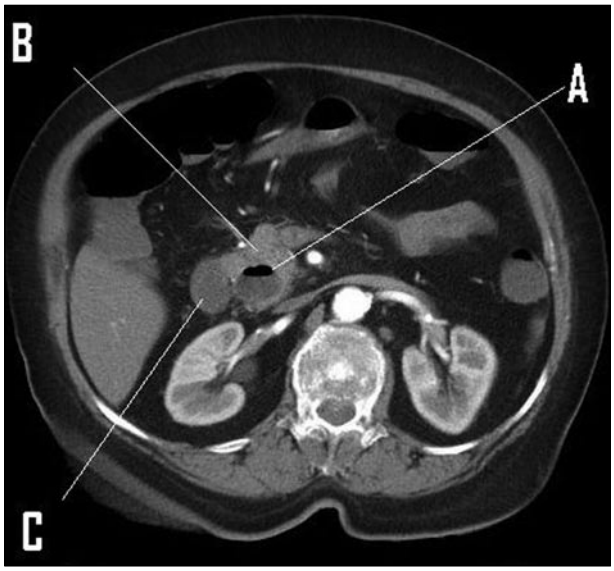

Fig. 1: Initial CT scan of the abdomen shows
A: Cystic lesion with air/fluid level in region of head of pancreas
B: Head of pancreas
C: 2nd part of duodenum

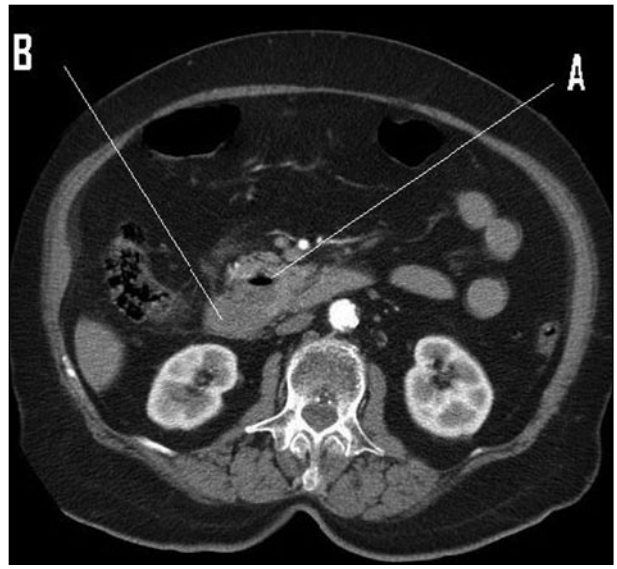

Fig. 2: Follow up CT scan of the abdomen shows
A: Cystic lesion with air / fluid and contrast
B: 2nd part of duodenum

increased intraluminal pressure causing herniation of the mucosa through the muscularis at the point where mesenteric vessels enter the wall[1].

Duodenal diverticula are incidentally discovered on upper gastrointestinal barium examinations in as many as 14.5% of patients and at autopsy in 22% of cadavers[4]. They are easily recognized on upper gastrointestinal barium examinations as collections of gas and barium in round or oval sack-like protrusions that usually arise from the medial aspect of the periampullary duodenum. The typical CT appearance of a duodenal diverticulum has been described as a thin-walled rounded collection of gas and oral contrast material situated along the medial border of the junction of the second and third portions of the duodenum[4].

On T2-weighted MR imaging, duodenal diverticula may contain both high-signal-intensity areas (related to the presence of fluid) and low-signal-intensity areas (related to the presence of gas). It has been reported that prompt oral administration of a super-paramagnetic iron oxide contrast agent allowed the correct diagnosis of duodenal diverticulum in subsequent MRCP images[2].

Duodenal diverticula are asymptomatic until they develop complications. The most frequent are inflammation, hemorrhage, pancreatitis and common bile duct obstruction. Perforation is considered to be the rarest complication, and is also the most serious, with a mortality of up to 20%[5]. They may also present a difficulty while cannulating the common bile duct during an endoscopic retrograde cholangio-pancreaticography (ERCP) procedure[4]. Misinterpretation of a duodenal diverticulum on CT as a pancreatic tumor, metastatic lymph node, pancreatic

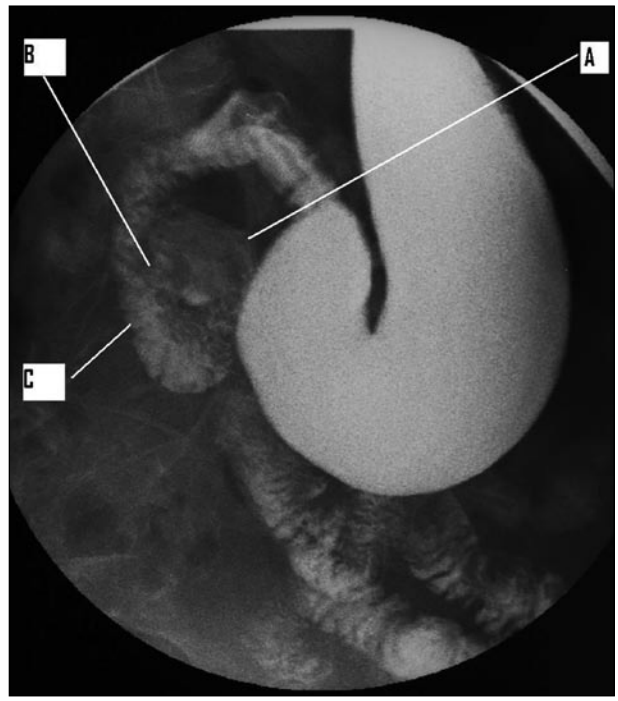

Fig. 3: Barium follow-through study shows
A: Sac of diverticulum
B: Tract between the sac and 2nd part of duodenum
C: 2nd part of duodenum

pseudocyst, or pancreatic abscess has been reported[4]. One may be unable to distinguish duodenal diverticula on CT or MR (magnetic resonance) imaging, if their content is purely fluid.

In a study of duodenal diverticula mimicking cystic pancreatic neoplasms, even retrospectively analyzing the images, they found that with only a single examination and without the benefit of past or future scans, it was not possible to definitively identify the diverticula in some cases[1].

CONCLUSION

A duodenal diverticulum should be considered in the differential diagnosis of any cystic lesion identified between the duodenum and the head of the pancreas on CT or MR imaging.

Thus careful review of imaging studies should always be performed. Further evaluation with barium studies and endoscopy are needed for confirmation prior to any surgical intervention.

REFERENCES

1. Macari M, Lazarus D, Israel G, Megibow A. Duodenal diverticula mimicking cystic neoplasms of the pancreas: CT and MR imaging findings in seven patients. AJR Am J Roentgenol 2003; 180:195-199.
2. Mazziotti S, Costa C, Ascenti G, Gaeta M, Pandolfo A, Blandino A. MR cholangiopancreatography diagnosis of juxtapapillary duodenal diverticulum simulating a cystic lesion of the pancreas: usefulness of an oral negative contrast agent. AJR AmJ Roentgenol 2005; 185:432-435.
3. To'o KJ, Raman SS, Yu NC, *et al*. Pancreatic and peripancreatic diseases mimicking primary pancreatic neoplasia. Radiographics 2005; 25:949-965.
4. Hariri A, Siegelman SS, Hruban RH. Duodenal diverticulum mimicking a cystic pancreatic neoplasm. Br J Radiol 2005; 78:562-564.
5. Martínez Cecilia D, Arjona- Sánchez A, Gomez-Álvarez M, *et al*. Conservative management of perforated duodenal diverticulum: A case report and review of the literature. World J Gastroenterol 2008; 28:1949–1951.

Case Report

Fenofibrate-Induced Rhabdomyolisis in a Dialysis Patient with Subclinical Hypothyroidism: Case Report

Funda Sari, Metin Sarikaya, Ramazan Cetinkaya
Division of Nephrology, Antalya Education and Research Hospital, Ministry of Health, Antalya, Turkey

Kuwait Medical Journal 2011; 43 (3): 227-229

ABSTRACT

Although there have been a few reports regarding fenofibrate-induced rhabdomyolysis in patients with hypothyroidism, there are no data in literature that this could occur in patients with subclinical hypothyroidism. We report a case of subclinical hypothyroidism and end-stage renal failure who presented with rhabdomyolysis while taking fenofibrate for dyslipidemia.

Two weeks after beginning fenofibrate, a 54-year-old male patient with end-stage renal failure was admitted to our hospital with complaints of myalgia and muscle weakness. Laboratory tests revealed a creatine kinase of 51,858 U/l, thyroid stimulating hormone of 10.26 μIU/ml, free T3 3.61 pg/ml, free T4 0.74 ng/dl. Fenofibrate was stopped and tiroxin dosage increased. Hemodialysis was performed four times. During follow-up, serum creatine kinase level decreased to 160 U/l at the end of one week.

Physicians should be aware of potentially lethal adverse effects including rhabdomyolysis after fenofibrate therapy in patients with subclinical hypothyroidism and end-stage renal failure. They should carefully follow-up hepatic and muscle enzymes.

KEY WORDS: dyslipidemia, end-stage renal failure, myalgia

INTRODUCTION

Rhabdomyolysis is a biochemical and clinical syndrome resulting from skeletal muscle injury and the release of muscle cell components into the extracellular compartments[1]. The presenting clinical features are myalgia, myoglobinuria and an elevated serum creatine kinase[2]. Rhabdomyolysis results from inherited muscle enzyme deficiencies, toxins such as alcohol abuse and cocaine, trauma, drugs such as statins, muscle overexertion, infections, and other disorders[3].

Drug-induced rhabdomyolysis occurs rarely. Fenofibrate is a potent hypolipemic agent, widely used in patients with renal insufficiency in whom dyslipidemia is frequent. Rhabdomyolysis with the use of fenofibrate alone has been reported in a few cases[4-6]. Hypothyroidism is a predisposing factor for fenofibrate-induced rhabdomyolysis[7-9]. In hypothyroidism, mitochondrial activity in muscle cell and some metabolic activities including fatty acid catabolism are inhibited[9,10].

CASE REPORT

A 54-year-old male patient was admitted to our hospital with complaints of myalgia and muscle weakness for the last week. His medical history revealed that totally thyroidectomy was performed for treatment of multinodular goiter 15 years ago. He was a case of end-stage renal failure secondary to hypertensive nephropathy treated with continuous ambulatory peritoneal dialysis (CAPD) for about 15 months. He was on aspirin 300 mg, calcium 1000 mg, folic acid 5 mg, amilodipine 10 mg, enapril 20 mg, iron 100 mg, calsitriol 0.5 ug and L-troksin 100 ug per day, and darbepoetin 0.25 ug/kg per week. Micronized fenofibate, 200 mg/day, was added to his medication because of an increasingly poor lipid control in spite of a low lipid diet two weeks ago. Indeed, before the fenofibrate therapy, his total triglyceride was noted to be 782 mg/dl (normal=50-179).

The physical examination was completely normal except for muscle weakness. Routine laboratory tests revealed a creatine kinase (CK) of 51,858 U/l (normal range: 24-195), which was approximately 265 times the upper limit of normal. Further laboratory results showed hemoglobin 11.8 g/dl, white blood cell count 8500 /mm^3, platelet count 317,000 mm^3. The erytrocyte sedimentation rate was 36 mm/h. His blood urea nitrogen (BUN) was 62 mg/dl (normal range: 7 - 18), creatinine 8.5 mg/dl (normal range: 0.7-1.3), fasting blood glucose 90 mg/dl (normal range: 65 - 100), albumin 4 g/dl (3.5 - 5), potassium 4.8 mmol/l (normal range: 3.5 - 5.1), calcium 9.0 mg/dl (normal range: 8.2-10.9), phosphorus 6.4 mg/dl (normal range: 2.7 - 4.5),

Address correspondence to:
Funda Sari, MD, Antalya Education and Research Hospital, Ministry of Health, Division of Nephrology, Antalya, Turkey. Tel: +90 242 2494400 Fax: +90 242 2494462, E-mail: fbahceci@inonu.edu.tr

aspartate aminotransferase (AST) 960 U/l (normal range: 5.0-45), alanine aminotransferase (ALT) 490 U/l (normal range: 5.0 - 45) and lactate dehydrogenase (LDH) 1912 U/l (normal range: 100 - 210). His thyroid stimulating hormone (TSH) serum concentration was 10.26 μIU/ml (normal range: 0.34-5.6), free T3 3.61 pg/ml (normal range: 2.5 - 3.9), free T4 0.74 ng/dl (normal range: 0.54 - 1.12). Fenofibrate was stopped and tiroxin dosage was increased. He was hospitalized for five days and hemodialysis was performed four times. During the follow-up period, serum CK level decreased to 160 U/l at the end of one week.

DISCUSSION

Hypertriglyceridemia is a common metabolic disorder in patients with chronic renal failure. Fenofibrate is a drug of the fibrate class that reduces triglycerides, very low density lipoprotein (VLDL), low density lipoprotein (LDL), and total cholesterol and increases high density lipoprotein (HDL). Fibrate derivatives are often used for lipid lowering in patients with chronic renal failure with adjusted dosage. However, fibrate-related adverse reaction still occasionally occurs. The most important side effect of fenofibrate is rhabdomyolysis[4-6]. Our case had end-stage renal disease and underwent peritoneal dialysis regularly, taking a reduced dosage of fenofibrate (200 mg/d) for refractory hypertriglyceridemia. He did not take any statins, cyclosporine, monoamine oxidase inhibitors, or warfarin concurrently.

Rhabdomyolysis is a biochemical and clinical syndrome resulting from skeletal muscle injury and the release of muscle cell components into the extracellular compartments. In our patient, the presenting clinical features were myalgias, myoglobinuria and an elevated serum creatine kinase. Fulminant rhabdomyolysis may be associated with tubular necrosis, acute renal failure, excessive hyperkalemia and hypocalcemia which may induce further life-thratening complications. Therefore, early diagnosis of rhabdomyolysis is most important for prevention of its potentially life-threatening sequelae like acute renal failure, electrolyte imbalance and shock.

Therapy of drug-induced rhabdomyolysis consists of supportive and specific measures. Withdrawal of the incriminated drug or detoxification in drug overdose should be followed by supportive measures including infusion therapy and correction of dehydration and electrolyte imbalance. Forced diuresis with sodium bicarbonate may protect the kidney function from acidosis and precipitation of myoglobin in tubules. Especially in patients with acute renal failure, hemodialysis is necessary. Fenofibrate treatment was discountinued immediately, hemodialysis was performed four times and serum CK level was decreased to normal range at the end of one week in our patient.

Rhabdomyolysis results from inherited muscle enzyme deficiencies, toxins such as alcohol abuse and cocaine, trauma, drugs such as statins, muscle overexertion, infections, and other disorders[3]. Drug-induced rhabdomyolysis occurs rarely. The development of rhabdomyolysis is rare with only simple fibrate treatment and has been reported in only a few cases. In nearly all of the presented cases, there was a predisposing factor for rhabdomyolysis such as diabetes, older age, renal insufficiency, and hypothyroidism[4-6]. Older age, hypothyroidism, diabetes, taking any drug and renal insufficiency may be a risk factor for rhabdomyolysis associated with fibrates. Fenofibrate is renally metabolized and (80%) is mainly excreted in urine. The tolerability of this drug seems generally good over the short and long term with a normal renal function. Since blood levels of fibric acid derivates and fenofibrate are increased in patients with renal failure, it is recommended to adjust dosage in patients with mild to moderate renal impairment. Rhabdomyolysis was precipitated by micronized fenofibrate which was prescribed at a dosage higher than recommended for renal failure.

Hypothyroidism is a rare cause of rhabdomyolysis. In addition, hypothyroidism is a predisposing factor for fenofibrate-induced rhabdomyolysis[7-9]. The precise pathophysiology remains unclear. Myolysis in hypothyroidism is caused by changes in muscle fibres from fast twitching type II to slow twitching type I fibres, deposition of glucosaminoglicans, poor contractility of actin-myosin units, low myosin ATPase activity and low ATP turnover in skeletal muscle. In hypothyroidism, there is an inhibition of mitochondrial activity in muscle cells as well as many metabolic pathways such as Krebs cycle, fatty acid catabolism and glycolytic energy production[7,8]. It seems that these underlying metabolic anomalies may sensitize the patient to the muscular adverse effects of fenofibrate. Although there have been a few reports that fenofibrate-induced rhabdomyolysis occurs in patients with hypothyroidism[7-9], there are no data in the literature that this occurs in patients with subclinical hypothyroidism. Our patient had subclinical hypothyroidism and end-stage renal failure and was on chronic renal replacement therapy while taking fenofibrate prescribed for his dyslipidemia. This led to the development of rhabdomyolysis.

CONCLUSION

Physicians should be aware of potentially lethal adverse effects including rhabdomyolysis after fenofibrate therapy in a patient with end-stage renal failure on chronic renal replacement therapy. Furthermore, they should carefully follow-up renal, hepatic, thyroid functions, and muscle enzymes in all

patients. Also, patients should be informed about risks and about symptoms of potential adverse effects of the fenofibrate such as myalgia and muscle weakness.

REFERENCES

1. Singh D, Chander V, Chopra K. Rhabdomyolysis. Methods Find Exp Clin Pharmacol 2005; 27:39-48.
2. Coco TJ, Klasner AE. Drug-induced rhabdomyolysis. Curr Opin Pediatr 2004; 16:206-210.
3. Melli G, Chaudhry V, Cornblath DR. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore) 2005; 84:377-385.
4. Barker BJ, Goodenough RR, Falko JM. Fenofibrate monotherapy induced rhabdomyolysis. Diabetes Care 2003; 26:2482-2483.
5. Archambeaud_Mouveroux F, Lopez S, Combes C, *et al*. Rhabdomyolysis induced by fenofibrate monotherapy. Rev Med Interne 2006; 27:573-574.
6. Yang KC, Fang CC, Su TC, Lee YT. Treatment of fibrate-induced rhabdomyolysis with plasma exchange in ESRD. Am J Kidney Dis 2005; 45:e57-e60.
7. Satarasinghe RL, Ramesh R, Riyaaz AA, Gunarathne PA, de Silva AP. Hypothyroidism is a predisposing factor for fenofibrate-induced rhabdomyolysis - patient report and literature review. Drug Metabol Drug Interact 2007; 22:279-283.
8. Clouatre Y, Leblanc M, Ouiment D, Pichette V. Fenofibrate-induced rhabdomyolysis in two dialysis patients with hypothyroidism. Nephrol Dial Transplant 1999; 14:1047-1048.
9. Kursat S, Alici T, Colak HB. A case of rhabdomyolysis induced acute renal failure secondary to statin-fibrate-derivate combination and occult hypothyroidism. Clin Nephrol 2005; 64:391-393.
10. Schlienger JL, Goichot B, Grunenberger F, Pradignac A. Thyroid myopathy disclosed by a fibrate. Rev Med Interne 1997; 18:167-170.

Case Report

Splenic Vein Thrombosis: A Rare Complication of Celiac Disease

Anwar QKHS Alenezi[1], Jamal Monzer Hilal[2], Ali Mahmoud Behbehani[2],
[1]Department of Gastroenterology and Hepatology, Al-Jahra Hospital, Kuwait
[2]Department of Internal Medicine, Al-Jahra Hospital, Kuwait

Kuwait Medical Journal 2011; 43 (3): 230-233

ABSTRACT

The principal cause of splenic vein thrombosis (SVT) is pancreatic disease. Isolated splenic vein thrombosis (ISVT) is a very rare complication of celiac disease. Only few cases are reported worldwide. Affected patients develop left-sided portal hypertension often complicated by splenomegaly and isolated gastric varices. The condition is usually asymptomatic, but patients may complain of non-specific abdominal pain. Gastric variceal bleeding in this context is uncommon but should it occur, it could be life threatening and splenectomy would be the treatment of choice. The role of anticoagulation is controversial and the risk of further thrombotic events must be balanced against that of variceal bleed.

We report a case of a patient with celiac disease (CD) who presented with a new onset non-specific abdominal pain, who was found to have ISVT complicated by portal hypertension, splenomegaly and non-bleeding isolated gastric varices. He was successfully managed with anticoagulation.

KEY WORDS: anticoagulation, celiac disease, gastric varices, splenic vein thrombosis

INTRODUCTION

The most common cause of splenic vein thrombosis (SVT) is pancreatic disease. Other causes include umbilical vein catheterization, inherited and acquired hypercoagulable states, abdominal surgery, retroperitoneal fibrosis, benign gastric ulcers and renal cysts[1,2]. Affected patients develop splenomegaly and gastric varices secondary to left-sided portal hypertension in the absence of liver cirrhosis.

SVT is a rare presentation of celiac disease (CD). Although the association has long been reported, the exact pathophysiology is not well understood.

Patients can have life-threatening variceal bleeding. Management, which is not well-defined in the literature, is not without risks.

CASE REPORT

A 38-year-old Pakistani gentleman presented in January 2005 to his local hospital in Pakistan complaining of chronic diarrhea and weight loss. An upper gastrointestinal (GI) endoscopy showed proximal small bowel villous atrophy. Duodenal biopsies revealed subtotal villous atrophy with mild lymphocytic infiltration of the intraepithelial cells. He had positive antigliadin antibodies (AGA), and was therefore diagnosed with CD. He was advised to adhere to a gluten free diet. Initially the patient experienced marked symptomatic improvement, but few months later he moved to Kuwait where he failed to adhere to a Gluten free diet and eventually relapsed.

He presented to our hospital in Kuwait in March 2006 complaining of fatigue and chronic cramping abdominal pain associated with loose bowel motions. He also reported abdominal distension with swelling of both lower limbs. He gave no history of weight loss or GI bleeding. On examination he had splenomegaly with shifting dullness and bilateral pitting lower limbs edema. He had no lymphadenopathy or signs of chronic liver disease. His laboratory investigations (Table 1) revealed pancytopenia with hypocalcemia, hypoalbuminemia and low serum ferritin and red cell folate. He had a normal coagulation profile. Stool analysis for infection and occult blood (OB) was negative. His celiac serology was strongly positive. A repeat upper GI endoscopy showed isolated ectopic gastric varices without endoscopic features of high variceal bleed risk. This finding raised the suspicion of thrombosis in the splanchnic circulation. An ultrasound scan of the abdomen confirmed the presence of portal hypertension with splenomegaly and ascites in the absence of liver cirrhosis. Doppler studies demonstrated splenic vein occlusion with multiple collaterals. A CT angiography of the abdomen (Fig. 1) confirmed the above findings beyond doubt.

Address correspondence to:
Ali Behbehani, MRCP (UK), Department of Internal Medicine, Al-Jahra Hospital, Kuwait. Tel: 00965-9751 7551, E-mail: allbah@hotmail.com

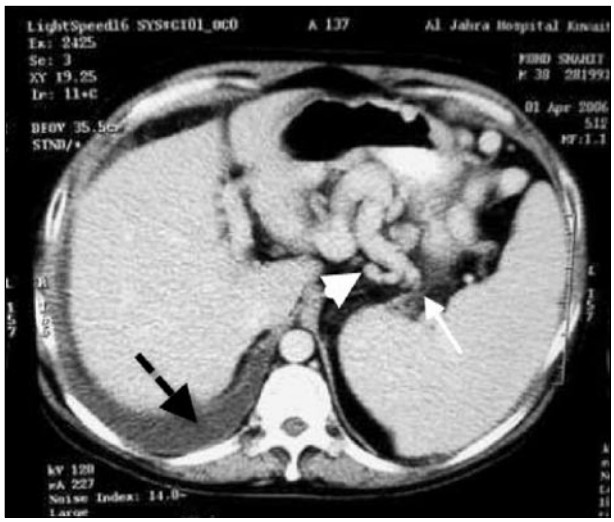

Fig. 1: Abdominal CT angiography showing splenomegaly, splenic vein thrombosis near the hilum (white arrow), collaterals (arrow head), and ascites (black dashed arrow)

Thrombophilia screen and hepatitis B and C serology were all negative. Ascitic fluid analysis revealed a transudate with a serum to ascitic albumin gradient (SAAG) > 11 g/l, consistent with portal hypertension. The patient was diagnosed with CD complicated by ISVT and left-sided portal hypertension. The pros and cons of anticoagulation were explained to the patient, and with his consent we started anticoagulation. Subcutaneous low molecular weight heparin was given first followed by warfarin, aiming for an international normalized ratio (INR) of 2 - 3. Stool OB was checked several times after anticoagulation and remained persistently negative. Hemoglobin levels were also stable and hence splenectomy was deferred.

DISCUSSION

CD is an immune-mediated enteropathy caused by sensitivity to gluten in genetically susceptible individuals[1]. The clinical presentation is highly variable, ranging from the classical malabsorption syndrome to an atypical disease; where extra-intestinal manifestations predominate. The disease can also run subclinical and latent courses [2].

CD is usually complicated by splenic atrophy with secondary hyposplenism and the appearance of Howell-Jolly bodies in the blood film, a complication that may lead to fatal infections by encapsulated bacteria[3-4].

Our patient had paradoxical splenomegaly with hypersplenism and secondary pancytopenia. His low serum ferritin and red cell folate may have also contributed to the cytopenia. Isolated gastric varices denote a left-sided portal hypertension. This picture should always alert the caring physician to the possibility of isolated splenic vein thrombosis (ISVT), a complication rarely seen in CD[5].

Other rare thrombotic phenomena reported in CD include: portal vein thrombosis[6], cerebral venous thrombosis[7], central retinal vein occlusion[8], deep venous thrombosis (DVT) of the legs[9], and Budd-Chiari syndrome[10-12].

The mechanism of thrombosis in CD is not clear. Case reports have occasionally stated a clear etiology such as antiphospholipid antibodies, anticardiolipin antibodies, lupus anticoagulant[13], protein S deficiency and hyperhomocysteinemia. However, except for hyperhomocysteinemia secondary to nutritional deficiencies (folate, B12, B6) and malabsorption[14-15], it is not clear whether these etiological factors are coincidental findings

Table 1: The patient's laboratory results

Test	Result	Normal range	Test	Result	Normal range
Hb	11.4 g/dl	13.6 - 17.5	AGA (IgA)	56 U/ML	< 30
MCV	72.3	80 - 100	(IgG)	14 U/ML	< 30
Total WCC	3.1 x 10^9/l	4.8 - 10.8	AEA	positive	Negative
Platelets	146 x 10^9/l	150 - 450	Anti tTG	23 U/mL	0 - 15 U/mL
ESR	21 mm/hr	< 10	ANA	Negative	
INR	1.119		Anti phospholipid	Negative	
Total protein	55.9 g/l	60 - 82	Anti cardiolipin	Negative	
Albumin	23.9 g/l	35 - 55	Lupus anticoagulant	29.0 S	26.3 - 46.3
Corrected calcium	1.7 mmol/l	2.1 - 2.6	Factor V Leiden	2.919 R	2.2 - 3.5
Phosphorus	1.01 mmol/l	0.8 - 1.6	Protein C	84.4%	70 - 140
ALP	142 IU/l	26 - 121	Protein S	79.6%	60 - 140
Glucose	4.71 mmol/l	3.9 - 6.1	Antithrombin	109%	71 - 115
Serum B12	210 pmol/l	133 - 675	Ascitic fluid		
Red cell folate	240 nmol/l	>372	Total wcc	110 cells/mm3	< 500
Ferritin	16 ug/l	20 - 400	Protein	12.9 g/L	
Plasma homocysteine	9.1 Mm/l	4 - 11.2 Mm/l	Albumin	< 10 g/L	
Urine homocysteine	Negative	Negative	Glucose	7.15 mmol/L	

Hb: hemoglobin, MCV: mean corpuscular volume, WCC: white cell count, ESR: erythrocyte sedimentation ratio, INR: international normalized ratio, ALP: alkaline phosphatase, AGA: anti-gliadin antibody, AEA: anti-endomyseal antibody, tTG: tissue transglutaminase, ANA: antinuclear antibody

or a manifestation of an autoimmune phenomenon. Our patient had normal homocysteine levels despite a low red cell folate.

Some authors suggested that factors such as dehydration and hyperviscosity due to high levels of circulating antibodies may predispose to thrombosis. In our case, the patient was not dehydrated, and although plasma viscosity was not checked, his ESR was low, voting against hyperviscosity.

Hypoalbuminemia is an important factor which (in our opinion) is often overlooked. Low circulating albumin causes extravasation of intravascular fluid, which in turn decreases plasma volume, and may predispose to thrombosis. Indeed, our patient had clear manifestation of fluid redistribution with ascites and lower limb edema. This, however, does not explain why patients with occult CD can still have thrombotic events.

Another interesting phenomenon is the homology between different forms of transglutaminase and coagulation factor XIII[16]. Some patients with CD have circulating IgA antibodies against Factor XIII. Although this has not been shown to lead to a hypercoagulable state, it nonetheless signals a connection between CD and the coagulation cascade.

The CT angiography in our patient excluded the possibilities of malignancy, pancreatic and renal diseases. The negative thrombophilia screen excluded the possibility of hereditary and acquired thrombophilic disorder, leaving CD as the sole cause.

Old methods of diagnosis of ISVT include spleno-portography. More recently late-phase celiac angiography and endoscopic ultrasonography have emerged as the investigations of choice[17,18]. Computed tomography, magnetic resonance, and ultrasound imaging are also used[19].

The natural history of ISVT is not well-documented. Older studies have suggested that ISVT results in a high likelihood of gastric variceal bleeding necessitating splenectomy. Advances in cross-sectional imaging have led to the identification of SVT in patients with minimal symptoms[19].

Heider *et al* demonstrated that gastric variceal bleeding occurs in only 4% of patients, suggesting that splenectomy should not be done routinely[20]. Thus, splenectomy was deferred in our patient.

The risk of major variceal hemorrhage is increased with warfarin therapy, and therefore some authors advise against it[21]. On the other hand, Ikeda *et al* found that patients with total SVT are at greater risk for thrombus propagation, and therefore, they are candidates for anticoagulation therapy[22]. Other authors recommend acute and chronic anticoagulation for SVT particularly when an underlying hypercoagulable condition is present[23].

Our patient had active disease due to non-compliance with gluten-free diet, resulting in a hypercoagulable state[24]. The aim of anticoagulation was to prevent further thrombus propagation and to aid recanalization until the disease goes into remission[25]. We were encouraged by the absence of endoscopic features of high variceal bleed risk[26] and the normal coagulation profile.

There is no clear evidence-based guidance for the duration and degree of anticoagulation in such cases. Our patient was anticoagulated for a total of six months to achieve an INR of 2 - 3. We are following him up closely for any signs of bleeding, and we intend to do a follow up endoscopy and CT angiography to assess his disease regression.

Splenectomy is the treatment of choice, should he bleed[27]. Sclerotherapy and gastric variceal banding have also been done successfully[28]. Splenic arterial embolization is not well studied and is associated with splenic abscess formation. It is performed in patients with high operative risk and those with diffuse metastatic disease[29].

CONCLUSION

Splenic vein thrombosis is a very rare complication of active and occult CD. The pathophysiology of thrombosis in CD is not clearly defined. Left-sided portal hypertension, splenomegaly with hypersplenism and gastric varices can occur, and rarely, can have fatal consequences. Splenectomy is the treatment of choice in the event of gastric variceal bleeding. The role of anticoagulation in such cases is not well-defined and need to be tailored to each case.

REFERENCES

1. Hill ID, Dirks MH, Liptak GS, *et al*. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005; 40:1-19.
2. Ferguson A, Arranz E, O'Mahony S. Clinical and pathological spectrum of celiac disease - active, silent, latent, potential. Gut 1993; 34:150-151.
3. Johnston SD, Robinson J. Fatal pneumococcal septicaemia in a celiac patient. Eur J Gastroenterol Hepatol 1998; 10:353-354.
4. Di Sabatino A, Rosado MM, Cazzola P, *et al*. Splenic hypofunction and the spectrum of autoimmune and malignant complications in celiac disease. Clin Gastroenterol Hepatol 2006; 4:179-186.
5. Andrès E, Pflumio F, Knab MC, *et al*. Splenic thrombosis and celiac disease: a fortuitous association? Presse Med. 2000; 29:1933-1934.
6. Karoui S, Sfar S, Kallel M, Boubaker J, Makni S, Filali A. Antiphospholipid syndrome revealed by portal vein thrombosis in a patient with celiac disease. Rev Med Interne 2004; 25:471-473.

7. Bahloul M, Chaari A, Khlaf-Bouaziz N, *et al*. Celiac disease, cerebral venous thrombosis and protein S deficiency, a fortuitous association? J Mal Vasc 2005; 30:228-230.
8. Lee ES, Pulido JS. Nonischemic central retinal vein occlusion associated with celiac disease. Mayo Clin Proc 2005; 80:157.
9. Beyan E, Pamukcuoglu M, Beyan C. Deep vein thrombosis associated with celiac disease. Bratisl Lek Listy 2009; 110:263-264.
10. Danalioglu A, Poturoglu S, Gungor Gulluoglu M, *et al*. Budd-Chiari syndrome in a young patient with celiac sprue: a case report. Turk J Gastroenterol 2003; 14:262-265.
11. Khanna S, Chaudhary D, Kumar P, Mazumdar S. Occult celiac disease presenting as splenic vein thrombosis. Indian J Gastroenterol. 2008; 27:38-39.
12. Moosa AR, Gadd MA. Isolated splenic vein thrombosis. World J Surg 1985; 9:348-390.
13. Chiurazzi F, Poggi V, Greco L, Rotoli B. Lupus anticoagulant and celiac disease: a case report. Haematologica 1987; 72:257-259.
14. Saibeni S, Lecchi A, Meucci G, *et al*. Prevalence of hyperhomocysteinemia in adult gluten-sensitive enteropathy at diagnosis: role of B12, folate, and genetics. Clin Gastroenterol Hepatol 2005; 3:574-580.
15. Kremer Hovinga JA, Baerlocher G, Wuillemin WA, Solenthaler M. Deep venous thrombosis of the leg in acquired thrombophilia--hyperhomocysteinemia as a sequela of undetected celiac disease. Ther Umsch 1999; 56:519-522.
16. Sjober K, Eriksson S, Tenngart B, Roth EB, Leffler H, Stenberg P. Factor XIII and tissue transglutaminase antibodies in celiac and inflammatory bowel disease. Autoimmunity 2002; 35:357-364.
17. Koklu S, Koksal A, Yolcu OF *et al*. Isolated splenic vein thrombosis: an unusual cause and review of the literature. Can J Gastroenterol 2004; 18:173-174.
18. Weber SM, Rikkers LF. Splenic vein thrombosis and gastrointestinal bleeding in chronic pancreatitis. World J Surg 2003; 27:1271-1274.
19. Lewis JD, Faigel DO, Morris JB, Siegelman ES, Kochman ML. Splenic vein thrombosis secondary to focal pancreatitis diagnosed by endoscopic ultrasonography. J Clin Gastroenterol 1998; 26:54-56.
20. Heider TR, Azeem S, Galanko JA, Behrns KE. The natural history of pancreatitis-induced splenic vein thrombosis. Ann Surg 2004; 239:876-880.
21. Thatipelli MR, McBane RD, Hodge DO, Wysokinski WE. Survival and recurrence in patients with splanchnic vein thromboses. Clin Gastroenterol Hepatol 2009. [Epub ahead of print]
22. Ikeda M, Sekimoto M, Takiguchi S, *et al*. Total splenic vein thrombosis after laparoscopic splenectomy: a possible candidate for treatment. Am J Surg. 2007; 193:21-25.
23. Kitchens CS, Alving BM, Kessler CM. Consultative hemostasis and thrombosis. Philadelphia, Saunders, 2002; 229.
24. Florholmen J, Waldum H, Nordøy A. Cerebral thrombosis in two patients with malabsorption syndrome treated with vitamin K. Br Med J 1980; 281:541.
25. Sogaard KK, Astrup LB, Vilstrup H, Gronbaek H. Portal vein thrombosis; risk factors, clinical presentation and treatment. BMC Gastroenterol 2007 15; 7:34.
26. Lee CH, Lee JH, Choi YS, *et al*. Natural history of gastric varices and risk factors for bleeding. Korean J Hepatol 2008; 14:331-341.
27. Bradley EL 3rd. The natural history of splenic vein thrombosis due to chronic pancreatitis: indications for surgery. Int J Pancreatol 1987; 2:87-92.
28. Dhiman RK, Chawla Y, Taneja S, Biswas R, Sharma TR, Dilawari JB. Endoscopic sclerotherapy of gastric variceal bleeding with N-butyl-2-cyanoacrylate. J Clin Gastroenterol 2002; 35: 222-227.
29. Covarelli P, Badolato M, Boselli C, *et al*. Splenic vein thrombosis complicated by massive gastric bleeding: treatment with arterious embolization. Am Surg 2008; 74:184-186.

Case Report

Traumatic Anterior Hip Dislocation (Perineal) with Ipsilateral Avulsion Fracture of the Greater and Lesser Trochanter in an Adolescent

Janko Heberle
Department of Orthopedics, Al Razi Orthopedic Hospital, Kuwait

Kuwait Medical Journal 2011; 43 (3): 234-237

ABSTRACT

A 14-year-old boy was involved in a road traffic accident as a front seat passenger. He sustained multiple injuries, including anterior (perineal) dislocation of the right hip with an ipsilateral avulsion fracture of the greater and lesser trochanter and a contralateral segmental fracture of the femur. After resuscitation and radiological evaluation a trial of closed reduction was performed under general anesthesia, but this was unsuccessful, necessitating open reduction of the dislocated hip and fixation of the segmental fracture of the left femur. The postoperative period was uneventful. The patient commenced full weight bearing four months after the injury. He developed avascular necrosis of the head of the right femur four months later.

KEY WORDS: femur head necrosis, high energy trauma, open reduction

INTRODUCTION

Traumatic dislocations of the hip in childhood are rare, the incidence being 10% of all traumatic hip dislocations[1,2]. Anterior hip dislocations represent around 10-15% of all traumatic hip dislocations in children[2,3], with the perineal variant being extremely rare. Barquet[4] mentioned only one case in his series of 80 documented anterior hip dislocations. Only a few cases have been reported in the literature[4,5].

Late complications are avascular necrosis of the head of the femur, myositis ossificans, osteoarthrosis and premature physeal arrest[6-8]. The commonest of these is avascular necrosis, with ratios of 3-15% reported in the literature[8].

CASE REPORT

A 14-year-old boy was involved in a road traffic accident as a front seat passenger. At the time of the accident the back of his seat was in the horizontal position, he was lying on the seat and was not wearing a seat belt. During the accident he was catapulted through the front window.

On arrival at the hospital, the patient was confused, he had multiple small cut wounds over the face, a swollen, bleeding nose, and his pupils were equal. His right lower limb was in extreme abduction, external rotation and knee flexion. The head of the femur was palpable in the area of the symphysis pubis. There was no vascular or nerve injury. He had a severe deformity of the left thigh with abnormal mobility and crepitus. After resuscitation, the patient's condition stabilized. Brain computed tomography (CT) showed a small intracerebral hematoma, and radiographs revealed a nasal bone fracture, anterior right hip dislocation (perineal variant), with an avulsion fracture of the greater and lesser trochanter (Fig. 1) and a contralateral segmental fracture of the femur.

The patient was immediately taken to the operating theater. Under general anesthesia a trial of closed reduction of the dislocation was performed, but this was unsuccessful, necessitating a surgical procedure. The hip was explored through an anterolateral approach. The surgical findings were: dislocation of the femoral head into the region of the symphysis pubis, separation of the greater and lesser trochanter, complete tear of the articular capsule (anterior and posterior), tear of the ligamentum teres and interposition of the adductor muscles. After reduction of the dislocation, the avulsed greater trochanter fell back into place. Fixation of the contralateral femoral fracture was performed at the same time.

Address correspondence to:
Dr Janko Heberle, Al Razi Orthopedic Hospital, Ministry of Health, P O Box 4235, 13043 Safat, Kuwait. Tel: +965 66239815, Fax: +965 24844240, E-mail: jankoheberle@hotmail.com

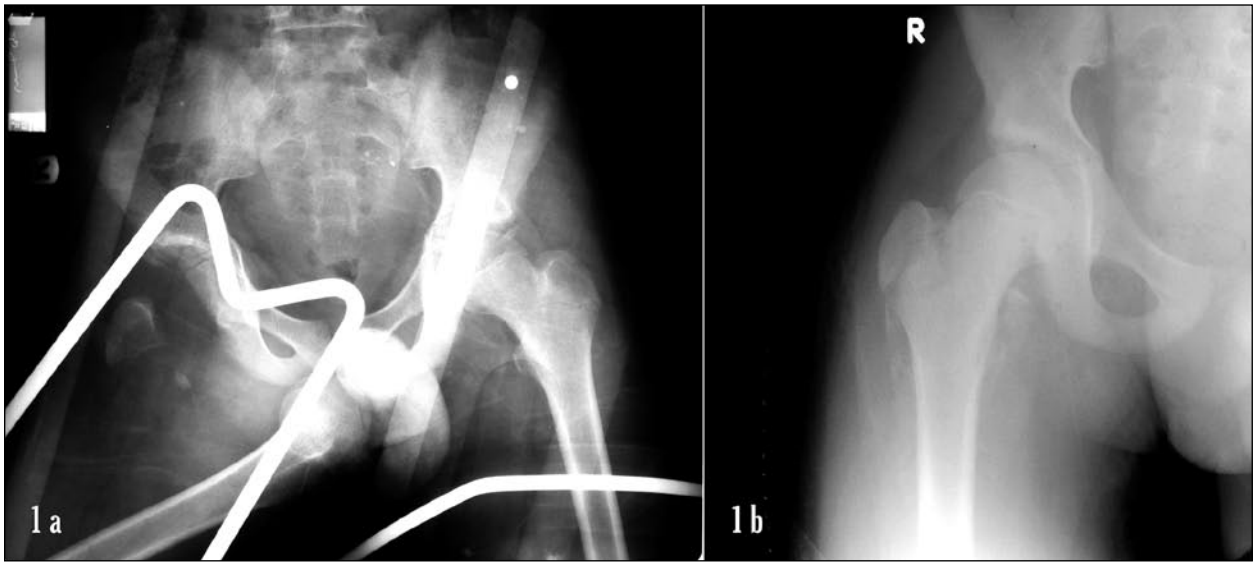

Fig. 1: Anteroposterior radiograph of the pelvis, presenting perineal right hip dislocation with ipsilateral avulsion fracture of the greater and lesser trochanter of the right femur before (a) and after (b) surgical procedure

The postoperative period was uneventful, with no sign of infection. The patient was treated with skeletal traction for five weeks, after which he was mobilized in bed. Walking was not permitted till the contralateral segmental fracture was healed. He started full weight bearing four months after the injury (Fig. 2). He was regularly followed up in the outpatient clinic and had regular magnetic resonance imaging screening. Eight months after the injury the patient started to complain about right hip pain, at first only on putting weight and later even when resting. Follow up radiographs proved avascular necrosis of the femoral head (Fig. 3).

He was advised avoidance of strain and weight bearing, physiotherapy, nonsteroidal anti-inflammatory drugs and close follow-up. In case of deterioration, he might need further surgical interference including core decompression and vascularized bone graft.

DISCUSSION

Traumatic hip dislocation in children is rare. Under the age of five years, it can occur following trivial trauma. Canale and King[9] noted that in this age group, the acetabulum is soft and pliable. Such an anatomical situation and additional generalized joint laxity can lead to hip dislocation after minimal trauma. If the hip is properly reduced without delay, avascular necrosis of the femoral head is an uncommon complication[9].

Over the age of five years, the hip joint is stable and considerable forces are necessary to provoke dislocation[10]. Epstein[1] and Pringle[11] stated that the most important factor producing anterior hip dislocation is forcible abduction combined with external rotation. This tends to force the femoral head forward through the capsule, while as a result of abduction, the femoral neck impinges upon the acetabular rim and the head is levered out of its socket through the anterior capsule. The occurrence of an associated avulsion fracture of the greater trochanter could be explained by the greater trochanter being driven against the acetabular rim. This might become detached as the head and neck of the femur move forward and inward during dislocation[4]. The avulsion fracture of the lesser trochanter could be explained on the basis of traction between the ileopsoas muscle, attached onto the lesser trochanter, and the proximal femur which is displaced medially[12]. Closed reduction of a fresh dislocation is usually effective. Offierski[13] reported that closed reduction failed in five out of 33 cases of traumatic hip dislocation, while Canale and Manugian[14] reported failure in nine out of 54 cases. Interposition of soft tissue and osteo-cartilaginous loose bodies could be responsible. Failure of closed reduction is an indication for operative treatment[4,15,16].

The surgical approach should be from the direction of the dislocation. Anterior dislocations should be approached anteriorly and posterior dislocations posteriorly to preserve the blood supply in the posterior or anterior capsule[17].

Avascular necrosis is not common occurring in 3 -15% of cases[8]. The incidence after anterior dislocation in a large series is similar to that in posterior dislocation[4]. It can occur or become evident between three weeks and 28 months after the injury[18]. The main blood supply for the femoral head runs through the posterior capsule, and when the head dislocates forward, the vessels distract or even tear because the distance between the posterior capsule and the femoral head is increased[4].

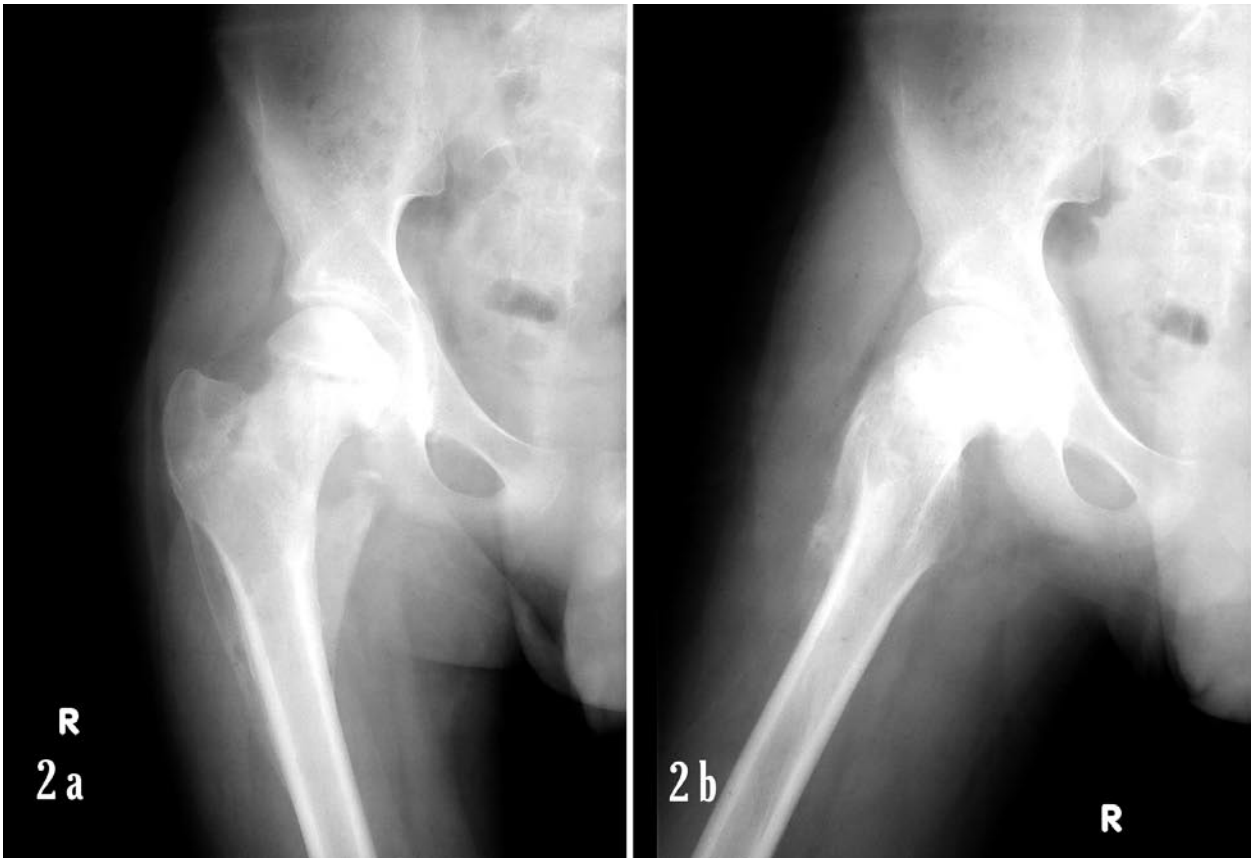

Fig. 2: Anteroposterior (a) and lateral (b) radiographs of the right hip four months after injury, presenting healed avulsed fractures of the greater and lesser trochanter and viable head of the right femur

Early diagnosis and treatment of the dislocation decrease the incidence. Delay in reduction (more than six hours), repeated attempts at closed reduction, open reduction, severity of the injury, presence of fracture dislocation, and age above five years are the most important factors implicated in the development of avascular necrosis[8,9,19,20]. The lowest incidence occurs in children under five years of age[9]. The recommended non-weight bearing period varies from four to six weeks[21] to as much as four months after reduction of the dislocation[15]. Several authors have documented that a prolonged non-weight bearing period does not significantly influence the development of the femoral head necrosis[22,23].

We assume that the decisive factor in the development of avascular necrosis in our patient was the severity of the injury, as the dislocation was perineal, with an additional avulsion fracture of the

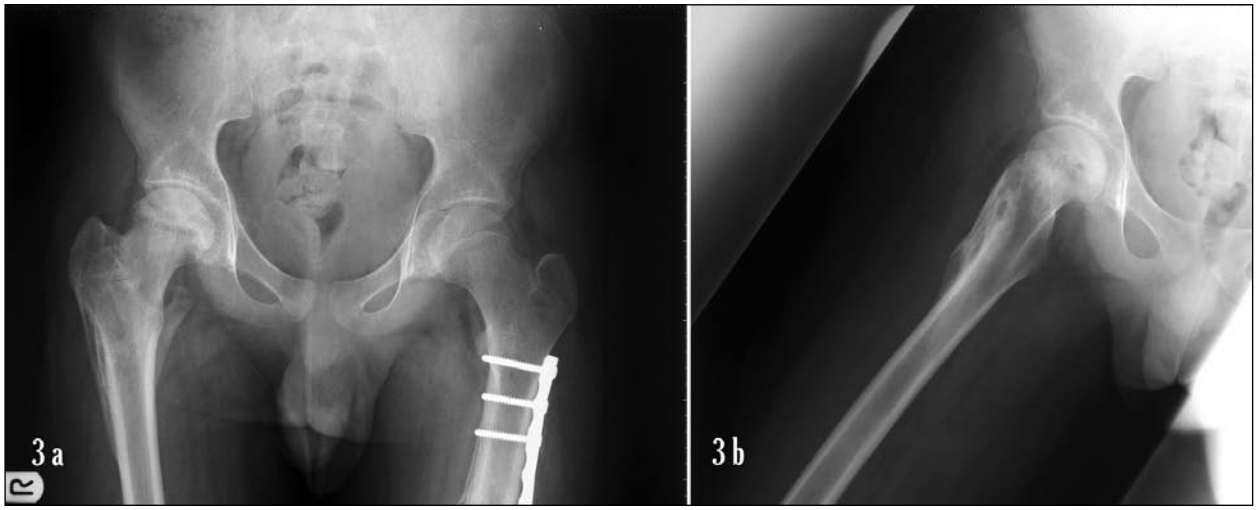

Fig. 3: Avascular necrosis of the right femoral head eight months after the injury, seen on anteroposterior (a) and lateral (b) radiographs

greater and lesser trochanter, tearing of the articular capsule and ligamentum teres and interposition of the adductor muscles. Apart from his age (14 years), there were no other risk factors.

CONCLUSION

Traumatic anterior dislocation of the hip in childhood is very rare, with the perineal variant being extremely rare. Closed reduction should be performed under general anesthesia. If unsuccessful, a surgical procedure should then be performed immediately, as was necessary in our patient. Avascular necrosis, although not very common, is the most serious complication. We assume that the severity of the injury played a decisive role in the development of this complication in our patient, who had no risk factors apart from age.

REFERENCES

1. Epstein HC. Traumatic dislocation of the hip. Clin Orthop 1973; 92:116-142.
2. Thompson VP, Epstein HC. Traumatic dislocation of the hip; a survey of two hundred and four cases covering a period of twenty one years. J Bone Joint Surg Am 1951; 33:746-788.
3. DeLee JC, Evans JA, Thomas J. Anterior dislocation of the hip and associated femoral head fractures. J Bone Joint Surg Am 1980; 62:960-964.
4. Barquet A. Traumatic anterior dislocation of the hip in childhood. Injury 1982; 13:435-440.
5. Sabat D, Singh D, Kumar V, Gupta A. Open perineal dislocation of hip in a child. Eur J Orthop Surg Traumatol 2009; 19:277-279.
6. Vialle R, Odent T, Pannier S, Pauthier F, Laumonier F, Glorion C. Traumatic hip dislocation hip in childhood. J Pediatr Orthop 2005; 25:138-144.
7. Salisbury RD, Eastwood DM. Traumatic dislocation of the hip in children. Clin Orthop Relat Res 2000; 377:106-111.
8. Mehlman CT, Hubbard GW, Crawford AH, Roy DR,Wall EJ. Traumatic hip dislocation in children. Long term followup of 42 patients. Clin Orthop Relat Res 2000; 376:68-79.
9. Canale ST, King RE. Pelvic and hip fractures. In: Rockwood CA, Wilkins RE, editors. Fractures in children. 3rd Ed. Philadelphia: Lippincott; 1991. p1093-1120.
10. Reggiori A, Brugo G. Traumatic anterior hip dislocation associated with anterior and inferior iliac spines avulsions and a capsular-labral lesion. Strategies Trauma Limb Reconstr 2008; 3:39-43.
11. Pringle JH. Traumatic dislocation at the hip joint. An experimental study in the cadaver. Glasgow Med J 1943; 21:25-40.
12. Metzmaker JN, Pappas AM. Avulsion fractures of the pelvis. Am J Sports Med 1985; 13:349-358.
13. Offierski CM. Traumatic dislocation of the hip in children. J Bone Joint Surg Br 1981; 63:194-197.
14. Canale ST, Manugian AH. Irreducible dislocations of the hip. J Bone Joint Surg Am 1979; 61: 7-14.
15. Funk FJ. Traumatic dislocation of the hip in children: factors influencing prognosis and treatment. J Bone Joint Surg Am 1962; 44:1135-1145.
16. Litton LO, Workman C. Traumatic anterior dislocation of the hip in children. J Bone Joint Surg Am 1958; 40:1419-1422.
17. Herrera-Soto JA, Price CT. Traumatic hip dislocations in children and adolescents: pitfalls and complications. J Am Acad Orthop Surg 2009; 17:15-21.
18. Heinrich SD. Proximal femur fractures: hip dislocations, In: MacEwen GD, Kasser JR, Heinrich SD, editors. Pediatric fractures: a practical approach to assessment and treatment. Baltimore: Lippincott Williams & Wilkins; 1993. p272-277.
19. Yamamoto K, Ko M, Masaoka T, Shishido T, Imakiire A. Traumatic anterior dislocation of the hip associated with ipsilateral femoral shaft fracture in a child: a case report. J Orthop Surg (Hong Kong) 2004; 12:126-132.
20. Blasier RD, Hughes LO. Hip dislocation in children. Fractures and traumatic dislocations of the hip in children, In: Beaty JH, Kasser JR, editors. Rockwood and Wilkins' fractures in children. 5th Ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p929-939.
21. Glass A, Powell HD. Traumatic dislocation of the hip in children: an analysis of forty- seven patients. J Bone Joint Surg Br 1961; 43:29-37.
22. Sahin V, Karakas ES, Aksu S, Atlihan D, Turk CY, Halici M. Traumatic dislocation and fracture-dislocation of the hip: a long-term follow-up study. J Trauma 2003; 54:520-529.
23. Hougaard K, Thomsen PB. Traumatic posterior dislocation of the hip - prognostic factors influencing the incidence of avascular necrosis of the femoral head. Arch Orthop Trauma Surg 1986; 106:32-35.

Case Report

Acquired Factor VIII Inhibitor in a Patient with Mixed Connective Tissue Disease: A Case Report

Ekhlas Alhumoud[1], Hani Al-Humoud[1], Hana Mohammad Abdulla[2]
[1]Department of Medicine, Mubarak Al-Kabeer hospital, Kuwait
[2]Department of Surgery, Al-Sabah hospital, Kuwait

Kuwait Medical Journal 2011; 43 (3): 238-240

ABSTRACT

Acquired hemophilia is an uncommon complication of rheumatologic diseases. We report a rare presentation of a patient who developed bruising and bleeding three years after the onset of mixed connective tissue disease. We demonstrated the presence of an inhibitor to Factor VIII which disappeared promptly and completely in association with an increase in corticosteroid therapy.

KEY WORDS: acquired hemophilia, factor VIII inhibitor, mixed connective tissue disease

INTRODUCTION

Anti factor VIII antibody is the most commonly recognized autoantibody directed against a clotting factor[1]. The synthesis of inhibitors depends upon the activation of CD4 (helper) T cells specific for factor VIII. Factor VIII inhibitors are usually of mixed immunoglobulin subclass with a dominant IgG4 fraction. These inhibitors typically bind to several critical binding sites in factor VIII, leading to steric hindrance of the interaction with factor Xa, phospholipid and /or vonWillebrand factor. Acquired autoimmune coagulant inhibitors can be associated with life-threatening bleeding complications. This is a very rare presentation of bleeding in a patient with an autoimmune disease secondary to acquired factor VIII inhibitors.

CASE REPORT

An 8-year-old girl with a three year history of mixed connective tissue disease (MCTD) initially presenting with arthritis and myositis developed easy bruising and epistaxis. She had a negative family history for bleeding disorders. Current therapy for MCTD was oral prednisone 5 mg daily, methotrexate 17.5 mg subcutaneously once per week and naproxen 125 mg twice daily. She was also taking omeprazole 20 mg daily for gastroesophageal reflux. On physical examination, there was one large bruise behind the right knee and one over the ulnar side of the right wrist. She had typical sausage shaped swelling of her fingers and mild restriction in range of motion of the small joints of her hands and wrists. There was no indication of active myositis.

Laboratory results were as follows: total leukocyte count 8.6 x 10^3 /l with normal differential, hemoglobin level 107 g/l, platelet count 574 x 10^9 /l, ESR 50 mm/hr and CRP 90 mg/l. Serum transaminase, creatine kinase and creatinine were normal, antinuclear antibody ≥ 1:320, anti-RNP antibody positive, anti-double-stranded DNA 64 IU/ml and anticardiolipin normal. Urinalysis showed moderate amount of blood but no proteinuria. The coagulation studies were as follows, INR 1.1 and aPTT 108 seconds. Total clotting and bleeding time were normal. Prolonged aPTT was not corrected by the addition of normal plasma indicating the presence of an inhibitor. Factor VIII was undetectable at less than 0.01 u/ml (normal: 0.5-1.50) and an inhibitor level of 25 units/ml was detected by Bethesda assay[2].

The prednisone dose was increased from 0.5 mg/kg to 1 mg/kg, then tapered to a maintenance dose of 5 mg daily over the following six months. The aPTT dropped in two weeks from 108 to 69 seconds with no further bruising. After four months of increased prednisone the factor VIII level was 0.42 u/ml and the aPTT was 37 seconds. After seven months the inhibitor was no longer detectable and the factor VIII was normal. Four years later, her aPTT has remained within normal limits although her MCTD is incompletely controlled.

Address correspondence to:
Dr.Ekhlas Alhumoud, Department of Medicine, Mubarak Al-Kabeer Hospital, Al-Jabriya, Kuwait. E-mail: alhumoudekhlas@yahoo.com

DISCUSSION

Acquired hemophilia A is a rare disorder, with an estimated incidence of approximately 1:1,000,000[3]. Males and females are affected equally. Two peaks in incidence are seen: the first in younger women, which is associated with pregnancy (8%), and a second peak in elderly patients in association with diseases like rheumatoid arthritis (8%), systemic lupus erythematosus (7%), drug allergy (*e.g.*, penicillin, ampicillin and phenytoin; 5%), malignancies (solid tumours as well as hematologic, 6%)[4,5].

Autoantibodies interfering with factor VIII function occur with very low frequency in rheumatologic diseases. In a 10-year survey, only 10 of 215 patients with factor VIII autoantibodies had lupus, 14 had rheumatoid arthritis and eight had other autoimmune disorders (dermatomyositis, polymyositis, Sjogren's syndrome, ulcerative colitis, myasthenia gravis and temporal arteritis) and all were adults[3]. Only nine of the 215 patients were children. Two appeared during penicillin or ampicillin therapy, two occurred in the immediate postoperative period and one was in association with asthma. Other cases in children have been reported with nephrotic syndrome[6], two weeks after oral penicillin treatment for post-streptococcal pharyngitis[7], and one of factor VIII inhibitor of unknown origin[8].

The diagnosis of acquired hemophilia is made by finding a prolonged aPTT, decreased factor VIII concentration, and a measurable titer of antibodies against factor VIII in the absence of a history of hemorrhagic diathesis.

In autoimmune diseases, hemorrhage is a significant cause of morbidity and mortality for several reasons. First, the acquired hemophiliac, unlike hereditary hemophiliac, is unprepared for hemorrhagic episodes. Second, a sudden major bleed can be the first symptom revealing the presence of a circulating anticoagulant. Third, the cause of bleeding may be further complicated by the overlapping of different types of inhibitors, especially in lupus[9,10].

The management of bleeding episodes in patients with inhibitors should take into consideration the inhibitor titer, the potential for anamnestic response to FVIII-containing products, and the historical responsiveness of the patient to bypass therapies (activated prothrombin complex concentrates). In patients with an inhibitor titer of less than 5-10 BU/ml experiencing life or limb threatening hemorrhage, infusion of high dose FVIII is usually preferable. Extracorporeal immunoadsorption offers the possibility of rapid reduction of plasma inhibitor levels in patients with higher titers, thus facilitating high dose FVIII infusion. Bypassing agents induce hemostasis in the absence of FVIII despite an incomplete understanding of the mechanism of action. rFVIIa may also be considered as a first line therapy in the treatment of severe hemorrhage[11].

Long term treatment of acquired hemophilia A is aimed at the elimination of factor VIII inhibitor activity. In a multicenter retrospective study of non-hemophilic patients with factor VIII inhibitor, Green and Lechner[3] observed more frequent spontaneous inhibitor disappearance in children. Owing to the rarity of the cases, controlled therapy trials are lacking, so the management of these patients is largely empirical. A 20-year literature review revealed no consensus on the treatment of factor VIII inhibitors associated with rheumatologic diseases. Corticosteroids were administered in SLE and Sjogren's syndrome overlap[12], in a rheumatoid arthritis patient with a lupus anticoagulant[9], combined immunosuppressive therapy with corticosteroids, azathioprine, cyclophosphamide, and cyclosporin followed by intravenous immunoglobulin in a case of SLE[13]; intravenous immunoglobulin, cyclophosphamide and cyclosporin in SLE[14]; plasmapheresis, corticosteroid, cyclophosphamide, methotrexate, immunoglobulins and vincristine in two SLE patients[15]; traneximic acid and corticosteroid in a postpartum patient with anti-double-stranded DNA antibodies[16].

Although spontaneous disappearance has been reported, immunosuppressive therapy is usually required. Corticosteroid, cyclophosphamide, azathioprine or cyclosporin as single or combination therapy has resulted in the disappearance of factor FVIII inhibitor[17]. Plasmapheresis and intravenous immunoglobulin administration have been reported to be successful as well[3,5,7]. Rituximab has been effective in cases that are resistant to conventional immunomodulatory therapy[18,19].

REFERENCES

1. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. Br J Haematol. 2003; 121:21-35.
2. Kasper CK, Aledort L, Aronson D. Proceedings: A more uniform measurement of factor VIII inhibitors. Thromb Diath Haemorrh 1975; 34:612.
3, Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to Factor VIII. Thromb Haemost 1981; 45:200-203.
4. Morrison AE, Ludlam CA. Acquired haemophilia and its management. Br J Haematol 1995; 89:231-236.
5. Hultin MB. Acquired inhibitors in malignant and nonmalignant disease states. Am J Med 1991; 91:S9-S13.
6: Sakai M, Shima M, Shirahata A. Successful steroid pulse treatment in childhood acquired haemophilia with nephrotic syndrome. Haemophilia 2005; 11:285-289.
7: Moraca RJ, Ragni MV. Acquired anti-FVIII inhibitors in children. Haemophilia. 2002 8:28-32.

8: Klukowska A, Laguna P, Obitko-Pludowska A, Niedzielska K, Malinowska I, Rokicka-Milewska R. Acquired factor VIII inhibitor in a non-haemophilic boy. Haemophilia 2003; 9:642-645.
9: Ballard HS, Nyamuswa G. Life-threatening haemorrhage in a patient with rheumatoid arthritis and a lupus anticoagulant coexisting with acquired autoantibodies against factor VIII. Br J Rheumatol 1993; 32:515-517.
10: Grossmann R, Wankmuller H, Schwender S, *et al*. The diagnosis and therapy of acquired factor-VIII inhibitors in combination with lupus anticoagulants. Dtsch Med Wochenschr 1996; 121:906-910.
11: Pizzuto J, Ambriz R, de la Paz Reyna M, *et al*. Acquired von Willebrand's syndrome during autoimmune disorder. Thromb Haemost 1980; 42:1523-1528.
12: Pirner K, Rosler W, Kalden JR, Manger B. Long-term remission after IV immunoglobulin therapy in acquired antihemophilic factor hemophilia with systemic lupus erythematosus. Z Rheumatol 1990; 49:378-381.
13: Schulman S, Langevitz P, Livneh A, Mortinowitz U, Seligsohn U, Varon D. Cyclosporine therapy for acquired factor VIII inhibitor in a patient with systemic lupus erythematosus. Thromb Haemost 1996; 76:344-346.
14: Lafferty TE, Smith JB, Schuster SJ, DeHoratius RJ. Treatment of acquired factor VIII inhibitor using intravenous immunoglobulin in two patients with systemic lupus erythematosus. Arthritis Rheum 1997; 40:775-778.
15: Jackson N, Hashim ZA, Zainal NA, Jamaluddin N. Puerperal acquired factor VIII inhibitor causing a von Willebrand-like syndrome in a patient with anti-DNA antibodies. Singapore Med J 1995; 36:230-231.
16: Ten Cate H, Bauer KA, Levi M, *et al*. The activation of factor X and prothrombin by recombinant factor VIIa in vivo is mediated by tissue factor. J Clin Invest 1993; 92:1207-1212.
17: Kasper CK. Treatment of factor VIII inhibitors. Prog Hemost Thromb 1989; 9:57-86.
18: Kain S, Copeland TS, Leahy MF. Treatment of refractory autoimmune (acquired) haemophilia with anti-CD20 (rituximab). Br J Haematol 2002; 119:578.
19: Ahrens N, Kingreen D, Seltsam A, Salama A. Treatment of refractory autoimmune haemolytic anaemia with anti-CD20(rituximab). Br J Haematol 2001; 114:244-245.

Case Report

Appendicitis Caused by Accidentally Ingested Metallic Pin: A Case Report

Lamya Al-Sarraf[1], Venugopal Naik Keluth Chavan[1], Renu Gupta[2]
[1]Department of Radiology, Mubarak Al-Kabir Hospital, Kuwait
[2]Department of Radiology, Faculty of Medicine, Kuwait University, Kuwait

Kuwait Medical Journal 2011; 43 (3):241-243

ABSTRACT

Foreign bodies (FB) are a rare cause of appendicitis. We report a case of a 29-year-old healthy female who presented to the emergency department after accidentally swallowing a pin while wearing head scarf. Plain abdominal radiograph revealed an opaque metallic pin in the left upper quadrant. She was sent home with reassurance. After a week, she presented to the emergency department again with intermittent abdominal pain. Abdominal radiograph at this stage showed the metallic pin in the right lower quadrant and the decision to intervene was made. Colonoscopic removal failed as the pin could not be visualized. Abdominal CT scan was performed which revealed the pin within the lumen of appendix. At surgery and histopathology, acute appendicitis with ulceration and neutrophilic infiltration at pin contact suggested foreign body appendicitis. Pre-operative CT scan was found to be useful for localization of FB as well as identification of complications.

KEY WORDS: appendicitis, CT scan, foreign body

INTRODUCTION

Foreign bodies (FB) are a rare cause of appendicitis. Most swallowed FB, whether intentional or accidental, eventually pass with no complications[1,2]. A vast variety of foreign bodies have been reported within the appendix and these can be classified into metallic, human/animal materials, plant materials and others[1]. Examples of some of these include pins, coins, dental material. These objects differ in their potential for complications like perforation as well as their translucency. It has been reported that long, sharp, pointed objects are more prone for perforation[1]. The investigations and management plans differ accordingly and have to be tailored to the case. For the few unfortunate ones, in which the foreign body does not pass spontaneously, or the risk of complications is high, intervention is usually indicated. There are several methods of retrieval of retained foreign bodies, endoscopically or through fluoroscopically assisted surgeries[3]. Sometimes, further radiological investigations maybe done prior to intervention. As in our case, the use of computed tomography (CT) scan offered the diagnosis and accurate localization of the foreign body. This helped guide the surgical team to the appropriate management, *i.e.*, the surgical approach. Usefulness of 3D reconstruction and reformatting in the coronal and sagittal planes in the evaluation of complicated ingested foreign bodies has been reported[4]. This case report emphasizes the importance of preoperative CT scan for localization of foreign bodies and identification of complications.

CASE HISTORY

A 29-year-old previously healthy female patient presents to the emergency department with complaints of accidental swallowing of a pin while wearing her headscarf (hijab). She did not have any symptoms at this time and physical examination was unremarkable, but she was anxious and concerned about the swallowed foreign body. The abdominal radiograph showed the radio opaque metallic pin in the left upper quadrant, probably in the jenjunal loops. She was sent home with reassurance as most of the swallowed foreign bodies eventually pass without intervention.

A week later, she presented to the emergency department with intermittent abdominal pain. Abdominal radiographs showed a radio- opaque metallic pin in the right lower quadrant with no other

Address correspondence to:
Dr. Renu Gupta, Professor, Department of Radiology, Faculty of Medicine, Kuwait University, P O Box 24923, Safat 13110, Kuwait. Tel: (965) 24986411, Fax: (965) 2533 0473, E-mail: renu@hsc.edu.kw

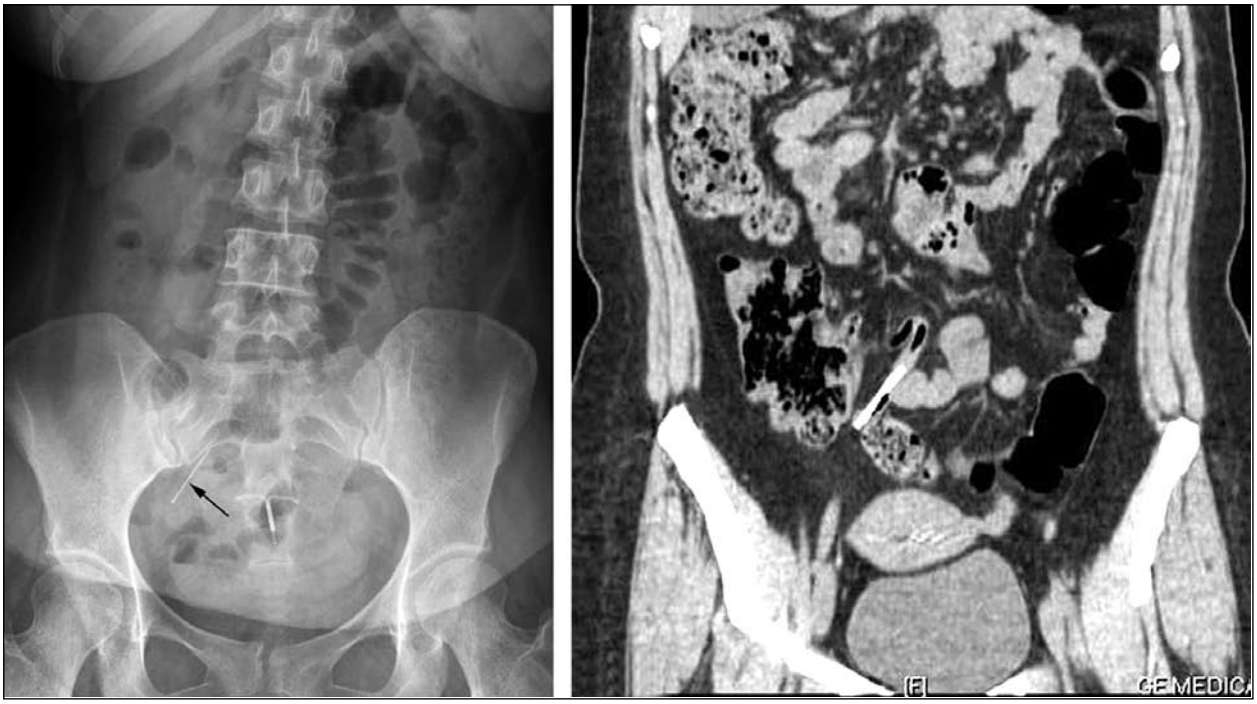

Fig 1: A) Plain X-ray of the abdomen showing the foreign body in the right iliac fossa, and **B)** a coronal reformatted CT image showing the foreign body located in the lumen of the normal appearing appendix

abnormalities. A conservative management with dietary advice was given. There was no evidence of evacuation of foreign body up to two months post ingestion. As patient continued to have intermittent right-sided abdominal pain and physical examination revealed tenderness in right iliac fossa, the decision to intervene was made. Repeated abdominal radiograph showed the pin still in the right lower quadrant, possibly in the distal small bowel or the cecum. Colonoscopic retrieval was attempted but the pin could not be visualized. A small bowel Barium follow-through examination showed the pin to be neither in the small or large bowel and there was no other abnormality. The appendix did not opacify during the examination. Further evaluation with abdominal CT scan was done for better localization. The CT study showed the pin within the lumen of the appendix (Fig. 1). No radiological evidence of appendicitis was noted. No other bowel abnormalities or perforation were present. The basic metabolic panel and the complete blood count of the patient were within normal range. A laparotomy revealed a grossly normal appendix with the pin retained intraluminally. An appendectomy was performed. Histopathological examination of the resected specimen showed changes of acute appendicitis in the form of ulceration and neutrophilic infiltration at the point of pin contact (Fig. 2). A final diagnosis of FB induced appendicitis was made. The patient had an uneventful postoperative period.

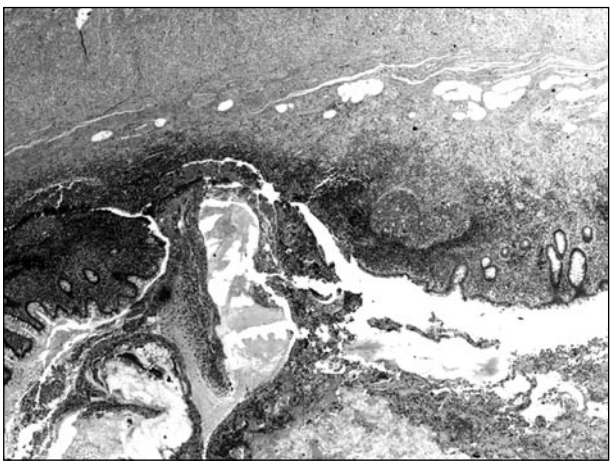

Fig 2: Photomicrograph shows changes of acute appendicitis

DISCUSSION

Most swallowed FB, whether intentional or accidental, eventually pass with no complications[1,2]. FB are a rare cause of appendicitis. A large review of appendectomies from Duke Hospital and the Durham Veterans Administration Hospital showed only seven of 13,228 appendectomies performed involved foreign bodies in the appendix, an incidence of 0.0005%[3].

A vast variety of FB have been reported within the appendix and these can be classified into metallic, human/animal materials, plant materials and others[1]. Examples of some of these include pins, coins, dental material. These objects differ in their potential for complications like perforation as well as their translucency. It has been reported that long, sharp, pointed objects are more prone for perforation[1].

The investigations and management plans differ accordingly and should be individualized. The usual initial investigation done in the casualty in cases of ingestion of radio-opaque FB is plain radiograph. In many cases, this is enough and no further investigations are needed because, as mentioned earlier, most objects pass uneventfully. For the few unfortunate ones, in which the foreign body does not pass spontaneously, or the risk of complications is high, intervention is usually indicated. There are several methods of retrieval of retained foreign bodies, endoscopically or through fluoroscopically assisted surgeries[4]. Sometimes, further radiological investigations may be done prior to intervention. In our case, the use of CT scan offered the diagnosis and accurate localization of the foreign body, which helped guide the surgical team to the appropriate management and surgical approach. Therefore, the examination has to be tailored according to each case. Reformatting in the coronal and sagittal planes also greatly helps. Another case report demonstrated the usefulness of 3D reconstruction in the evaluation of complicated ingested FB[5].

There are many reported cases of FB appendicitis in the literature. However, sophisticated radiological procedures like CT have not been utilized much. As mentioned earlier, only a few selected cases would need to proceed to CT scanning. The decision, as well as timing, of the CT depends on the managing team and most adopt a "wait and close observation" policy first[2].

CONCLUSION

FB are a rare cause of appendicitis. In cases of retained ingested foreign bodies, especially those prone to complications, pre-operative radiological investigation with CT scan is useful in some cases for localization as well as identification of complications.

ACKNOWLEDGMENT

Authors acknowledge the contributions by the Department of Surgery and Histopathology, Mubarak Al Kabir Hospital, Kuwait, for management of this case.

REFERENCES

1. Klinger PJ, Seelig MH, DeVault KR, *et al*. Ingested foreign bodies within the appendix: a 100-year review of the literature. Dig Dis 1998; 16:308-314.
2. Pavlidis TE, Marakis GN, Triantafyllou A, Psarras K, Kontoulis TM, Sakantamis AK. Management of ingested foreign bodies: How justifiable is a waiting policy? Surg Laparosc Endosc Percutan Tech 2008; 18:286-287.
3. Balch CM, Silver D. Foreign bodies in the appendix: Report of eight cases and review of the literature. Arch Surg 1971; 102:14-20.
4. Hartin CW Jr, Lau ST, Caty MG. Metallic foreign body in the appendix of a 3-year old boy. J Pediatr Surg 2008; 43:2106-2108.
5. Takada M, Kashiwagi R, Sakane M, Tabata F, Kuroda Y. 3D-CT diagnosis for ingested foreign bodies. Am J Emerg Med 2000; 18:192-193.

Case Report

Complex Regional Pain Syndrome in a Child: First Case Report from Kuwait

Aida Abdul-Malik, Zaid Al-Harbash, Khalid Al-Othman
Department of Pediatrics, Al-Amiri Hospital, Kuwait

Kuwait Medical Journal 2011; 43 (3): 244-246

ABSTRACT

Complex regional pain syndrome (CRPS) has been reported in adults for many years. It is a rare disorder in children, probably due to under-diagnosis. The etiology of CRPS remains unclear. The prognostic indicator in adults as well as in children is early recognition and treatment. CRPS should be included as part of the differential diagnosis of limb pain in children. The purpose of this report is to help pediatricians recognize CRPS promptly and to provide timely care and prevent any functional impairment.

KEY WORDS: anti-inflammatory agents, reflex sympathetic dystrophy

INTRODUCTION

Complex regional pain syndrome (CRPS) is a rare and under-diagnosed disorder in childhood. The majority of studies to date have been described in adult populations. Veldman *et al* studied 829 patients with the disease among which there was just one patient less than nine years old[1]. We present the case of an 11-year-old Kuwaiti girl with CRPS. To the best of our knowledge this is the first pediatric case report from Kuwait.

CASE REPORT

S.A. is an 11-year-old girl who had history of a fall on her back while playing which was followed two weeks later by severe progressive right leg pain to the extent of not tolerating even light touch. Her pain was severe, and burning in nature and occupying the whole right limb mainly the right thigh and knee. It was aggravated by cold and tactile stimulus. The affected limb was often guarded even from physical examination and clothing. She was unable to walk except with assistance. During her hospital stay she had episodes of bluish discoloration of her affected limb with swelling and changes in temperature that subsided spontaneously. She was never incontinent of her bladder or bowel movements.

S.A. is a product of full-term normal vaginal delivery. She is the fourth child of consanguineous parents with a family history of thalassemia and sickle cell disease. She is a high achiever at school but, unfortunately, she did not attend school since the onset of her pain and disability. She lives with her parents and there were some psychosocial problems in the family. Her mother was suffering from some psychological disorder and was on treatment. S.A. had witnessed several incidents of verbal and physical abuse between her parents, though she had never been abused herself. Her parents are currently planning to get divorced.

On examination, she looked generally well but had intermittent crying episodes from pain. Her vital signs were stable. She was overweight (weight 72 kg, *i.e.*, above 95th percentile). Chest and heart examination was normal. Abdomen was soft and lax with no organomegaly. Her motor system, cranial nerves, and deep tendon reflexes were normal and there was no sensory loss. There was regional right lower limb pain that did not follow any specific dermatome or nerve distribution. She was able to walk but with great difficulty and needed assistance due to her severe pain. The right lower limb was tender to touch with very painful and restricted movements around the hip and knee regions. There was asymmetry in the color and temperature of the lower limbs with a difference of 1 cm in leg circumference. The affected limb intermittently became warm, swollen and blue in color.

Her complete hemogram showed white blood cells 9.1 x 10^9/l, hemoglobin 123 g/l, platelets 284 x 10^9/l, ESR 18 mm/hr, and blood film showed no abnormal cells. Hb electrophoresis: HbA 55.78%, HbA2 3.77%, HbF 1.94%, and HbS 38.51%. Blood glucose was 5.9 mmol/l,

Address correspondence to:
Dr. Zaid Al-Harbash, P O Box 22775, 13088 Safat, Kuwait. Mobile: +96597402555, E-mail: zaid73@mac.com

urea 4.3 mmol/l, creatinine 55 Umol/l, serum sodium 141 mmol/l, potassium 4.1 mmol/l, bicarbonate 24 mmol/l, calcium 2.49 mmol/l, albumin 40 g/l, alkaline phosphatase 159 IU/l. ferritin 185 ng/ml. Renal function and electrolytes were normal. C-reactive protein 3 mg/l, ASO-titer < 20 Todd units, rheumatoid factor < 20 IU/l, CK 141 IU/l, LDH 191 IU/l. Blood, urine and throat cultures showed no growth.

Doppler ultrasound of right lower limb (done twice) showed no evidence of deep vein thrombosis. Magnetic resonance imaging (MRI) of the hip showed that the posterior column of the right acetabulum including the ischial bone had low signal intensity on T1-weighted images, with a thin rim of high signal intensity seen in the soft tissue medial to the right acetabulum with significant enhancement of this abnormal signal intensity. Minimal right-sided joint effusion was seen. There was normal joint congruity with no evidence of slipped capital femoral epiphysis. In addition, a CT study was performed that showed no lytic or sclerotic lesions and no cortical destruction. An MRI of the lumbosacral spine showed that the lumbar intervertebral disks were normal in signal intensity. There were minor disk bulges seen from L3-4 to L5-S1. These were touching the thecal sac but not affecting the nerves. There was minimal bilateral narrowing of the lower part of the neural foramen at L4-5. The other inter-vertebral disks and the canal and foraminae at these levels were all within normal limits.

A neurosurgical specialist evaluated the patient and he was of the opinion that the radiological findings did not correlate with the clinical picture and ruled out any neurosurgical problems. This led to us to perform a bone scan that showed hyperemia of the right hip joint region during the flow and blood pool. The delayed whole body and static images showed increased tracer uptake of the right hip joint, right ischium, trochanteric region, knee joint, ankle joint and the right foot. The rest of the skeleton was unremarkable. This bone scan led to the diagnosis of right lower limb reflex sympathetic dystrophy.

S.A. remained in hospital for five weeks with restricted movement and refusing physiotherapy due to pain. She started receiving transcutaneous nerve stimulator treatment and seemed to be satisfied. A pediatric rheumatologist saw the patient and his opinion was consistent with the diagnosis of CRPS. He advised to start physiotherapy, naproxen, an oral non-steroidal anti-inflammatory drug (NSAID), and ranitidine. The patient did not show any improvement after four weeks of NSAID and it was stopped. Carbamazepine was started by 5 mg/kg and gradually was built up to 10 mg/kg. She started to sleep better and her pain improved slightly. The pain service offered our patient a spinal block but her mother refused all other modalities of treatment since they were traveling to the UK for further management.

DISCUSSION

CRPS is defined as chronic musculoskeletal pain dysfunction. In children, there is a female to male predilection, and 80% of cases involve the lower extremity[2-4]. According to the International Association for the Study of Pain, the characteristic features required to establish its diagnosis are as follows: (1) the presence of an initiating noxious event or a cause of immobilization; (2) continuing pain, allodynia, or hyperalgesia with pain disproportionate to any inciting event; (3) evidence at some time of edema, changes in skin blood flow, or abnormal sudomotor activity in the region of the pain; and (4) the exclusion of medical conditions that would otherwise account for the degree of pain and dysfunction[4,5]. Our patient fulfilled the above criteria. We excluded other conditions that might cause pain and dysfunction like osteomyelitis, deep venous thrombosis, orthopedic or other neurosurgical conditions. Her normal inflammatory markers (including ESR, CRP, WBC, platelets, and rheumatoid factor) and the clinical picture excluded connective tissue disorders.

The onset of CRPS is usually linked to a history of trauma, immobilization, or surgery. There is no correlation between the severity of the initial injury and the ensuing painful syndrome[4]. The pain in our patient started two weeks after a minor trauma and was disproportionate to the inciting event. Psychological factors, such as stressful life events and inadequate coping mechanisms, are potential risk factors that influence the severity of symptoms in CRPS[4]. This may have been a risk factor in our patient due to her family's poor psychosocial situation.

The clinical presentation consists of a triad of sensory, autonomic, and motor signs and symptoms[3,5,6]. Pain in CRPS varies in quality from a deep ache to a sharp stinging or burning sensation. Often, patients report that the pain is worsened by environmental (cold, humidity) and emotional (anxiety, stress) factors. Cutaneous hypersensitivity presents as pain on contact with clothing or exposure to a cool breeze. The involved extremity is often guarded, even from the examining physician. Patients frequently experience pain from tactile stimuli (allodynia) and have an increased response to painful stimuli (hyperalgesia)[4]. The pain that was described in our patient was burning in nature, worsened by cold and improved with hot baths. She experienced pain even in contact with clothing or with light touch.

MRI is often normal or shows non-specific soft tissue changes[7] (*e.g.*, periarticular marrow edema often involving more than one bone, soft tissue swelling, joint effusions[8] and a subchondral band of low T1-weighted intensity). The MRI of our patient showed low signal intensity on T1-weighted images involving the acetabulum and the ischial bone with minimal joint effusion. The three-phase bone scan plays an

important role in diagnosis of this syndrome because there are often few, if any other radiologic modalities that show an abnormality[9]. Our patient's diagnosis was made by performing a bone scan that showed the classical appearance of intense periarticular activity in the involved extremity on the delayed phase of the scan preceded by hyperemia in a similar distribution on the immediate postinjection blood flow and blood pool phases of the scan[10].

The best prediction of success in the management of CRPS is early treatment. Therefore, prompt diagnosis and treatment of CRPS provide palliation and allow recovery[11]. The treatment goal in CRPS is pain relief, functional recovery, and psychological improvement. This often requires a multidisciplinary approach[4].

The most important part of treatment is an appropriate and intensive physical therapy program that should be initiated early. Medications such as tricyclic antidepressant and anticonvulsants are frequently used and are typically prescribed by pain clinics. Calcium channel blockers have also shown some benefit. Sympathetic blocks may be used and have been beneficial[2]. One therapeutic intervention is transcutaneous nerve stimulator (TENS). It decreases symptoms by increasing nutritional flow[11]. The recurrence risk in CRPS is 25%. The prognosis is generally good in contrast to adults who have a poorer prognosis[11].

Frustration during treatment is common because the pathophysiology of CRPS is not completely understood and the therapeutic efforts may fail. A trial-and-error approach to treatment is often mandatory. Early recognition of CRPS and prompt intervention, however, provide the best opportunity for clinical improvement[11].

CONCLUSION

It should be emphasized that CRPS is a chronic, painful disease associated with significant morbidity in children and adolescents and may cause temporary or permanent functional incapacitation. Pediatricians should be alert, since the diagnosis is made on clinical suspicion and when made early the prognosis improves.

ACKNOWLEDGMENT

We would like to thank Dr. Khalda Al-Zaabi from the Department of Nuclear Medicine for her valuable contribution in the diagnosis of our patient.

REFERENCES

1. Veldman PH, Reynen HM, Arntz IE, Goris RJ. Signs and symptoms of reflex sympathetic dystrophy: prospective study of 829 patients. Lancet 1993; 342:1012-1016.
2. Wilder RT, Berde CB, Wolohan M, Vieyra MA, Masek BJ, Micheli LJ. Reflex sympathetic dystrophy in children. Clinical characteristics and follow-up of seventy patients. J Bone Joint Surg Am 1992; 74:910-919.
3. Small E. Reflex sympathetic dystrophy in pediatric patients: Reflection from clinician, In Greydanus D, Patel D, editors. Adolescent Medicine: State of the art reviews. NY: American Academy of Pediatrics; 2007. p221-225.
4. Raja SN, Grabow TS. Complex regional pain syndrome I (reflex sympathetic dystrophy). Anesthesiology 2002; 96:1254-1260.
5. Stanton RP, Malcolm JR, Wesdock KA, Singsen BH. Reflex sympathetic dystrophy in children: an orthopedic perspective. Orthopedics 1993; 16:773-779.
6. Sherry DD, Wallace CA, Kelley C, Kidder M, Sapp L. Short and long-term outcomes of children with complex regional pain syndrome type I treated with exercise therapy. Clin J Pain 1999; 15:218-223.
7. Small E. Chronic musculoskeletal pain in young athletes. Pediatr Clin North Am 2002; 49: 655-662.
8. Graif M, Schweitzer ME, Marks B, Matteucci T, Mandel S. Synovial effusion in reflex sympathetic dystrophy: an additional sign for diagnosis and staging. Skeletal Radiol 1998; 27:262-265.
9. Nadel HR, Stilwell ME. Nuclear medicine topics in pediatric musculoskeletal disease: techniques and applications. Radiol Clin North Am 2001; 39:619-651.
10. Kozin F, Soin JS, Ryan LM, Carrera GF, Wortmann RL. Bone scintigraphy in the reflex sympathetic dystrophy syndrome. Radiology 1981; 138:437-443.
11. Teasdall RD, Smith BP, Koman LA. Complex regional pain syndrome (reflex sympathetic dystrophy). Clin Sports Med 2004; 23:145-155.

Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2011, 43 (3): 247-250

Chewing Areca Nut, Betel Quid, Oral Snuff, Cigarette Smoking And the Risk of Oesophageal Squamous-Cell Carcinoma in South Asians: A Multicentre Case-Control Study

Akhtar S, Sheikh AA, Qureshi HU
Faculty of Medicine, Kuwait University, Jabriya, Kuwait
Faculty of Health Sciences, Aga Khan University, Karachi, Pakistan

Eur J Cancer 2011 Jul 4 [Epub ahead of print]

Oesophageal cancer remains an important public health problem worldwide. This multicentre matched case-control study examined the chewing areca nut alone, betel quid with tobacco, oral snuff (snuff dipping) and cigarette smoking as the risk factors for oesophageal squamous-cell carcinoma. We enrolled 91 cases of oesophageal squamous-cell carcinoma and 364 matched controls from three tertiary-care hospitals in Karachi, Pakistan. A structured questionnaire was used to collect the data through face-to-face interview of the participants. Multivariable conditional logistic regression model showed that after adjusting for the effect of ethnicity, ever chewed areca nut alone (adjusted matched odds ratio (mOR(adj)) = 3.7; 95% confidence interval (CI): 1.6 - 8.5), ever chewed betel quid with tobacco (mOR(adj) = 12.8; 95% CI: 6.3-26.2), ever practiced snuff dipping (mOR(adj) = 4.3; 95% CI: 1.6 - 11.7) and ever smoked cigarettes (mOR(adj) = 2.9; 95% CI: 1.4 - 5.9) were significantly and independently associated with oesophageal squamous-cell carcinoma status. The adjusted summary population attributable risk (PAR) percent for all four substances together was 67.0. Furthermore, despite incomplete synergy, there was manifold increase in the risk of oesophageal squamous-cell carcinoma, if the respondents ever smoked cigarettes and ever chewed betel quid with tobacco (mOR(adj) = 21.4; 95% CI: 6.3 - 72.4) or if they ever smoked cigarettes and ever practiced snuff dipping (mOR(adj) = 14.4; 95% CI: 2.3 - 91.1). The adjusted PAR (%) was higher for the dual practice of smoking cigarettes and chewing betel quid with tobacco (64.3) than dual practice of smoking cigarettes and snuff dipping (32.2). Public awareness to curtail the addiction to these substances may result in a substantial reduction in the incidence of oesophageal squamous-cell carcinoma and related mortality in this and similar settings.

Pattern and Etiology of Culture-Proven Early-Onset Neonatal Sepsis: A Five-Year Prospective Study

Al-Taiar A, Hammoud MS, Thalib L, Isaacs D
Department of Community Medicine and Behavioral Sciences, Faculty of Medicine, Kuwait University, Kuwait

Int J Infect Dis 2011 Jun 27 [Epub ahead of print]

Objectives: To investigate the incidence of early-onset neonatal sepsis and identify the main pathogens over a 5-year period in Kuwait.
Methods: Blood samples were collected from all infants with any clinical or laboratory feature suggestive of sepsis, at the main maternity hospital in Kuwait. Cases of early-onset neonatal infection were defined as culture of a single potentially pathogenic organism from blood or cerebrospinal fluid from infants younger

than 7 days of age, in association with clinical or laboratory findings consistent with infection.
Results: The overall incidence of early-onset neonatal infection was 2.7 (95% confidence interval (CI) 2.3-3.2) episodes per 1000 live-births. The case-fatality was 13.1% (95% CI 8.6-18.9%). Group B Streptococcus (GBS) accounted for 17.6% of infections among infants younger than 7 days (incidence 0.48 per 1000 live-births), but 38.1% of infections in the first 2 days of life. Neither the incidence of early-onset infection by GBS nor by Escherichia coli changed significantly over the study period.
Conclusions: Although the incidence of GBS infections was relatively low, GBS accounted for most early-onset infections. Intrapartum antibiotic prophylaxis against GBS should be strengthened. There was no evidence to suggest that early-onset infection due to non-GBS organisms such E. coli has increased in the last 5 years.

Knowledge and Attitudes towards HIV/AIDS amongst Kuwait University Dental Students

Ellepola AN, Joseph BK, Sundaram DB, Sharma PN
Department of Bioclinical Sciences, Faculty of Dentistry, Kuwait University
Department of Diagnostic Sciences, Faculty of Dentistry, Kuwait University Office of Vice President, Health Sciences Center, Kuwait University, Safat, Kuwait

Eur J Dent Educ 2011; 15:165-171

The HIV and AIDS have emerged as complex health threats to the world population. As future dentists, it is pertinent that the dental students have sufficient knowledge and a positive approach towards the disease. Accordingly, the aim of this study was to assess the HIV / AIDS related knowledge and attitudes amongst clinical dental students at Kuwait University. A cross-sectional survey was conducted amongst the clinical dental students using a structured questionnaire with 60 questions to examine their knowledge under various categories and 13 questions to examine their attitudes towards the disease. The survey revealed that almost 58% of the respondents demonstrated a high level of knowledge (mean score: 45.23 ± 4.35 SD). Majority of the students (63.6%) expressed negative attitude (mean score: 5.36 ± 2.56 SD). The mean knowledge score of the fifth year dental students was significantly higher ($P = 0.022$) than that of the final year dental students regarding the knowledge of virus and disease process. However, no significant difference was observed with respect to other knowledge categories. Despite their high level of knowledge, the majority displayed a negative attitude towards HIV / AIDS. Hence, the findings imply that there is a need to address, more clearly, the students' misconceptions and attitudes towards the disease.

Filtering Effect of Wind Flow Turbulence on Atmospheric Pollutant Dispersion

Yassin MF
Department of Environmental Technology and Management, Kuwait University, P.O. Box 5969, Kuwait, Safat, 13060, Kuwait. E-mail: Mohamed_f_yassin@hotmail.com

Environ Monit Assess 2011 Jul 16 [Epub ahead of print]

This paper presents a model for coupling the statistics of wind velocity distribution and atmospheric pollutant dispersion. The effect of wind velocity distribution is modeled as a three-dimensional finite-impulse response (3D-FIR) filter. A phase space representation of the 3D-FIR filter window is discussed. The resulting pollutant dispersion is the multiplication in the phase space of the 3-D Fourier transform of the pollutant concentration and the volume described by the filter window

coefficients. The shape of the filter window in the phase space enables representing such effects as vortex shedding thermal currents, etc. The impact of spatial distribution of the sensors on the resulting pollutant spatial distribution and the 3-D FIR filter model employed also discuss. The case of a neutrally buoyant plume emitted from an elevated point source in a turbulent boundary layer considers. The results show that wind turbulence is an important factor in the pollutant dispersion and introduces expected random fluctuations in pollutant distribution and leads to spreading the distribution due to wind mixing.

The Adverse Events of Deep Fractional CO(2) : A Retrospective Study of 490 Treatments in 374 Patients

Shamsaldeen O, Peterson JD, Goldman MP
Resident, Department of Dermatology, Farwaniya Hospital, Farwaniya, Kuwait. E-mail: dr.omar@geldeya.com

Lasers Surg Med 2011; 43:453-456

Background: Fractionated carbon dioxide CO(2) laser resurfacing unites the idea of fractional photothermolysis with an ablative 10,600-nm wavelength. This technology permits effective treatment of deeper rhytides, photodamaged skin, and scars, with shorter recovery and a decreased side effect profile as compared to traditional CO(2) laser resurfacing.
Objectives: To study the rate of the adverse events associated with the use of deep fractional CO(2) laser.
Methods: A retrospective study of 490 fractionated CO(2) laser treatments in 374 patients by ten physicians within one practice was performed between March 3, 2008 and July 28, 2010. Treatment areas included the face, neck, chest, hands, back, and abdomen.
Results: Of the 490 treatments, 365 were of both superficial and deep fractional treatments while 125 treatments were deep. Patients treated were of Fitzpatrick skin types I-IV. Four hundred ninety treatments resulted in 67 adverse events (13.6%) in 63 patients (16.8%), the most frequent adverse events were acneiform eruption (5.3%), herpes simplex outbreak (2.2%), bacterial infections (1.8%), yeast infections (1.2%), hyperpigmentation (1.2%), prolonged erythema beyond 1 month (0.8%), and (0.8%) contact dermatitis. There were no reports of scarring or hypopigmentation.
Conclusions: Fractional deep CO(2) laser is a safe method for treating rhytides, photodamaged skin, and scars with a low incidence of adverse events.

Influence of Coconut Oil Administration on Some Hematologic and Metabolic Parameters in Pregnant Rats

Nandakumaran M, Angelaki E, Al-Azemi N, Al-Sarraf H, Al-Saleh E
Departments of Obstetrics and Gynecology, Faculty of Medicine, University of Kuwait, Kuwait City, Kuwait

Matern Fetal Neonatal Med. 2011 Jul 7 [Epub ahead of print]

Objective: Data on the effect of coconut oil intake on various hematologic and metabolic parameters in pregnant women or animals are scanty. Hence we attempted to assess the effect of oral administration of graded doses of this edible oil during pregnancy, on various hematologic and metabolic parameters in rats.
Methods: Groups of pregnant Sprague Dawley rats were given oral doses of 1 ml, 2 ml, and 4 ml coconut oil twice per day, respectively. Control group of rats were given tap water. Oral feeding of oil was done continuously for a period of 20 days and at the end of the study period the animals were lightly anaesthetized with ether and sacrificed to collect blood samples for analysis. Various hematologic parameters such as

red blood cell (RBC) count, white blood cell (WBC) count, hemoglobin (Hg), platelets, lymphocytes, and mean corpuscular hemoglobin concentration (MCHC) were analyzed by a hematology blood analyzer, while metabolic parameters such as cholesterol, triglycerides, urea, uric acid, creatinine, and protein were analyzed by specific analytical kits. Activities of antioxidant enzyme, superoxide dismutase (SOD), glutathione peroxidase (GPX), and total antioxidant activity (TAO) were assessed by specific analytical kits. Statistical analysis of data was performed using a SPSS data analytical package.

Results: Oral administration of coconut oil for 20 continuous days of pregnancy did not significantly alter any of the hematologic parameters studied, compared to control group even when the oil was administered at a relatively massive dose of 4 ml/day. Administration of coconut oil appeared to decrease WBC, Hg, platelet, and lymphocyte blood concentrations in treated rats, but the difference, however, was not statistically significant (ANOVA test; $p > 0.05$). However, platelet concentration was significantly lower ($p < 0.05$) in rats receiving 1 ml/day of coconut oil compared to control group rats. Administration of coconut oil did not alter the concentrations of protein, cholesterol, urea, triglycerides, uric acid, and creatinine in treated groups of rats significantly (Student's t-test, $p > 0.05$) compared to those of control rats. SOD, GPX, and TAO levels in control and treated groups were not significantly different (ANOVA test, $p > 0.05$) than controls.

Conclusions: We conclude that oral administration of coconut oil during pregnancy in rats, even in massive doses, does not cause any significant alterations in hematologic and metabolic parameters. More detailed studies, however, are warranted before extrapolating these results to human situations.

Medullary Carcinoma of the Breast: Ten Year Clinical Experience of the Kuwait Cancer Control Centre

Samir SM, Fayaz MS, Elbasmi A, Motawy MM, Abuzallouf S, George T, Abdelhady M, Bedair A
Radiation Oncology Department, Kuwait Cancer Control Center, Kuwait
Email: suzannemona@yahoo.co.uk

Gulf J Oncolog 2011; 1:45-52

Background: Medullary carcinomas of the breast account for fewer than 7% of all invasive breast cancers. Some investigators include medullary carcinomas in the favourable histologic subtype, despite its aggressive histologic appearance. However, others fail to confirm its favourable prognosis.

Methods: This was a retrospective analysis of sixty-one (61) cases of breast cancer cases diagnosed with Medullary Carcinoma, presenting to the Kuwait Cancer Control Center between 1995 and 2005.

Results: Median survival time was 122 months and the seven-year disease free survival was 82%. Overall survival rate was not assessed as no cases died during the study period. No cases were metastatic from the start and only eight cases developed metastases, local recurrence or contralateral breast primary. 68.8% of the cases were Stage I or IIA (*i.e.* no lymph node affection).

Conclusion: There is no overt favourable prognosis of medullary carcinoma when compared to invasive ductal carcinoma. Prognosis is more related to stage than histologic subtyping. The majority of cases were negative estrogen and progesterone receptor status and node negative.

Forthcoming Conferences and Meetings

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2010; 43 (3): 251-259

6th World Congress on **Itch**
Sep 4 - 6, 2011
Oceanopolis, Brest, *France*
Contact: Pr Laurent Misery, Brest University Hospital, 24 Rue Chauchat, 75009 *Paris*
Tel: + 33 298 22 33 15; Fax: + 33 298 22 33 82
Email: registration@itchbrest.com

World Endometriosis Society 11th World Congress on **Endometriosis**
Sep 04 - 07, 2011
Montpellier, *France*
Contact: Congress Secretariat
Phone: 33-467-619-414; Fax: 33-467-634-395
E-Mail: mail@ams.fr

ISMRM Workshop on Mapping Functional Networks for **Brain Surgery**
Sep 7 - 9, 2011
Melia Milano, Milan, *Italy*
Contact: Melisa Martinez, 2030 Addison St. Suite 700, Berkeley, CA 94704
Tel: +1 (510) 841-1899; Fax: +1 510-841-2340
Email: info@ismrm.org

45th Annual Meeting American Society of **Head and Neck Radiology** (ASHNR)
Sep 07 - 11, 2011
San Diego, CA, *United States*
Contact: Meeting Organiser: ASHNR, 2210 Midwest Road, Suite 207 Oak Brook, Illinois 60523-8205
Tel: 630-574-0220; Fax: 630-574-0661

30th Annual ESRA Congress - European Society of Regional **Anaesthesia & Pain Therapy**
Sep 7-10, 2011
Maritim Hotel & Internationales Congress Center Dresden, Dresden, *Germany*
Contact: Kenes International, 1-3, Rue de Chantepoulet, Geneva CH-1211, Switzerland
Tel: +41 22 908 0488
Email: esra-congress@kenes.com

International Congress on Controversies in Stem Cell **Transplantation and Cellular Therapies** (COSTEM)
Sep 8 - 11, 2011
Berlin, *Germany*
Contact: Organizing Secretariat, 53, Rothschild Boulevard, 61000, Tel Aviv, Israel
Tel: 97235666166; Fax: 97235666177
Email: costem@comtecmed.com

2011 **Hematology & Medical Oncology** Best Practices Course
Sep 8 - 15, 2011
Grand Hyatt, Washington, DC, *United States*
Contact: Julie Vastyan, 2300 Eye Street, NW, Ross Hall, Suite 313D, Washington, DC 20037
Tel: 202-994-4285
Email: cehp@gwumc.edu

Preventive Medicine
Sep 9 - 19, 2011
Celebrity Cruises' Millennium, Vancouver, *Canada*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711 Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Neurosurgical Topics for the Mid-Level Practitioner
Sep 9-10, 2011
Intercontinental Hotel, Chicago, IL, *United States*
Contact: Heather Hodge, 5550 Meadowbrook Dr., Rolling Meadows, IL 60008
Tel: 847-378-0500 Fax: 847-378-0600
Email: epm@aans.org

14th Annual **Endocrinology & Metabolism** Board Review 2011
Sep 9-11, 2011
InterContinental Hotel and Bank of America Conference Center, Cleveland, OH, *United States*
Contact: Jennifer Wasner, 3050 Science Park Dr., Cleveland, OH
Tel: 216-448-0812; Fax: 216-448-0782
Email: wasnerj@ccf.org

15th Congress of the European Federation of **Neurological** Societies
Sep 10-13, 2011
Budapest Hungexpo, Budapest, *Germany*
Contact: Secretariat, 1-3 rue de Chantepoulet, 1211 Geneva 1, Switzerland
Tel: +41 22 908 04 88; Fax: +41 22 732 28 50
Email: efns2011@kenes.com

17th International Meeting of the European Society of **Gynaecological Oncology**
Sep 11 - 14, 2011
Milan Convention Center (MIC), Milano, *Italy*
Contact: Secretariat, 1-3 rue de Chantepoulet, CH-1211 Geneva, Switzerland
Tel: +41 22 908 0488; Fax: +41 22 906 9140
Email: laryngology@gmail.com

Pediatric Review 2011
Sep 11-18, 2011
Royal Caribbean's Navigator of the Seas, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Obstetrical Ultrasound with Hands-On Scanning
Sep 12 - 16, 2011
Wake Forest School of Medicine, Winston-Salem, NC, *United States*
Contact: Program for Medical Ultrasound, Medical Center Blvd.
Tel: 336-716-4505, 800-277-7654 ext.64505; Fax: 336-716-2447
Email: cmu@wakehealth.edu

IVF Medical Events and Conferences, **Embryology**
Sep 14 - 18, 2011
India, Mumbai,Chennai,Delhi, *India*
Contact: Bindu Shah, 26 A, Raju Industrial Estate,Penkarpada Road, Near Dahisar Check Naka, Mira
Tel: 91 - 22 -28456768 Fax: 91- 22 - 2845 6766
Email: alpha.eart.workshop@gmail.com

European **Burns** Association Congress 2011
Sep 14 - 17, 2011
The Hague, *Netherlands*
Contact : Rob Zikkenheimer
Tel: 31-73-690-1415; Fax: 31-73-690-1417
E-Mail: r.zikkenheimer@congresscare.com

Mayo Clinic **Nutrition in Health and Disease**
Sep 15 - 16, 2011
Hyatt at Olive 8, Seattle, WA, *United States*
Contact: Kari Schilling, 200 First Street SW, Rochester, MN 55902
Tel: 507-284-4370 Fax: 507-538-7234
Email: schilling.kari@mayo.edu

3rd National Conference: **Reproductive Medicine** 2011
Sep 15-16, 2011
Hallam Conference Centre, London, *United Kingdom*
Contact: Florence Doel, St Judes Church, Dulwich Road, Herne Hill, London SE24 0PB
Tel: +44 (0) 207 501 6762 Fax: +44 (0) 207 978 8319
Email: flo.doel@markallengroup.com

Reproductive Health 2011
Sep 15-17, 2011
The Cosmopolitan, Las Vegas, NV, *United States*
Contact: Registration Dept at Contemporary Forums, 6377 Clark Ave., Suite 200, Dublin, CA 94568
Tel: 800-377-7707 Fax: 800-329-9923
Email: info@cforums.com

Pediatric Sedation Simulation Workshops
September 16, 2011
Fairmont Copley Plaza, Boston, MA, *United States*
Contact: Amanda Buckley, 300 Longwood Avenue, Boston, MA 02115
Tel: 617 355 5775 Fax: 617 730 0610
Email: amanda.buckley@childrens.harvard.edu

Family Medicine Review
Sep 16 - 23, 2011
Holland America's ms Amsterdam, Seattle, WA, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711 Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

12th Bienniel Conference of the Indian Society of **Stereotaxy and Functional Neurosurgery**
Sep 16 - 18, 2011
Raintree Hotel, Chennai, *India*
Tel: +91 44 42291297; Fax: +91 44 42291292
Email: info@issfn2011.co.in

Pediatric Sedation Outside of the Operating Room
Sep 17 - 18, 2011
The Fairmont Copley Plaza, Boston, MA, *United States*,
Contact: Amanda Buckley, 300 Longwood Avenue
Tel: 617 355 5775; Fax: 617 730 0610
Email: amanda.buckley@childrens.harvard.edu

Women's Health
Sep 19 - 30, 2011
Celebrity Cruises' Equinox, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

North American Congress of **Clinical Toxicology**
Omni Shoreham Hotel, Washington, DC, *United States*
Sep 21 - 26, 2011
Tel: 800-377-7707; Fax: 800-329-9923
Email: info@cforums.com

5th National Conference: Recent Advances in **Inflammatory Bowel Disease**
Sep 22 - 23, 2011
Hallam Conference Centre, London, *United Kingdom*
Contact: Florence Doel, St Judes Church, Dulwich Road, Herne Hill, London SE24 0PB
Tel: +44 (0) 207 501 6762; Fax: +44 (0) 207 978 8319
Email: flo.doel@markallengroup.com

Putting Probiotics into Practice: Applications for Health
Sep 23 - 24, 2011
Hotel Monaco Alexandria, Alexandria, VA, *United States*
Contact: Annual Probiotic Symposium,10439 Double R Blvd., Reno, NV 89521
Tel: 866-216-6127
Email: info@probioticsymposium.com

Medical Ethics & Legal Medicine
Sep 25 - Oct 2, 2011
Royal Caribbean's brand new Allure of the Seas, Ft. Lauderdale, FL, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Infectious Disease
Sep 25 - Oct 2, 2011
NCL Epic, Barcelona, *Spain*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Topics in **Acute Care, Women's Health, Emergency Medicine and Family Medicine**
Sep 25 - Oct 2, 2011
Royal Caribbean's brand new Allure of the Seas, Ft. Lauderdale, FL, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

3rd Annual **Diabetes and the Heart**: Clinical Strategies for Diabetes and Cardiovascular Comorbidities
Sep 26 - 27, 2011
InterContinental Hotel and Bank of America Conference Center, Cleveland, OH, *United States*
Contact: Jennifer Wasner, 3050 Science Park Dr., Cleveland, OH
Telephone: 216-448-0812; Fax: 216-448-0782
Email: wasnerj@ccf.org

Brain Injuries
Sep 28 - Oct 1, 2011
Hyatt Regency, San Francisco, CA, *United States*
Contact: Registration Dept at Contemporary Forums, 6377 Clark Ave., Suite 200, Dublin, CA 94568
Tel: 800-377-7707 Fax: 800-329-9923
Email: info@cforums.com

Chronic Pain: Challenges and Solutions for Primary Care
Sep 28, 2011
Continuing Education and Conference Center, 1890 Buford Avenue, St. Paul, MN, *United States*
Contact: Mia Lynch, 2829 University Avenue SE, St. Paul, MN
Tel: 612-626-7893 Fax: 612-626-7766
Email: cme@umn.edu

School and Public Health Nursing: Don't forget school-aged children!
Sep 28, 2011
The Centre Conference Venue, Slough, *United Kingdom*
Contact: Florence Doel, St Judes Church, Dulwich Road, Herne Hill, London SE24 0PB
Tele: +44 (0) 207 501 676l; Fax: +44 (0) 207 978 8319
Email: flo.doel@markallengroup.com

Practical **Paediatric Gastroenterology**
Sep 29 - 30, 2011
Lecture Theatre at Institute of Child Health The UCL Institute of Child Health, London, *United Kingdom*
Contact: Kenes UK Ltd, 385 Euston Road, London
Tel: +44 (0) 207 383 8030; Fax: +44 (0) 207 383 8040
Email: apg@kenes.com

Advances in **Emergency Surgery**
Sep 29 - 30, 2011
Hallam Conference Centre, London, *United Kingdom*
Contact: Nazma Rahman, MA Healthcare Ltd, Dulwich Road, London SE24 0PB
Tel: + 44 (0) 20 7501 6711
Email: nazma.rahman@markallengroup.com

XVI World Congress of **Cardiology, Echocardiography & Allied Imaging Techniques**
Sep 29 - Oct 02, 2011
Delhi, NCR, *India*
Contact: Raju Gandha
Tel: 91-124-456-300; Fax91-124-456-3100
E-Mail: worldcon2011@in.kuoni.com

10th Annual Update in **Nephrology and Kidney/ Pancreas Transplantation**
Sep 30 - Oct 1, 2011
Siebens Medical Education Building, Phillips Auditorium, Rochester, MN, *United States*
Contact: Sheila Fick/Sheryl Dohrmann, 200 1st Street SW/GO6-138, Rochester, MN 55905
Tel: 507-284-0536/507-266-6703; Fax: 507-284-0536
Email: rstdomcme@mayo.edu

ICJR 12th Annual Insall Scott Kelly Institute **Sports Medicine and Total Knee & Hip Course**
Sep 30 - Oct 2, 2011
Sheraton New York Hotel & Towers, New York, NY, *United States*
Contact: Sylke Anderson, 2033 San Elijo Ave., #351, Palm Springs, CA
Tel: 760-942-7859
Email: sanderson@icjr.net

Twin Cities **Sports Medicine 2011**
Sep 30 - Oct 1, 2011
Doubletree Hotel Minneapolis - Park Place, Minneapolis, MN, *United States*
Contact: Office of Continuing Medical Education, University Park Plaza Suite 601; 2829 University Ave SE; Minneapolis, MN 55414
Tel: 612-626-7600 or 800-776-8636; Fax: 612-626-7766
Email: cme@umn.edu

9th National Conference: **Autism Today** 2011 Winter Meeting
Oct 4 - 5, 2011
Royal College of Physicians Edinburgh, Edinburgh, *United Kingdom*
Contact: Florence Doel, St Judes Church, Dulwich Road, Herne Hill, London SE24 0PB
Tel: +44 (0) 207 501 6762;
Fax: +44 (0) 207 978 8319
Email: flo.doel@markallengroup.com

Pediatric **Critical Care Nursing**
Oct 4 - 8, 2011
Vegas Hilton, Las Vegas, NV, *United States*
Contact: Registration Dept at Contemporary Forums, 6377 Clark Ave., Suite 200, Dublin, CA 94568
Tel: 800-377-7707; Fax: 800-329-9923
Email: info@cforums.com

Family Medicine
Oct 5 - 15, 2011
Holland America's ms Noordam, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Phlebotomy 2011: Innovations in Quality, Service and Patient Care
Oct 6 - 7, 2011
Kahler Grand Hotel, Rochester, MN, *United States*
Contact: Diane Strain, 3050 Superior Drive NW, Rochester, MN 55901
Tel: 800-533-1710 or 507-284-0286
Email: strain.diane@mayo.edu

43rd International Danube **Neurology** Symposium 2011
Oct 6 - 8, 2011Technical University of Dresden, Dresden, *Germany*
Contact: Vanessa Jansen, Zum Ehrenhain 34, 22885 Barsbüttel
Tel: 0406708820
Email: danube2011@cpo-hanser.de

14th European Congress of **Neurosurgery**
Oct 9 - 14, 2011
Palazzo dei Congressi, Rome, *Italy*
Type of Event: Conference
Contact: Kenes International, 1-3 Rue de Chantepoulet, Geneva CH-1211, Switzerland
Tel: + 41 22 908 0488
Email: eans@kenes.com

Medical Ethics & Legal Medicine
Oct 9 - 16, 2011
Holland America's ms Ryndam, Barcelona, *Spain*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax:1 727 522 8304
Email: contactus@continuingeducation.net

An Overview of **Perioperative Medicine 2011**
Oct 12 - 15, 2011
Swissotel Chicago, Chicago, IL, *United States*
Contact: Cathy Schilling, 200 FIrst Street SW, Rochester, MN
Tel: 507-266-7484 Fax: 507-538-7234
Email: schilling.catherine@mayo.edu

Transplant Immunosuppression 2011: The Difficult Issues
Oct 12 - 15, 2011
Radisson University Hotel, Minneapolis, MN, *United States*
Contact: Office of Continuing Medical Education, University Park Plaza Suite 601; 2829 University Ave SE; Minneapolis, MN 55414
Tel: 612-626-7600 or 800-776-8636 Fax: 612-626-7766
Email: cme@umn.edu

5th World Congress on **Controversies in Neurology** (CONy)
Oct 13 - 16, 2011
China World Hotel, Beijing, Beijing, *China*
Contact: Secretariat, 53 Rothschild Blvd, Tel Aviv, 61000,Israel
Tel: +972-3-5666166
Email: cony@comtecmed.com

ISMRM Workshop on **Neuroimaging Biomarkers of Psychiatric Disorders:** What Are They?
Oct 13 - 16, 2011
Hotel Schloss Montabaur, Montabaur, *Germany*
Contact: Melisa Martinez, 2030 Addison St. Suite 700, Berkeley, CA 94704
Tel: +1 (510) 841-1899; Fax: +1 510-841-2340
Email: info@ismrm.org

ASA 2012: American Society of **Anesthesiologists** Annual Meeting
Oct 13 - 17, 2012
Washington, DC, *United States*
Contact: Meeting Organiser
E-Mail: annmtg@asahq.org

2nd National Conference: **Endocrinology 2011**
Oct 13 - 14, 2011
Mayfair Conference Centre, London, *United Kingdom*
Contact: Florence Doel, St Judes Church, Dulwich Road, Herne Hill, London SE24 0PB
Tel: +44 (0) 207 501 6762 Fax: +44 (0) 207 978 8319
Email: flo.doel@markallengroup.com

2011 **Heart Valve Summit**: Medical, Surgical and Interventional Decision Making
Oct 13 - 15, 2011
JW Marriott Chicago, Chicago, IL, *United States*
Contact: Amy Doucette, CMP, 900 Cummings Center, Suite 221-U
Tel: 978.927.8330
Email: adoucette@aats.org

Oncology for the Gastroenterologist: Horizons for the Future
Oct 14 - 15, 2011
The Westin Georgetown, Washington, DC, *United States*
Contact: AGA, 4930 Del Ray Avenue Bethesda, MD 20814
Tele: 301-654-2055 Fax: 301-654-5920
Email: member@gastro.org

Hematologic Malignancies: New Therapies and the Evolving Role of Transplant
Oct 14 -1 5, 2011
InterContinental Chicago Magnificent Mile, Chicago, IL, *United States*
Contact: Vicki Klein, 200 First St., Plummer 2-60, Rochester, MN
Tel: 507-266-7992; Fax: 507-538-7234
Email: klein.vicki@mayo.edu

Emerging Issues in **Organ Transplantation** - A Colloquium
Oct 14 - 15, 2011
InterContinental Hotel and Bank of America Conference Center, Cleveland, OH, *United States*
Contact: Lindsay, 3050 Science Park Drive, Beachwood, Ohio 44122
Tel: 216.448.0795
Email: FullerL2@ccf.org

Oncology for the Gastroenterologist: Horizons for the Future
Oct 14 - 15, 2011
Westin Georgetown, Washington, DC, *United States*
Contact: Jennifer Gibson, 4930 Del Ray Avenue, Bethesda, MD 20814
Tel: 301-654-2055
Email: jgibson@gastro.org

ASA 2011: American Society of **Anesthesiologists** Annual Meeting
Oct 15 - 19, 2011
Chicago, IL, *United States*
Contact: Meeting Organiser
E-Mail: annmtg@asahq.org

Dermatology and Oral Diseases
Oct 15 - 26, 2011
Norwegian Cruise Line's Jade, Civitavecchia, *Italy*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703 , USA
Tel: 1 800 422 0711 Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

Neurovascular Ultrasound Scanning (Carotid & Transcranial Doppler) with Hands-On Scanning
Oct 17 - 21, 2011
Wake Forest School of Medicine, Winston-Salem, NC, *United States*
Contact: Program for Medical Ultrasound, Medical Center Blvd.
Tel: 336-716-4505, 800-277-7654 ext.64505; Fax: 336-716-2447
Email: cmu@wakehealth.edu

Carotid only Ultrasound with Hands-On Scanning
Oct 17 - 19, 2011
Wake Forest School of Medicine, Winston-Salem, NC, *United States*
Contact: Program for Medical Ultrasound, Medical Center Blvd.
Tel: 336-716-4505, 800-277-7654 ext.64505; Fax: 336-716-2447
Email: cmu@wakehealth.edu

Clinical State of the Art: **Body MRI**
Oct 17 - 18, 2011
NYU Langone Medical Center, New York, NY, *United States*
Contact: Marisa, 462 First Avenue, New York, NY 10016
Tel: 2122630724
Email: marisa.bruno@nyumc.org

2011 **Cardiometabolic Health** Congress
Oct 19-22, 2011
Sheraton Hotel, Boston, MA, *United States*
Type of Event: Conference
Contact: Jennifer Meola, 788 Shrewsbury Avenue, Suite 102, Boston, MA
Tel: 877-571-4700; Fax: 866-218-9168
Email: jen@cardiometabolichealth.org

7th International Congress on **Vascular Dementia**
Oct 20 - 23, 2011
Revel Hotel Riga, Riga, *Latvia*
Contact: Secretariat, 1-3, rue de Chantepoulet, CH-1211 Geneva 1
Tel: +41 22 908 0488; Fax: +41 22 906 9140
Email: vascular@kenes.com

2011 Advances in **Inflammatory Bowel Diseases**
Oct 21 - 23, 2011
Hollywood, FL, *United States*
Contact: Theresa Jones
Tel: 678-242-0906; Fax: 678-242-0920
E-Mail: meetings@imedex.com

The Canadian **Cardiovascular** Congress 2011
Oct 21 - 26, 2011
Vancouver, BC, *Canada*
Contact: Jacqueline Lane
Tel: 613-569-3407 ext 404; Fax: 613-569-6574
E-Mail: lane@ccs.ca

Orthopaedics and Sports Medicine
Oct 22 - 29, 2011
Royal Caribbean's Liberty of the Seas, Barcelona, *Spain*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711; Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

2011 Annual Meeting of the American Academy of **Ophthalmology**
Oct 22 - 25, 2011
Orlando, FL, *United States*
Contact: American Academy of Ophthalmology
Tel: 415-447-0320
E-Mail: meetings@aao.org

9th International Congress on **Coronary Artery Disease** from Prevention to Intervention
Oct 23 - 26, 2011
Hilton Molino Stucky, Venice, *Italy*
Contact: Secretariat, 1-3 rue de Chantepoulet,Geneva CH-1211, Switzerland
Tel: +41 22 908 0488; Fax: +41 22 906 9140
Email: coronary@kenes.com

American College of **Surgeons** 97th Annual Meeting
Oct 23 - 27, 2011
San Francisco, CA, *United States*
Contact: American College of Surgeons
Tel: 312-202-5000; Fax: 312-202-5001
E-Mail: postmaster@facs.org

81st Annual Meeting of the American **Thyroid** Association
Oct 26 - 30, 2011
Indian Wells, CA, *United States*
Contact: American Thyroid Association
Tel: 703-998-8890; Fax: 703-998-8893
E-Mail: thyroid@thyroid.org

Internal Medicine | Istanbul to Luxor cruise
Oct 29 - Nov 12, 2011
Istanbul, *Turkey*
Contact: Sea Courses Cruises
Tel: 1-888-647-7327; Fax: 1-888-547-7337
E-Mail: cruises@seacourses.com

Peripheral Angioplasty and All That Jazz
Oct 31 - Nov 2, 2011
Roosevelt Hotel, New Orleans, LA, *United States*
Contact: CCM, 11440 N Kendall Drive Miami, FL 33176
Tel: 3052792263
Email: questions@ccmcme.com

Allergy and Asthma in High Performance Sport
Nov 1, 2011
Governors Hall, St Thomas' Hospital, London, *United Kingdom*
Contact: Kenes UK Ltd, 385 Euston Rd
Tel: 44 (0) 207 383 8030
Email: allergyacademy@kenes.com

7th National Conference on **Tobacco or Health**
Nov 1 - 3, 2011
Toronto, *Canada*
Contact: Conference Organizers, 192 Bank St., Ottawa, Ontario, K2P 1W8
Tel: (613) 567-3050
Email: conference@cctc.ca

20th International Conference on **Oral and Maxillofacial Surgery**
Nov 1 - 4, 2011
Casa Piedra, Santiago, *Chile*
Contact: Secretariat, La Concepcín 266 Office 501, Santiago, Chile
Tel: +56 2 946 2633; Fax: +56-2 946 2643
Email: icoms2011@kenes.com

WINFOCUS 2011: 7th World Congress on **Ultrasound in Emergency & Critical Care** Medicine
Nov 02 - 06, 2011
New Delhi, *India*
Contact: Winfocus Secretariat
Tel: 39-051-230-385; Fax: 39-051-221-894
E-Mail: secretariat@winfocus.org

The AICR Annual Research Conference 2011 on **Food, Nutrition, Physical Activity & Cancer**
Nov 3 - 4, 2011
Capital Hilton Hotel, Washington, DC, DC, *United States*
Contact: Research Department, 1759 R Street, NW, Washington, DC 20009
Tel: (800) 843-8114; Fax: 202-328-7226
Email: research@aicr.org

Acute Care **Psychiatry** Clinical Review
Nov 3 - 5, 2011
The Palace Hotel, San Francisco, CA, *United States*
Contact: Meeting Registrar, 200 First Street SW, Rochester, MN 55902
Tel: 1-507-284-2509; Fax: 1-507-284-0532
Email: cme@mayo.edu

Contraceptive Technology: Quest for Excellence
Nov 3 - 5, 2011
Hyatt Regency Atlanta, Atlanta, GA, *United States*
Contact: Registration Dept at Contemporary Forums, 6377 Clark Ave., Suite 200, Dublin, CA 94568
Tel: 800-377-7707; Fax: 800-329-9923
Email: info@cforums.com

4th Clinical Trials on **Alzheimer's disease** (CTAD)
Nov 3 - 5, 2011
US Grant Hotel, SAN DIEGO, *United States*
Contact: Congress Secretariat, 154 aven ue de lodève 34070 Montpellier France
Tel: +33 4 67 10 92 23
Email: ctad@ant-congres.com

Thirteenth Annual **Echocardiography** Symposium
Nov 4 - 5, 2011
Doral Marriott Resort, Miami, FL, *United States*
Contact: Julie Zimmett, 8900 N. Kendall Drive
Tel: 786-596-2398
Email: juliez@baptisthealth.net

Pharmacology for Advanced Practice Clinicians NV
Nov 7 - 13, 2011
Paris Las Vegas, Las Vegas, NV, *United States*
Contact: Registration Dept. at CF, 6377 Clark Ave., Suite 200
Tel: 800-377-7707; Fax: 800-329-9923
Email: info@cforums.com

Peripheral Vascular Ultrasound with Hands-On Scanning
Nov 7 - 10, 2011
Wake Forest School of Medicine, Winston-Salem, NC, *United States*
Contact: Program for Medical Ultrasound, Medical Center Blvd.
Tel: 336-716-4505, 800-277-7654 ext.64505 Fax: 336-716-2447
Email: cmu@wakehealth.edu

ASN **Renal** Week 2011
Nov 08 - 13, 2011
Philadelphia, PA, *United Kingdom*
Contact: The American Society of Nephrology, 1725 I Street, NW, Suite 510, Washington, DC 20006
Tel: 202-659-0599; Fax:202-659-0709
E-Mail: email@asn-online.org

The Fetus & Newborn: State of Art Care
Nov 9 - 12, 2011
Paris Las Vegas, Las Vegas, NV, *United States*
Contact: Registration Dept at Contemporary Forums, CF
Tel: 800-377-7707; Fax: 800-329-9923
Email: info@cforums.com

Endoscopic Sinus and Skull Base Surgery: State-of-the-Art
Nov 10 - 12, 2011
Mayo Clinic, Scottsdale, AZ, *United States*
Contact: Mayo Clinic, 13400 E. Shea Blvd., Scottsdale, AZ
Tel: 480-301-4580 Fax: 480-301-8323
Email: mca.cme@mayo.edu

ICJR 3rd Annual Modern Trends in **Joint Replacement**
Nov 10 - 12, 2011
Hyatt Grand Champions, Palm Springs, CA, *United States*
Contact: Sylke Anderson, 2033 San Elijo Ave., #351, Palm Springs, CA
Tel: 760-942-7859

2011 NEI Global **Psychopharmacology** Congress
Nov 10 - 13, 2011
The Broadmoor, Colorado Springs, CO, *United States*
Contact: Zamanda Garcia, 1930 Palomar Point Way Suite 101, Carlsbad CA 92008
Tel: 760-931-8857; Fax: 760-931-8713
Email: zgarcia@neiglobal.com

Pathology Update 2011
November 11-12, 2011
Toronto, *Canada*
Contact: Continuing Education & Professional Development, 650-500 University Ave
Tel: 416.978.2719; Fax: 416.946.7028
Email: info-lmp1101@cepdtoronto.ca

Back Talk | A Comprehensive Review and Practical Approach to **Spinal Diagnosis** and **Treatment**
Nov 11 - 12, 2011
Renaissance Indianapolis North Hotel, Carmel, IN, *United States*
Contact: Lisa Kriech/ Karen Busse, 8402 Harcourt Rd, #400, Indpls, IN 46220
Tel: 3172287000; Fax: 3172289029
Email: kbusse@indianaspinegroup.com

Sepsis Congress 2011
Nov 12 - 13, 2011
The Leela Kempinski hotel, New Delhi, *India*
Contact: Dr O Singh/ Dr Y Javeri, Department of Critical Care Medicine, Max Super Specialty Hospital 1, Press Enclave Road, Saket, New Delhi, India 110017
Tel: +91-9999261685
Email: sepsis.congress@gmail.com

Mayo Clinic Cancer Center Lung Cancer Symposium: **Thoracic Oncology** for the Non-Oncologist
Nov 12, 2011
Mayo Clinic - Ashton B. Taylor Auditorium, Scottsdale, AZ, *United States*
Contact: Mayo CME Team, 13400 E. Shea Boulevard, Scottsdale, AZ 85259
Tel: (480) 301-4580; Fax: (480) 301-8323
Email: mca.cme@mayo.edu

Laser Aesthetics Course
Nov 12 - 13, 2011
Beckman Laser Institute, Irvine, CA, *United States*
Contact: Barb Brown, 2100 Stewart Avenue, Wausau, WI 54401
Tel: 715-845-9283; Fax: 715-848-2493
Email: barb@aslms.org

Third Annual **Coronary CTA in the ED**: A Hands On Workshop
Nov 12 - 13, 2011
Fontainebleau Hotel, Miami Beach, FL, *United States*
Contact: Julie Zimmett, 8900 N. Kendall Drive, Miami, FL
Tel: 7865962398
Email: juliez@baptisthealth.net

XX World Congress of **Neurology**
Nov 12 - 17, 2011
Palais des Congrès de la Palmeraie, Marrakesh, *Morocco*
Contact: Secretariat, 1-3 Rue de Chantepoulet, CH-1211 Geneva 1
Tel: +41 22 908 0488; Fax: +41 22 906 9140
Email: wcn@kenes.com

Family Medicine: **Pulmonology and Sleep Disorders**
Novr 12 - 19, 2011
Norwegian Cruise Line's Pride of America, Honolulu, HI, *United States*
Contact: Reservations, 5700 4th Street N. St Petersburg, Florida 33703
Tel: 1 800 422 0711 Fax: 1 727 522 8304
Email: contactus@continuingeducation.net

7th World Congress of the World Society for **Pediatric Infectious Diseases**
Nov 16 - 19, 2011
Melbourne Convention Exhibition Centre, Melbourne, *Australia*
Contact: Secretariat, 1-3, rue de Chantepoulet, Geneva 1
Tel: +41 22 908 0488; Fax: +41 22 906 9140
Email: wspid@kenes.com

Laboratory **Diagnosis of Fungal Infections**: The Last Course
Nov 16-18, 2011
Kahler Grand Hotel, Rochester, MN, *United States*
Contact: Kay Kenitz, 3050 Superior Drive NW, Rochester, Minnesota 55901
Tel: 800-533-1710
Email: kenitz.mary@mayo.edu

5th **Autoimmunity** Congress Asia
Nov 17 - 19, 2011
Suntec Singapore, Singapore, *Singapore*
Contact: Secretariat, 1-3, Rue de Chantepoulet,CH-1211 Geneva 1
Tel: +41 22 908 0488; Fax: +41 22 906 9140
Email: aca@kenes.com

14th World Congress on Controversies in **Obstetrics, Gynecology & Infertility** (COGITM)
Nov 17 - 20, 2011
Le Meridien Montparnasse, Paris, *France*
Contact: Ruthi Yahav, 10 quai Charles de Gaulle, Lyon 69463, France
Tel: 33 4 78 176 176; Fax: 33 4 78 176 257
Email: cogi@congressmed.com

WHO-Facts Sheet

1. Hepatitis C
2. Yellow fever
3. Disability and Health
4. Environmental and Occupational Cancers
5. Chronic Obstructive Pulmonary Disease (COPD)

Compiled and edited by
Babichan K Chandy

Kuwait Medical Journal 2011, 43 (3): 259-266

1. HEPATITIS C

Hepatitis C is a contagious liver disease that results from infection with hepatitis C virus (HCV). It can range in severity from a mild illness lasting a few weeks to a serious, lifelong illness. HCV is usually spread when blood from a person infected with HCV enters the body of someone who is not infected. HCV is among the most common viruses that infect the liver.

It is estimated that 3 – 4 million people are infected with HCV each year. Some 130 –170 million people are chronically infected with HCV and at risk of developing liver cirrhosis and/or liver cancer. More than 350,000 people die from HCV-related liver diseases each year.

HCV infection is found worldwide. Countries with high rates of chronic infection are Egypt (22%), Pakistan (4.8%) and China (3.2%). The main mode of transmission in these countries is attributed to unsafe injections using contaminated equipment.

KEY FACTS

- Hepatitis C is a liver disease caused by the hepatitis C virus (HCV).
- HCV infection sometimes results in an acute symtomatic illness. It can range in severity from a mild illness lasting a few weeks to a serious, lifelong chronic condition that can lead to cirrhosis of the liver and liver cancer.
- HCV is transmitted through contact with the blood of an infected person.
- About 130 – 170 million people are chronically infected with hepatitis C virus, and more than 350,000 people die from hepatitis C-related liver diseases each year.
- HCV infection is curable using increasingly effective antivirals.
- Despite ongoing research, there is currently no vaccine to prevent hepatitis C virus infection.

Transmission

The virus is most commonly transmitted through exposure to infectious blood such as through: receipt of contaminated blood transfusions, blood products, and organ transplants; injections given with contaminated syringes, needle-stick injuries in health-care settings; injection drug use; being born to an HCV-infected mother. It is less commonly transmitted through sex with an infected person and sharing of personal items contaminated with infectious blood.

Hepatitis C is not spread through breastmilk, food or water or by casual contact such as hugging, kissing and sharing food or drinks with an infected person.

Getting tested

Knowing one's infection status can prevent health problems that may result from HCV infection and prevent transmission to family and close contacts. Some countries recommend screening for individuals who may be at risk for infection. These include:

- individuals who received blood, blood products or organs before screening for HCV was implemented or where screening was not yet widespread;
- current or former injecting drug users (even those who injected drugs once many years ago);
- patients on long-term hemodialysis;
- health-care workers;
- people living with HIV;
- individuals with abnormal liver tests or liver disease;
- infants born to infected mothers.

PREVENTION

Primary prevention

No vaccine exists to prevent HCV infection, unlike those for hepatitis A and B virus. The risk of infection can be reduced by avoiding:

- unnecessary and unsafe injections;
- unsafe blood products;

Address correspondence to:
Office of the Spokesperson, WHO, Geneva. Tel.: (+41 22) 791 2599; Fax (+41 22) 791 4858; Email: inf@who.int; Web site: http://www.who.int/

- unsafe sharps waste collection and disposal;
- use of illicit drugs and sharing of injection equipment;
- unprotected sex with HCV-infected persons;
- sharing of sharp personal items that may be contaminated with infected blood;
- tattoos, piercings and acupuncture performed with contaminated equipment.

Secondary and tertiary prevention

If a person is infected with HCV, they should:

- receive education and counselling on options for care and treatement;
- be immunized with hepatitis A and B vaccine, to prevent co-infection from these hepatitis viruses, to protect their liver;
- get early and appropriate medical management including antiviral therapy if appropriate; and
- get regular monitoring for early diagnosis of liver disease.

Diagnosis

Diagnosis of acute infection is often missed because the infected person has no symtoms. Common methods of antibody detection cannot differentiate between acute and chronic infection. The presence of antibodies against HCV (anti-HCV) indicates that a person is or has been infected. HCV recombinant immunoblot assay (RIBA) and HCV RNA testing are used to confirm the diagnosis of HCV infection.

Diagnosis of chronic infection diagnosis is made when anti-HCV is present for more than six months. Similar to acute infections, diagnosis should be confirmed with an additional test. Specialized tests are often used to evaluate patients for liver disease including cirrhosis and liver cancer.

Disease progression

Following initial infection, approximately 80% of people do not exhibit any symptoms. Those people who are acutely symptomatic may exhibit fever, fatigue, decreased appetite, nausea, vomiting, abdominal pain, dark urine, grey-coloured faeces, joint pain, and jaundice (yellowing of skin and the whites of the eyes). When a chronically-infected person develops symptoms, it may indicate advanced liver disease.

Statistically, 60–70% of chronically-infected persons develop chronic liver disease, 5-20% develop cirrhosis, and 1–5% die from cirrhosis or liver cancer.

Treatment

Interferon and ribaviron-based therapy has been the mainstay of HCV treatment. Unfortunately, interferon is not widely available globally, is not always well tolerated, some genotypes respond better than others, and many people who take it do not finish their treatment. While HCV is generally considered to be a curable disease, for many persons this is not a reality. Fortunately, scientific advances and intense research and development have led to the development of many new oral antiviral drugs for HCV infection. The future seems to hold great promise for HCV specific oral drugs that will be more effective and better tolerated. Much still needs to be done to ensure that these advances lead to greater access and treatment globally.

For more information contact:
WHO Media centre, Telephone: +41 22 791 2222;
E-mail: mediainquiries@who.int

2. YELLOW FEVER

Signs and symptoms

Once contracted, the virus incubates in the body for 3 - 6 days, followed by infection that can occur in one or two phases. The first, "acute", phase usually causes fever, muscle pain with prominent backache, headache, shivers, loss of appetite, and nausea or vomiting. Most patients improve and their symptoms disappear after 3 - 4 days.

However, 15% of patients enter a second, more toxic phase within 24 hours of the initial remission. High fever returns and several body systems are affected. The patient rapidly develops jaundice and complains of abdominal pain with vomiting. Bleeding can occur from the mouth, nose, eyes or stomach. Once this happens, blood appears in the vomit and faeces. Kidney function deteriorates. Half of the patients who enter the toxic phase die within 10 to 14 days, the rest recover without significant organ damage.

Yellow fever is difficult to diagnose, especially during the early stages. It can be confused with severe malaria, dengue hemorrhagic fever, leptospirosis, viral hepatitis (especially the fulminating forms of hepatitis B and D), other hemorrhagic fevers (Bolivian, Argentine, Venezuelan hemorrhagic fevers and others flavivirus as West Nile, Zika virus etc) and other diseases, as well as poisoning. Blood tests can detect yellow fever antibodies produced in response to the infection. Several other techniques are used to identify the virus in blood specimens or liver tissue collected after death. These tests require highly trained laboratory staff and specialized equipment and materials.

KEY FACTS

- Yellow fever is an acute viral haemorrhagic disease transmitted by infected mosquitoes. The "yellow" in the name refers to the jaundice that affects some patients.
- Up to 50% of severely affected persons without

treatment will die from yellow fever.
- There are an estimated 200,000 cases of yellow fever, causing 30,000 deaths, worldwide each year.
- The virus is endemic in tropical areas of Africa and Latin America, with a combined population of over 900 million people.
- The number of yellow fever cases has increased over the past two decades due to declining population immunity to infection, deforestation, urbanization, population movements and climate change.
- There is no cure for yellow fever. Treatment is symptomatic, aimed at reducing the symptoms for the comfort of the patient.
- Vaccination is the most important preventive measure against yellow fever. The vaccine is safe, affordable and highly effective, and appears to provide protection for 30 – 35 years or more. The vaccine provides effective immunity within one week for 95% of persons vaccinated.

Populations at risk

Forty-five endemic countries in Africa and Latin America, with a combined population of over 900 million, are at risk. In Africa, an estimated 508 million people live in 32 countries at risk. The remaining population at risk are in 13 countries in Latin America, with Bolivia, Brazil, Colombia, Ecuador and Peru at greatest risk.

There are an estimated 200,000 cases of yellow fever (causing 30,000 deaths) worldwide each year. Small numbers of imported cases occur in countries free of yellow fever. Although the disease has never been reported in Asia, the region is at risk because the conditions required for transmission are present there. In the past centuries (XVII to XIX), outbreaks of yellow fever were reported in North America (New York, Philadelphia, Charleston, New Orleans, etc) and Europe (Ireland, England, France, Italy, Spain and Portugal).

Transmission

The yellow fever virus is an arbovirus of the flavivirus genus, and the mosquito is the primary vector. It carries the virus from one host to another, primarily between monkeys, from monkeys to humans, and from person to person.

Several different species of the Aedes and Haemogogus mosquitoes transmit the virus. The mosquitoes either breed around houses (domestic), in the jungle (wild) or in both habitats (semi-domestic). There are three types of transmission cycles.
- Sylvatic (or jungle) yellow fever: In tropical rainforests, yellow fever occurs in monkeys that are infected by wild mosquitoes. The infected monkeys then pass the virus to other mosquitoes that feed on them. The infected mosquitoes bite humans entering the forest, resulting in occasional cases of yellow fever. The majority of infections occur in young men working in the forest (e.g. for logging).
- Intermediate yellow fever: In humid or semi-humid parts of Africa, small-scale epidemics occur. Semi-domestic mosquitoes (that breed in the wild and around households) infect both monkeys and humans. Increased contact between people and infected mosquitoes leads to transmission. Many separate villages in an area can suffer cases simultaneously. This is the most common type of outbreak in Africa. An outbreak can become a more severe epidemic, if the infection is carried into an area populated with both domestic mosquitoes and unvaccinated people.
- Urban yellow fever: Large epidemics occur when infected people introduce the virus into densely populated areas with a high number of non-immune people and Aedes mosquitoes. Infected mosquitoes transmit the virus from person to person.

Treatment

There is no specific treatment for yellow fever, only supportive care to treat dehydration and fever. Associated bacterial infections can be treated with antibiotics. Supportive care may improve outcomes for seriously ill patients, but it is rarely available in poorer areas.

PREVENTION

1. Vaccination

Vaccination is the single most important measure for preventing yellow fever. In high risk areas where vaccination coverage is low, prompt recognition and control of outbreaks through immunization is critical to prevent epidemics. To prevent outbreaks throughout affected regions, vaccination coverage must reach at least 60% to 80% of a population at risk. Few endemic countries that recently benefited from a preventive mass vaccination campaign in Africa currently have this level of coverage.

Preventive vaccination can be offered through routine infant immunization and one-time mass campaigns to increase vaccination coverage in countries at risk, as well as for travelers to yellow fever endemic area. WHO strongly recommends routine yellow fever vaccination for children in areas at risk for the disease.

The yellow fever vaccine is safe and affordable, providing effective immunity against yellow fever within one week for 95% of those vaccinated. A single dose provides protection for 30 – 35 years or more, and probably for life. Serious side effects are extremely rare. Serious adverse events have been reported rarely following immunization in a few endemic areas and among vaccinated travelers (e.g. in Brazil, Australia,

the United States, Peru and Togo). Scientists are investigating the causes.

The risk of death from yellow fever is far greater than the risks related to the vaccine. People who should not be vaccinated include:

- children aged less than 9 months for routine immunization (or less than 6 months during an epidemic);
- pregnant women – except during a yellow fever outbreak when the risk of infection is high;
- people with severe allergies to egg protein; and
- people with severe immunodeficiency due to symptomatic HIV/AIDS or other causes, or in the presence of a thymus disorder.

Travelers, particularly those arriving to Asia from Africa or Latin America must have a certificate of yellow fever vaccination. If there are medical grounds for not getting vaccinated, International Health Regulations state that this must be certified by the appropriate authorities.

2. Mosquito control

In some situations, mosquito control is vital until vaccination takes effect. The risk of yellow fever transmission in urban areas can be reduced by eliminating potential mosquito breeding sites and applying insecticides to water where they develop in their earliest stages. Application of spray insecticides to kill adult mosquitoes during urban epidemics, combined with emergency vaccination campaigns, can reduce or halt yellow fever transmission, "buying time" for vaccinated populations to build immunity.

Historically, mosquito control campaigns successfully eliminated Aedes aegypti, the urban yellow fever vector, from most mainland countries of central and South America. However, this mosquito species has re-colonized urban areas in the region and poses a renewed risk of urban yellow fever.

Mosquito control programmes targeting wild mosquitoes in forested areas are not practical for preventing jungle (or sylvatic) yellow fever transmission.

3. Epidemic preparedness and response

Prompt detection of yellow fever and rapid response through emergency vaccination campaigns are essential for controlling outbreaks. However, underreporting is a concern – the true number of cases is estimated to be 10 to 250 times what is now being reported.

WHO recommends that every at-risk country have at least one national laboratory where basic yellow fever blood tests can be performed. One confirmed case of yellow fever in an unvaccinated population should be considered an outbreak, and a confirmed case in any context must be fully investigated, particularly in any area where most of the population has been vaccinated. Investigation teams must assess and respond to the outbreak with both emergency measures and longer-term immunization plans.

For more information contact:
WHO Media centre. Telephone: +41 22 791 2222;
E-mail: mediainquiries@who.int

3. DISABILITY AND HEALTH

The International Classification of Functioning, Disability and Health (ICF) defines disability as an umbrella term for impairments, activity limitations and participation restrictions. Disability is the interaction between individuals with a health condition (e.g. cerebral palsy, Down syndrome and depression) and personal and environmental factors (e.g. negative attitudes, inaccessible transportation and public buildings, and limited social supports).

Over a billion people are estimated to live with some form of disability. This corresponds to about 15% of the world's population. Between 110 million (2.2%) and 190 million (3.8%) people, 15 years and older, have significant difficulties in functioning. Furthermore, the rates of disability are increasing in part due to ageing populations and an increase in chronic health conditions.

KEY FACTS

- Over a billion people, about 15% of the world's population, have some form of disability.
- Between 110 million and 190 million people have significant difficulties in functioning.
- Rates of disability are increasing due to population ageing and increases in chronic health conditions, among other causes.
- People with disabilities have less access to health care services and therefore, experience unmet health care needs.

Disability is extremely diverse. While some health conditions associated with disability result in poor health and extensive health care needs, others do not. However, all people with disabilities have the same general health care needs as everyone else, and therefore, need access to mainstream health care services. Article 25 of the UN Convention on the Rights of Persons with Disabilities (CRPD) reinforces the right of persons with disabilities to attain the highest standard of health care, without discrimination.

Unmet needs for health care

People with disabilities report seeking more health care than people without disabilities and have greater unmet needs. For example, a recent survey of people with serious mental disorders, showed that between 35% and 50% of people in developed countries, and between 76% and 85% in developing countries, received no treatment in the year prior to the study.

Health promotion and prevention activities seldom target people with disabilities. For example women with disabilities receive less screening for breast and cervical cancer than women without disabilities. People with intellectual impairments and diabetes are less likely to have their weight checked. Adolescents and adults with disabilities are more likely to be excluded from sex education programmes.

How are the lives of people with disabilities affected?

People with disabilities are particularly vulnerable to deficiencies in health care services. Depending on the group and setting, persons with disabilities may experience greater vulnerability to secondary conditions, co-morbid conditions, age-related conditions, engaging in health risk behaviors and higher rates of premature death.

Secondary conditions

Secondary conditions occur in addition to (and are related to) a primary health condition, and are both predictable and therefore, preventable. Examples include pressure ulcers, urinary tract infections, osteoporosis and pain.

Co-morbid conditions

Co-morbid conditions occur in addition to (and are unrelated to) a primary health condition associated with disability. For example the prevalence of diabetes in people with schizophrenia is around 15% compared to a rate of 2 - 3% for the general population.

Age-related conditions

The ageing process for some groups of people with disabilities begins earlier than usual. For example some people with developmental disabilities show signs of premature ageing in their 40s and 50s.

Engaging in health risk behaviours

Some studies have indicated that people with disabilities have higher rates of risky behaviours such as smoking, poor diet and physical inactivity.

Higher rates of premature death

Mortality rates for people with disabilities vary depending on the health condition. However, an investigation in the United Kingdom found that people with mental health disorders and intellectual impairments had a lower life expectancy.

BARRIERS TO HEALTH CARE

People with disabilities encounter a range of barriers when they attempt to access health care including the following.

Prohibitive costs

Affordability of health services and transportation are two main reasons why people with disabilities do not receive needed health care in low-income countries: 32 - 33% of non-disabled people are unable to afford health care compared to 51 - 53% of people with disabilities.

Limited availability of services

The lack of appropriate services for people with disabilities is a significant barrier to health care. For example, research in Uttar Pradesh and Tamil Nadu states of India found that after the cost, the lack of services in the area was the second most significant barrier to using health facilities.

Physical barriers

Uneven access to buildings (hospitals, health centres), inaccessible medical equipment, poor signage, narrow doorways, internal steps, inadequate bathroom facilities, and inaccessible parking areas create barriers to health care facilities. For example, women with mobility difficulties are often unable to access breast and cervical cancer screening because examination tables are not height-adjustable and mammography equipment only accommodates women who are able to stand.

Inadequate skills and knowledge of health workers

People with disabilities were more than twice as likely to report finding health care provider skills inadequate to meet their needs, four times more likely to report being treated badly and nearly three times more likely to report being denied care.

ADDRESSING BARRIERS TO HEALTH CARE

Governments can improve health outcomes for people with disabilities by improving access to quality, affordable health care services, which make the best use of available resources. As several factors interact to inhibit access to health care, reforms in all the interacting components of the health care system are required.

Policy and legislation

Assess existing policies and services, identify priorities to reduce health inequalities and plan improvements for access and inclusion. Make changes to comply with the CRPD. Establish health care standards related to care of persons with disabilities with enforcement mechanisms.

Financing

Where private health insurance dominates health care financing, ensure that people with disabilities are

covered and consider measures to make the premiums affordable. Ensure that people with disabilities benefit equally from public health care programmes. Use financial incentives to encourage health-care providers to make services accessible and provide comprehensive assessments, treatment, and follow-ups. Consider options for reducing or removing out-of-pocket payments for people with disabilities who do not have other means of financing health care services.

Service delivery

Provide a broad range of modifications and adjustments (reasonable accommodation) to facilitate access to health care services. For example changing the physical layout of clinics to provide access for people with mobility difficulties or communicating health information in accessible formats such as Braille. Empower people with disabilities to maximize their health by providing information, training, and peer support. Promote community-based rehabilitation (CBR) to facilitate access for disabled people to existing services. Identify groups that require alternative service delivery models, for example, targeted services or care coordination to improve access to health care.

Human resources

Integrate disability education into undergraduate and continuing education for all health-care professionals. Train community workers so that they can play a role in preventive health care services. Provide evidence-based guidelines for assessment and treatment.

Data and research

Include people with disabilities in health care surveillance. Conduct more research on the needs, barriers, and health outcomes for people with disabilities.

WHO response

In order to improve access to health services for people with disabilities, WHO:

- guides and supports Member States to increase awareness of disability issues, and promotes the inclusion of disability as a component in national health policies and programmes;
- facilitates data collection and dissemination of disability-related data and information;
- develops normative tools, including guidelines to strengthen health care;
- builds capacity among health policy-makers and service providers;
- promotes scaling up of CBR;
- promotes strategies to ensure that people with disabilities are knowledgeable about their own health conditions, and that health-care personnel support and protect the rights and dignity of persons with disabilities.

For more information contact:
WHO Media centre. Telephone: +41 22 791 2222. E-mail: mediainquiries@who.int

4. ENVIRONMENTAL AND OCCUPATIONAL CANCERS

What are occupational and environmental causes of cancer?

Cancer is a leading cause of death worldwide, with 12.7 millions new cases and 7.6 million deaths in 2008. Currently, 63% of all cancers deaths are reported from low- and middle-income countries and this figure is predicted to increase. Globally, 19% of all cancers are attributable to the environment, including work setting, resulting in 1.3 million deaths each year.

KEY FACTS

- Cancer is a leading cause of death worldwide, with 12.7 million new cases and 7.6 million deaths in 2008.
- Globally, 19% of all cancers are attributable to the environment, including work setting resulting in 1.3 million deaths each year.
- WHO has classified 107 agents, mixtures, and exposure situations as carcinogenic to humans.
- External environmental causes of cancer are factors in the environment that increase risk of cancer such as air pollution, UV radiation and indoor radon.
- Every tenth lung cancer death is closely related to risks in the workplace.
- Lung cancer, mesothelioma, and bladder cancer are among the most common types of occupational cancers.

WHO's International Agency for Research on Cancer (IARC) has classified 107 agents, mixtures, and exposure situations as carcinogenic to humans. These include all forms of asbestos and a number of agents found in the environment such as benzene, arsenic in water, cadmium, ethylene oxide, benzo[a]pyrene, silica, ionizing radiation including radon, ultraviolet radiation including tanning devices, aluminium and coke production, iron and steel founding, or the rubber manufacturing industry.

Most of the exposure risks for occupational cancer are preventable. About 125 million people in the world are exposed to asbestos at the workplace. According to WHO estimates, more than 107,000 people die each year from asbestos-related lung cancer, mesothelioma and asbestosis resulting from occupational exposures. One in three deaths from occupational cancer is caused by asbestos.

External environmental causes of cancer are factors in the environment such as pollutants that increase risk for cancer. For example, indoor radon exposure was estimated to cause between 3 -14 % of all lung cancers in 2004, the second most important cause of lung cancer in many countries.

Air pollution caused 165 000 lung cancer deaths globally in 2004 of which:

- 108,000 were caused by outdoor air pollution
- 36,000 were due to solid fuels used for cooking and heating
- 21,000 were due to second-hand smoke.
- UV radiation was estimated to cause 60,000 deaths in 2002 of which:
  - 48,000 were melanomas
  - 12,000 were basal and squamous skin carcinomas.

WHO response

In 2005, a resolution on cancer prevention and control by the World Health Assembly urged countries to develop programmes aimed at reducing cancer incidence and mortality. It recommends including preventable tumours (such as those of lung, colon, rectum, skin and liver): to avoid and reduce exposure to risk factors (such as tobacco use, unhealthy diets, harmful use of alcohol, sedentariness, excess exposure to sunlight, communicable agents, and occupational exposures), in national cancer control programmes.

WHO developed a number of tools for prevention of cancer arising from environmental exposures, including:

- WHO Framework Convention on Tobacco Control;
- policy on elimination of asbestos-related diseases;
- guidelines for air quality and drinking water quality;
- policy options for prevention and mitigation of radon;
- practical advice and information on health effects of UV exposure;
- safety standards for chemicals and food, including cancer-causing contaminants like dioxins and aflatoxins;
- the International Programme on Chemical Safety, including Ten chemicals of major public health concern;
- WHO's global plan of action on workers' health.

For more information contact:
WHO Media centre. Telephone: +41 22 791 2222. E-mail: mediainquiries@who.int

5. CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic obstructive pulmonary disease (COPD) is a lung ailment that is characterized by a persistent blockage of airflow from the lungs. It is an under-diagnosed, life-threatening lung disease that interferes with normal breathing and is not fully reversible. The more familiar terms of chronic bronchitis and emphysema are no longer used; they are now included within the COPD diagnosis.

KEY FACTS

- Chronic obstructive pulmonary disease (COPD) is a life-threatening lung disease that interferes with normal breathing – it is more than a "smoker's cough".
- An estimated 64 million people have COPD worldwide in 2004.
- More than 3 million people died of COPD in 2005, which is equal to 5% of all deaths globally that year.
- Almost 90% of COPD deaths occur in low- and middle-income countries.
- The primary cause of COPD is tobacco smoke (through tobacco use or second-hand smoke).
- The disease now affects men and women almost equally, due in part to increased tobacco use among women in high-income countries.
- COPD is not curable, but treatment can slow the progress of the disease.
- Total deaths from COPD are projected to increase by more than 30% in the next 10 years without interventions to cut risks, particularly exposure to tobacco smoke.

Symptoms

The most common symptoms of COPD are breathlessness (or a "need for air"), abnormal sputum (a mix of saliva and mucus in the airway), and a chronic cough. Daily activities, such as walking up a short flight of stairs or carrying a suitcase, can become very difficult as the condition gradually worsens.

Diagnosis and treatment

COPD is confirmed by a simple diagnostic test called "spirometry" that measures how much air a person can inhale and exhale, and how fast air can move into and out of the lungs. Because COPD develops slowly, it is frequently diagnosed in people aged 40 or older.

COPD is not curable. Various forms of treatment can help control its symptoms and increase quality of life for people with the illness. For example, medicines that help dilate major air passages of the lungs can improve shortness of breath.

Who is at risk?

At one time, COPD was more common in men, but because of increased tobacco use among women in high-income countries, and the higher risk of exposure to indoor air pollution (such as solid fuel used for cooking and heating) in low-income countries, the disease now affects men and women almost equally.

Almost 90% of COPD deaths occur in low- and middle-income countries, where effective strategies for prevention and control are not always implemented or accessible.

Risk factors

COPD is preventable. The primary cause of COPD is tobacco smoke (including second-hand or passive exposure). Other risk factors include:

- indoor air pollution (such as solid fuel used for cooking and heating);
- outdoor air pollution;
- occupational dusts and chemicals (vapors, irritants, and fumes);
- frequent lower respiratory infections during childhood.

Total deaths from COPD are projected to increase by more than 30% in the next 10 years unless urgent action is taken to reduce underlying risk factors, especially tobacco use.

WHO response

WHO's work on COPD is part of the organization's overall efforts to prevent and control chronic diseases. WHO aims to:

- raise awareness about the global epidemic of chronic diseases;
- create more healthy environments, especially for poor and disadvantaged populations;
- decrease common chronic disease risk factors, such as tobacco use, unhealthy diet and physical inactivity;
- prevent premature deaths and avoidable disabilities from major chronic diseases.

The WHO Framework Convention on Tobacco Control (WHO FCTC) was developed in response to the globalization of the tobacco epidemic, with the aim to protect billions of people from harmful exposure to tobacco. It is the first global health treaty negotiated by World Health Organization, and has been ratified by more than 167 countries.

WHO also leads the Global Alliance against Chronic Respiratory Diseases (GARD), a voluntary alliance of national and international organizations, institutions, and agencies working towards the common goal of reducing the global burden of chronic respiratory diseases. Its vision is a world where all people breathe freely. GARD focuses specifically on the needs of low- and middle-income countries and vulnerable populations.

For more information contact:
WHO Media centre; Telephone: +41 22 791 222;
E-mail: mediainquiries@who.int