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About Majmaah University

Al Majma'ah is a city and a governorate in Ar Riyad Province, Saudi Arabia. It has an area of 30,000 square kilometers. The population of the town is around 45,000, while the population of the governorate as a whole is approximately 97,349 . Al-Majma'ah Governorate borders the Eastern Province and Al-Qasim to the north, Thadig and Shaqra to the south, Rumah to the east, and Zulfi and al-Ghat on the west. Founded in 1417 CE by an immigrant from the Shammar tribe, Al-Majma'ah was historically considered the capital of the region of Sudair.

Majmaa'h University is considered one of the most recent universities in the kingdom, established in Ramadan 1430 AH (August , 2009 AD).

It started with nine colleges and now they are thirteen and planned to reach thirty six colleges in the future. The total number of the students are 15000 distributed in five Province, and cities ; Majmaa'h -Zulfa – Al-Ghat - Hawtat Sudair and Rammah, where this university will serve large geographical area covering several counties and cities to achieve the goal of the Ministry of higher education which is the expansion in higher education to include all parts of the Kingdom. To serve the community in several areas of social awareness, education and training. And through research, programs and studies that are compatible with what was planned for this university to achieve its high mission and to reach its planned goals, Allah willing.

FOREWORD

I am delighted to present the inaugral issue of Majmaah Journal of Health Sciences, another initiative of Majmaah University, which shall be published biannualy. I wish to extend my gratitude to the Editor-in Chief Prof. Mohammad Othman Al- Rukban and his editorial team for their passionate and creative contribution in accomplishing the daunting task of publishing the first issue. I would also like to thank all the reviweres for their contribution in examining the scientific content of the manuscripts and providing their valuble recommendations.

I would like to emphasize the compelling reasons for launching a new open-access peer reviwed journal in this ever expanding field of health sciences as well as our aspirations and vision for the future. The focus of this year's edition is centered upon the development of a framework for continuity of the Journal's operations. To achieve this goal, we strive to improve the formalization of submission review and feedback process, online access, search engine indexing, and distribution of the journal.

I believe that it is important to have a journal which gives free access to its contents, promotes high-quality research and intellectual output of reserchers. This journal aims to bridge the gap between the research and practice in the field of health sciences, thus providing an opportunity to the authors to disseminate their high-quality scientific achievements to a wider audience. I believe we will be publishing a significant number of high-quality original research articles and scientific reviews from authors around the world.
We hope this Journal becomes an increasingly customary piece of the accademic culture at this university and look forward watching it grow.

Dr. Khalid bin Saad Al-Meqrin,
Rector, Majmaah University
Al-Majmaah, Kingdom of Saudi Arabia

PREFACE

Majmaah University is pleased to announce the launch of Majmaah Journal of Health Science (MJHS). From time immemorial research and publication have been the foundation of today's science. Out of all the thousands of specialty subspecialty journals, the readers focus on their own specialty and rarely look for other subjects. Due to inadequate multidisciplinary knowledge, there has been lack of integrated approach to the patient care and better health.

Majmaah Journal of Health Science (MJHS) is a peer-reviewed, open access biomedical journal covering all aspects of basic and clinical sciences, medical education, public health, research and publication ethics from all medical and health sciences background. The Journal aims at establishing itself as the leading international journal in medical sciences and deals in publishing original scientific studies, review articles, technical reports, and short communications commenting on the public health, community health, environmental health, behavioural health, health policy, health service, health education, health economics, medical ethics, health protection, and equity in health that are not published or not being considered for publication elsewhere.

We would like to take this opportunity to thank all those who helped in starting this new journal. Special thanks to His Excellency Dr. Khalid bin Saad Al-Meqrin, without his direction & support this endeavour wouldn't have been possible. I would also like to thank the then Vice Rector Dr. Mohsen Al-Mohsen and the incumbent Vice Rector Dr. Mohammed Abdullah Al-Shaya for their proactive role in providing all the support. I commend the efforts of the members of Editorial Committee and Editorial Board of MJHS who made it possible for timely publishing of this journal. MJHS heavily rely on their personal epistemology for reviewing and making their outstanding and invaluable contribution to the journal and we are really grateful to them for giving their time and expertise.

Prof. Mohammad Othman Al Rukban
Editor in Chief, MJHS,
Vice Rector, Academic Affairs,
Dean, College of Medicine, Majmaah University

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We welcome all contributions that enhance or illuminate medical sciences. In addition to scientific articles, letters, news, and comments are welcome if they serve the purpose of transfer of original and valuable information to our readers.

To give an equal publishing chance to manuscripts from different environments, we will normally publish no more than two papers by the same author or co-author within one calendar year. This rule also applies to editors. Also, we recommend authors not to separate fragments of a study into individual reports, but rather to present a full report on the topic.

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The Editor-in-Chief reads every manuscript received and assigns it a general priority level: (a) manuscripts sent to reviewers immediately; (b) manuscripts returned to authors with suggestions for the improvement of data presentation; and (c) rejected manuscripts. Editors-in-Chief read the revised manuscript. If the manuscript is improved adequately, it is sent to two reviewers for extramural review and to the Statistical Editor, if it contains numerical data. This editorial procedure reinforces our author helpful policy because all manuscripts undergo editorial scrutiny and advice.

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According to the International Committee on Medical Journal Ethics (ICMJE), an author is defined as one who has made substantial contributions to the conception and development of a manuscript. Majmaah Journal of Health Sciences adheres to the ICMJE guidelines (http://www.icmje.org/#author), which state that "authorship credit should be based on all of the following: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or advising it critically for important intellectual content; and 3) final approval of the version to be published. All submissions are expected to comply with the above definition. Changes to the authorship list after submission will result in a query from the publisher requesting written explanation.

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All manuscripts will be subjected to confidential peer review by experts in the field and, on the basis of reviewers' feedback; papers will be accepted unconditionally, accepted subject to revision or rejected.

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As all editors and Editorial Board members are active professionals and researchers, it may happen that they would want to submit their articles to the Majmaah Journal of Health Sciences. This represents a potential conflict of interest, especially in cases of submissions from decision-making editors. In reviewing submissions from its editors and Editorial Board members, we follows the guidelines for good editorial practice set by international editorial organizations, such as World Association of Medical Editors (WAME; http://www.wame.org/resources/publication-ethics-policies-for-medical-journals#conflicts) and Committee on

Publication Ethics (COPE; http://publicationethics.org/case/editor-author-own-journal).

The review of such manuscripts will not be handled by the submitting editor(s); the review process will be supervised and decisions made by a senior editor who will act independently of other editors. In some cases, the review process will be handled by an outside independent expert to minimize possible bias in reviewing submissions from editors.

REVIEW PROCESS

1. Authorship statement. Upon the receipt of the submission, authors will receive the Authorship Statement form, which should be filled in, signed and returned to the Editor. In this way, the authors confirm the originality of the report and validity of authorship, and assert compliance with the review process, i.e, that he or she shall not withdraw the paper until it is published or rejected. We advise the authors to promptly send back the filled out authorship statements, or otherwise the editorial processing of the manuscript may be delayed.

2. Pre-review (if necessary). One to three weeks after submission of the manuscript, the author may receive Editor's letter with a copy of the manuscript with suggestions for the improvement of data presentation. This is the manuscript pre-review. The author should closely follow the instructions, revise the manuscript, and submit the revised version.

3. Peer review. The Majmaah Journal of Health Sciences promotes expert refereeing by peers as a best available method for the maintenance of standards of excellence in the scientific community, and is committed to promoting its peer review quality and fairness, as well as its speed and efficiency. Authors are welcome to suggest up to three potential reviewers for their manuscript (excluding co-authors or collaborators for the last three years), or to ask for the exclusion of reviewer(s) and the reasons for it. The reviewers are asked to treat the manuscript with confidentiality, and reveal any research conflict of interest with the reviewed manuscript. Reviewers do not have to sign the review forms with suggestions to the authors, but may do so if they wish. Within two months of submission of the manuscript, the authors will receive the reviews. The comments and suggestions made by the reviewers should be addressed and closely followed. In this respect, the Editor's accompanying letter will give clear general instructions for further work on the manuscript.

4. Author's cover letter accompanying the revised version of the paper. The authors should state clearly and precisely every step taken in accordance with the reviewers' requests. The description should be listed on a numbered basis, in the order of reviewers' comments. Altered paragraphs in the new version of the manuscript should be specified using page and paragraph numbers. Paragraph on top of a page is considered No. 1, even if it does not begin on that page.

ACCEPTANCE CRITERIA

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one or more reviewers' recommendations for "major review," are sent, after revision, with the respective author's cover letter, to the same reviewer, who makes the final recommendation on acceptance or rejection. To ensure the transparency of the editorial process and responsibilities of all authors, the formal letter of acceptance is sent to all authors on the manuscript, and not just to the corresponding author. In the case of rejection, the authors have the right to appeal if they think that the reviewers did not understand or appreciate some points in the manuscript. The editors of the Majmaah Journal of Health Sciences will then decide if there are grounds for reconsidering the manuscript.

Scientific integrity The Editorial Board is devoted to the promotion of scientific integrity as a vital component of the research process. The Research Integrity Editor will deal with all issues related to possible scientific misconduct in manuscripts submitted to or published in the journal. Majmaah Journal of Health Sciences follows the ethics flowcharts developed for dealing with cases of possible misconduct. The COPE flowcharts are available at: http://publicationethics.org/flowcharts.
The following brief guidelines are aimed to increase awareness of our authors and decrease misunderstandings about the publication process in a scientific journal. Although rare events, duplicate publication and scientific fraud (falsification and fabrication of data, and plagiarism) are important issues with serious impact on the integrity of the scientific community. The Majmaah Journal of Health Sciences will not consider papers that have already been published as an article or have been submitted or accepted for publication elsewhere in print or in electronic media. This policy does not preclude consideration of a paper that has been rejected by another journal or of a complete report that follows publication of a preliminary report, such as an abstract or poster displayed at a professional meeting. Short abstracts (400 words) of preliminary research findings presented at conferences and included in conference proceedings are not considered previous publications. Authors should indicate this on the first page of the manuscript and in the cover letter. Presentations longer than an abstract may disqualify the paper. The author should alert the Editor if the work includes subjects on which a previous report has been published.

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MEDICAL HYPNOSIS – A POORLY UNDERSTOOD THERAPEUTIC MODALITY

[1*]Riaz Qureshi

It would be difficult to find a subject, which is more controversial and poorly understood, than hypnosis in the entire medical field. This controversy related to the medical use of hypnosis has had a convoluted rout and history, since the time of Franz Mesmer in 1765, to the time in 1953, when British Medical Association issued a report, which supported its beneficial role in certain conditions/illnesses [1,6,7].

Definition of Hypnosis

It is a particular state of mind in which the suggestions are not only accepted readily, but are also acted upon, much more powerfully than a waking state.[1,3,6]

It is induced in one person by another, but can also be self- induced.

Franz Mesmer, an Austrian Physician and the founder of mesmerism, believed that the human body is immersed in a magnetic fluid, which needs to be manipulated through some means, in order to get rid of the symptoms a person may be suffering from. The presence of a magnetic fluid among the patients, who were treated by Mesmer, was found to be incorrect by a commission of enquiry, established by the ruler of France, the country in which Mesmer had his practice. In response to this finding, Mesmer was forced to leave France, in-spite of the fact that, a significant number of his patients had a remarkable recovery from their illnesses, especially psychoneurotic ones. The level of interest of physicians in treatment by hypnosis has been variable over the 19th as well as the early part of 20th century.

In 1953, medical use of hypnosis received a major boost, when a committee established by the British Medical Association reported that a hypnotic phenomenon does exist, which sheds a great deal of light on the role played by the unconscious mind on human behaviour. This report stated that hypnotherapy (treatment by hypnosis) could be a method of choice in the treatment of certain psychosomatic and psychoneurotic illnesses. The report also found that hypnosis could sometime play a part in Surgery, Obstetrics and Dentistry as an analgesic and an anaesthetic.

The main objectives of this brief review of medical hypnosis are to make the readers aware of:

1. What is hypnosis? Its nature and how it works in clinical practice?
2. What clinical conditions may be managed with hypnosis?
3. Sharing of the author's own experience in the practice of hypnotherapy, over the last 40 years?

In a 'hypnotic state', the conscious mind and its power of criticism are suppressed and suggestions consequently enter the individual's unconscious mind, which does not have the power of criticism and therefore, unable to reject them.[2,3,6,7]

Susceptibility to Hypnosis

90% of the population can be hypnotized.

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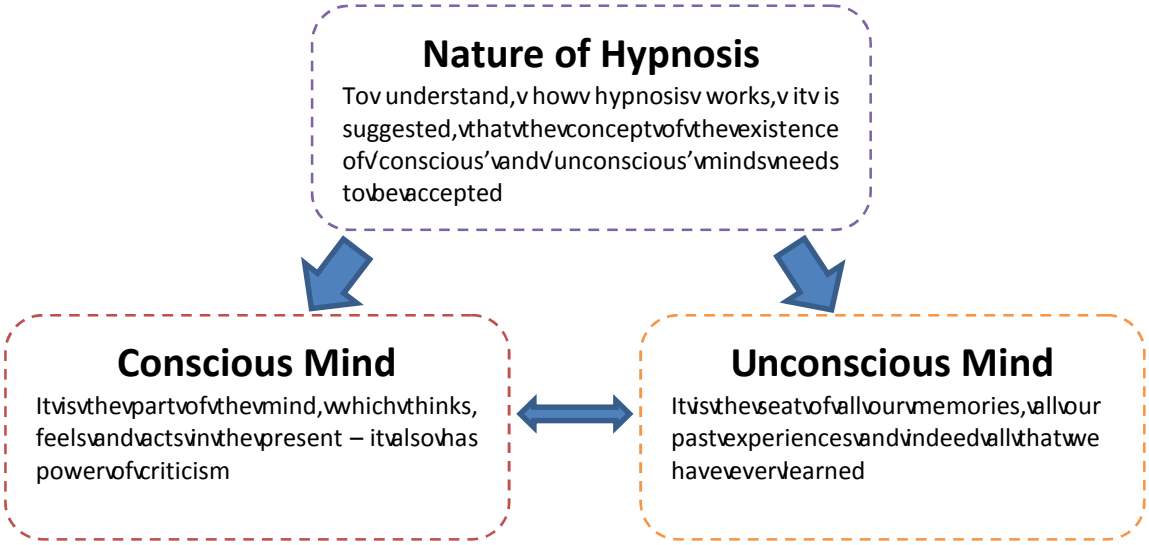

Light hypnosis can be achieved by 10% patients medium- depth- hypnosis by 70-80 % of patients and deep level of hypnosis by10-20% of the patients. Children, teenagers, members of armed forces, actors and actresses are usually excellent subjects.

Induction of Hypnosis:

There are many methods of inducting hypnosis in a subject. The following are the steps of a simple hypnosis induction technique, which the author has himself practiced effectively over many years:

- Eye-fixtaion, by the patient on an object of his own choice, with distraction.
- Progressive muscle relaxation from one end of the body to the other end.
- Relaxation through deep breathing exercise
- Deepening of the relaxation trance by visual imaging of a nice scene of patient's own choice.
- Post-hypnotic suggestions.
    - Ego strengthening
    - Specific suggestions related to the problem concerned
- Autohypnosis / self-hypnosis training.
- Awakening the subject.

Training of patients to practice the hypnotherapy session (self-hypnosis) at home is an essential requirement for this treatment modality. A patient under hypnotic trance may appear asleep or unconscious, but in reality, he is fully aware of his surroundings (it is not a true natural sleep). Under medical hypnosis, patient cannot be made to do anything against his will.

If there is an unexpected emergency situation during the hypnosis session, the patient comes out of the trance and copes with the emergency, even better than normal. [6,7]

Hypnotic Analgesia:

Complete analgesia (relief from pain) is achieved in less than 20% of subjects with deep hypnosis. Partial analgesia is achieved through medium depth hypnosis. Negligible analgesia can be achieved through light hypnosis.

Pain threshold can be raised through hypnosis. Distraction theory is applied to achieve hypnotic analgesia

Therapeutics use of Hypnosis (Medical Hypnosis):

A wide variety of medical and dental conditions/Illnesses respond to hypnotherapy, according to the published literature. The problems/ illnesses quoted below belong to a limited number of conditions/ illnesses, which respond well to hypnotherapy, in the personal experience of the author.

Medical Hypnosis in Dentistry helps in

1. Obtaining relaxation – raises patient's pain threshold.
2. Ensuring co-operation.
3. Reduction of fear and anxiety.
4. Preparation for local and general anesthesia.
5. The production of amnesia in deep trance.
6. The control of fainting.
7. Reduced bleeding.
8. Locking of jaw, so that it is widely open for the procedure.[6,7,9]

Medical Hypnosis in Incurable and Painful Illness:

- Hypnosis can reduce:
  - The actual pain itself.
  - The distress that it causes.
- Pain is more easily tolerated.
- It helps the patient to accept his illness through relaxation and reduction of tension.
- It can raise the threshold of pain with reduction in medication.[6,7,8,9].

Medical Hypnosis in Some Other Painful Conditions:

Irritable bowel syndrome and Nervous dyspepsia, Chronic back pain / Neck pain, Tension - headache and Migraine, Dysmenorrhoea, Non-specific pain with Somatization. [6,7,8,9]

Medical Hypnosis in other Clinical Conditions:

1. **Respiratory/ENT-**Asthma, hyperventilation, frequent Sore Throat and Allergy[5,6]
2. **Cardio Vascular-**Hypertension and Palpitation [5,6,7]
3. **Neurology-**Headache / Migraine, Neuropathic pain[6,7,9]
4. **Gastroenterology-**Irritable bowel, Nervous dyspepsia and Constipation [6,7,8,10]
5. **Endocrinology-**Obesity [6,7]
6. **Psychiatry-**Anxiety, Insomnia, Phobia, Substance abuse & Alcohol[6,7]
7. **Miscellaneous-**Academic field, lack of confidence, tics, speech disorder, sports & smoking.[5,6,7]

Advantages of Medical Hypnosis in Obstetrics:

1. Increases the patient's ability to relax.
2. There is no depression of the respiratory or circulatory functions.
3. There is some shortening of the first stage of labour.
4. Increases the patient's resistance to obstetric shock and the patient is much less exhausted.
5. Does not interfere with the mechanics of labour.
6. Reduces pain by relieving the `fear pain tension' syndrome.
7. Acute pain is most likely to be felt as the head crowns, but its intensity may be greatly reduced.
8. It affords better control over the rate of expulsion of the head and shoulders.
9. Episiotomy can be performed quite painlessly.

Most women feel remarkably fit and well after hypnotic delivery.[4,5,6,7,11]

8. **Childhood Behavior Disorders-** Nocturnal enuresis, school phobia and nail biting / thumb sucking. [6]
9. **Dermatology-**Eczema, allergic rashes and warts.[6,7]

Conclusion: Medical Hypnosis is not a miracle-worker, but it can be a valuable non-pharmacological therapeutic modality in the treatment of a variety of conditions/illnesses, in the hands of a caring and competent physician.

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REFERENCES

1. Tinterow M M. Foundation of Hypnosis: From Mesmer to Freud.Springfield111. Charles. C Thomas ;1970
2. Snaith R P. A method of psychotherapy based on relaxation techniques. BJPsych. 1974;124:473-81.
3. Ellenberger H F. The Discovery of the unconcious. New York: Basic Books.1970
4. Stewart H, Fry A. The Scope of hypnosis in general practice. BMJ.1957(1):1325
5. Cracilneck H B, Hall J A. Clinical hypnosis: Principles and Applications. New York: Grune & Stratton ;1975.
6. Hartland J. Medical and Dental Hypnosis and its Clinical Applications, 2nd ed. London: Baillieére Tindall ;1971.
7. Ambrose A, Newbold G. A Handbook of Medical Hypnosis, 4th ed. London: Ballieére Tindall ;1980.
8. Wilson S, Madison T, Roberts L, Greenfield S. Systematic review: the effectiveness of hypnotherapy in the management of irritable bowel syndrome. AP&T 2006 Sept;24 (5): 769-80.
9. Grondahi JR, Rosvold E O. Hypnosis as a treatment of chronic widespread pain in general practice: a randomized controlled pilot trial. BMC Musculoskeletal Disorders .2008 Sep 18; 9: 124
10. Lindfors P, Unge P, Arvidsson P, Nyhlin H. Effects of gut-directed hypnotherapy on IBS in different clinical settings-results from two randomized controlled trial. Am J Gastroenterol.2012 Feb; 107(2): 276-85
11. Madden K, Middleton P, Cyna AM, Mathewson M, Jones L. Hypnosis for pain management during labour and childbirth. Chochrane Database of systematic Reviews 2012, Available on- http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009356.pub2/abstract : Accessed on 1.2.2013.

CDP-CHOLINE NEUROPROTECTION AND VASCULAR REMODELLING VIA IRS-1 MECHANISMS IN VASCULAR DEMENTIA

GROWING NEURONS ATOP MICROELECTRONIC CHIPS AS A NEW MODEL FOR NEURODEGENERATION

[1*]Raid Al -Baradie, [2]Stephen Lynch, [3]J Borresen, [4]Jerzy Krupinski [5]Mark Slevin

ABSTRACT

Over the past couple of decades there have been no major improvements in the treatment of either acute ischaemic stroke or one of its major complications, neurodegenerative dementia. The majority of promising clinical trials associated with attempts to protect against the debilitating effects of Alzheimer's disease have ended prematurely following exasperation of the condition. Citicoline has been used extensively in patient trials following stroke but strong evidence for its ability to enhance neuroprotection and improve recovery are still lacking. Following our demonstration that this molecule can also enhance angiogenesis/vascularization we hypothesized that it could benefit patients suffering from vascular dementia. Here we describe our recent findings, discuss citicoline signalling and possible links to neurovascular degradation/protection, and consider novel mathematical-biological systems methodology for the identification of potential protective/therapeutic agents against this disease.

ملخص: على مدى العقدين الماضيين لم يكن هنالك أي تطور كبير في علاج السكتة الدماغية الحادة أو احد مضاعفاتها الرئيسية وهو الخرف الناتج من تلف الاعصاب وغالبية التجارب السريرية الواعدة المرتبطة بمحاولات الحماية من الآثار المدمرة لمرض الزهايمر توقفت قبل اوانها. استخدم السيتيكولين على نطاق واسع في التجارب علي مرضي السكتة الدماغية ولكن لا توجد براهين قوية علي قدرته على تعزيز الحماية العصبية وتحسين الشفاء. حسب تجربتنا فيمكن لهذا الجزيء ان يعزز تكوين الأوعية الدموية مما يؤدي للافتراض بأنه يمكن أن يستفيد منه المرضى الذين يعانون من الخرف الوعائي. سنوصف هنا النتائج التي توصلنا إليها مؤخرا، وسنناقش إشارات السيتيكولين والروابط الممكنة لحماية الاوعية الدموية للأعصاب من التلف، كما سننظر في منهجية النظم الرياضية البيولوجية لتحديد العوامل الوقائية و العلاجية المحتملة ضد هذا المرض.

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INTRODUCTION

Evidence of reduced blood-brain barrier (BBB) integrity preceding other Alzheimer's disease (AD) pathology provides a strong link between cerebrovascular pathology and AD. In animals models, amyloid-β peptide - injected animals exhibited a commonality in perturbations of microvessels compared with those evident in AD brain[22]. It was suggested that amyloidogenesis promotes extensive neoangiogenesis leading to increased vascular permeability and subsequent hypervascularization in AD. In human patients hypervascularity was corroborated in a comparison of postmortem brain tissues from AD. Brain microvessels derived from patients with AD expressed numerous factors implicated in vascular activation and angiogenesis. Signaling cascades associated with vascular activation and angiogenesis were upregulated in AD-derived brain microvessels[21]. However, these newly formed blood vessels may be non-functional. All above provides a new paradigm for integrating vascular remodeling with the pathophysiology observed in AD[20]. Therefore, vascular activation hypothesis could be a novel, unexplored therapeutic target in AD.

Background of our own recent investigations: In our recent study, we have, for the first time, demonstrated both a vascular protective, and proangiogenic effect of citicoline using *in vivo* and *in vitro* models[19]. Our data suggests a strong protective effect against the damaging process of excitotoxicity and hypoxia, similar to that experienced after acute ischaemic stroke. In regard to the possible mechanism our protein studies demonstrated that citicoline induced pERK1/2 expression, a key mitogenic signalling protein known to be involved in angiogenesis and generally stimulated by growth factors through interaction with their receptors[23].

There is the potential of citicoline to activate intra-cellular signal transduction pathways and induce phosphorylation of down-stream angiogenic molecules; hence we investigated this ability in more detail by analysis of the Kinexus-phospho-protein Western screening following treatment of vascular EC with citicoline.

Interestingly, treatment with citicoline modified the expression of only several of the >500 proteins on the array showing a degree of specificity. Insulin receptor substrate-1 (IRS-1) was phosphorylated in the presence of citicoline. IRS-1 over-expression was attributed to increased angiogenesis in human EC in association with increased Akt and VEGF-A expression [Stephens et al, 2012], whilst *in vivo*, antisense IRS-1 sequences delivered by sub-conjunctival injection inhibited rat corneal neovascularisation[18], and when delivered by means of eye-drops (GS-101) were found to be tolerable in a phase-1 clinical trial and may be sufficient to prevent neovascularisation in disease such as retinopathy and neovascular glaucoma [15].

Therefore, IRS-1 represents a potent modulator of pro-angiogenic signalling cascades in vascular EC and as such, since we have shown both *in vitro*, and in the rat model of temporary MCAO that citicoline induces phosphorylation of IRS-1 and concomitant EC activation and increased vascularisation. This could be a key novel mechanism of action of citicoline implicated in stroke recovery pathways and angiogenesis until now. This may be an extremely valuable novel finding in regard to understanding the potential mechanisms through which citicoline treatment results in patient recovery, since both protection of EC and induction and maintenance of angiogenesis is key to both short-term and

chronic re-vascularization after stroke impacting indirectly but significantly also on neuronal survival and re-integration[17]. Figure one for details[19].

IRS-1 in neurodegeneration: Only recently, it has been demonstrated that beta-amyloid (Abeta) oligomers are implicated in Alzheimer's disease leading to phosphorylation and degradation of the adaptor protein insulin receptor substrate-1 (IRS-1). IRS-1 couples insulin and other trophic factor receptors to downstream kinases and neuroprotective signaling. Increased phospho-IRS-1 is found in AD brain. Levels of IRS-1 and their activated kinases correlated positively with those of oligomeric Aβ plaques and are negatively associated with episodic and working memory, even after adjusting for Aβ plaques, neurofibrillary tangles, and APOE ε4. Brain insulin resistance thus appears to be an early and common feature of AD, a phenomenon accompanied by IGF-1 resistance and closely associated with IRS-1 dysfunction potentially triggered by Aβ oligomers and yet promoting cognitive decline independent of classic AD pathology[17,18]

New assays for neuronal degeneration: It is now understood that periodic behaviour is not confined to a limited number of physiological processes but is abundant in most biological systems. Periodicity in processes of the human body encompass phenomena such as genetic interactions, heartbeat rhythms, oscillating secretory, retina and muscle cells, cytoskeletal structures, bacterial oscillations, rhythmic behaviour in growth and development, and most importantly for this study, neuronal oscillations[1-3]. In 1952, whilst modelling neurons, Hodgkin and Huxley were able to accurately model the action potential in the giant squid axon[4]. Their nonlinear ordinary differential equations approximate electrical characteristics of excitable oscillatory cells such as cardiomyocytes and neurons. In 2009, Borresen and Lynch[5] published a paper suggesting a novel idea based on biological neural computing utilising the Hodgkin-Huxley equations, and following this work, three years later UK and International patents were published[6]. The patent illustrates how it is possible to construct binary logic gates from biological neurons grown on a chip. It is proposed that neurons could be grown on a chip and that they could be trained to perform certain logical operations. Binary oscillator logic gates could then be used to test drugs that may halt or reverse symptoms of neurological disorders such as Alzheimer's, Parkinson's disease and epilepsy. A number of research groups are

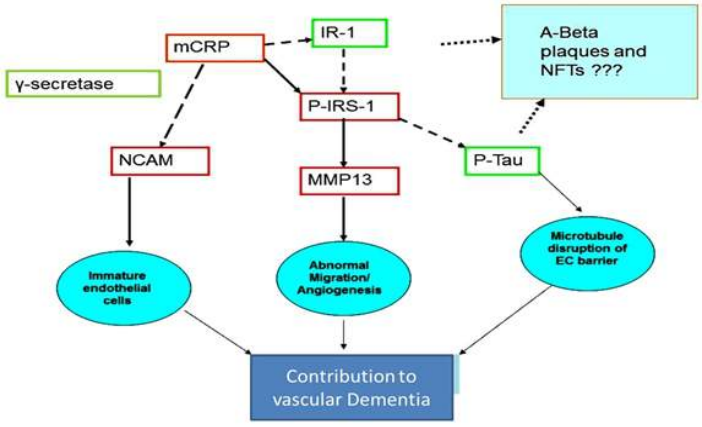

Figure 1 shows the operation of a binary half-adder based on Fitzhugh-Nagumo oscillators (which are simplified versions of the Hodgkin-Huxley models).

now able to grow neurons on chips using a variety of techniques including an aligned micro-contact printing technique, patch clamping (which yields very accurate information but is invasive) and extracellular recordings by means of external micro-transducers or optical measurements (which are non-invasive)[8-13], and it has recently been shown that Parkin diseased neurons can also be grown on a chip[14]. In 2012[15], it was shown that citicoline could be used as a protective treatment against Alzheimer's following a stroke.

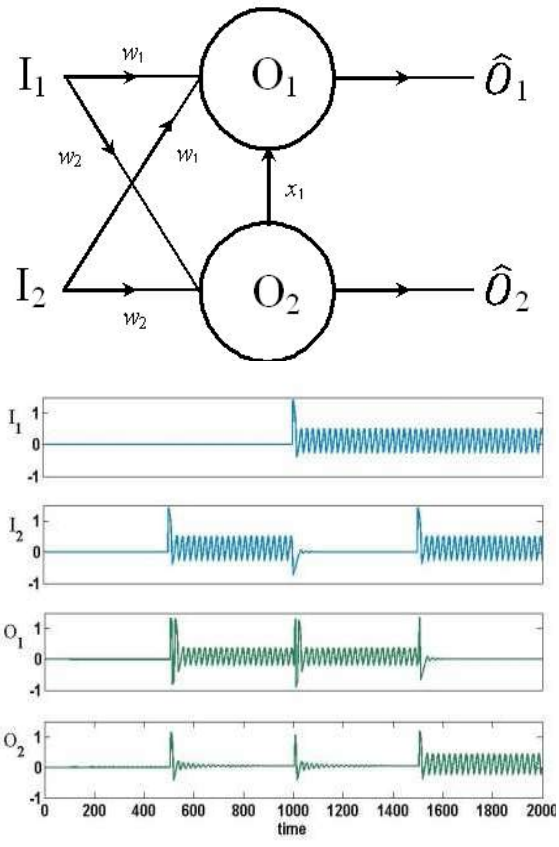

Figure 2: (a) Schematic of a binary oscillator half-adder. (b) Numerical simulation: Time series showing correct logic function of a half-adder. An oscillation corresponds to a 1 in binary and no oscillation is a zero. The sum oscillator O_1 will oscillate if either I_1 or I_2 is active. The carry oscillator O_2 will oscillate if both I_1 and I_2 are active. An inhibitory connection, say x_1, from O_2 to O_1 suppresses oscillator O_1 if O_2 is active.

Based on our previous results and citicoline involvement in blood vessel remodelling via IRS-1 pathway together with a new evidence of vascular hypothesis in AD, we aim to develop an *in vitro* assay for neuronal degradation of Alzheimer's diseased neurons. In this model we will study effects of citicoline/IRS-1 pathways on neurones grown on atop microelectronic chips in conditions of ischemia and neurodegeneration. It is a multidisciplinary project drawing on Medicine, Biology, Mathematics, Chemistry, Physics, Engineering and Computing.

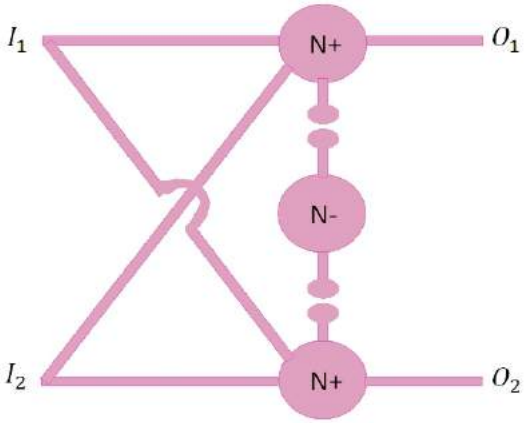

Figure 3: Schematic of a binary oscillator half-adder using biological neurons. Neurons N+ depict excitatory neurons and neuron N- depicts an inhibitory interneuron. Using the logic circuitry highlighted by Lynch et al[6,7,16], we believe it is possible to build an assay for neuronal degradation. Implementation of the half-adder using biological neurons on a chip will require three neurons as neurons are either excitatory or inhibitory, they cannot be both. Figure 3 shows a schematic of the biological half-adder

FUTURE DEVELOPMENTS

We have already shown that it is possible to construct logic gates and memory using threshold oscillator logic[16]. We demonstrated how coupled threshold oscillators (neurons) may be used to perform binary logic in a manner entirely

consistent with modern computer architectures.

Figure 2(a) demonstrates a viable circuit schematic for half-adder implementation using two neuronal oscillators labelled O_1 and O_2 and two inputs I_1 and I_2, which may themselves be the output from other neurons in a more complex circuit. In order to perform the logical operations it is necessary that either neurons with differing thresholds be used or the connections between the neurons should be of differing weights, indicated by w_1 and w_2 in the figure. Figure 2(b) displays a time series plot of a binary half-adder. Schematics and time series for a two oscillator full adder, a three oscillator seven input full adder, a 2x2 bit binary multiplier and a set reset flip-flop (used for memory) are also displayed[16].

CONCLUSIONS

Future work: Our current work is structured in five main steps:

1. Growing neurons on chips. 2. Design of a new model of threshold logic based on biological neurons. 3. Simulation of threshold oscillator logic using a suitable mathematical package. 4. Building neuronal logic circuits using neurons. 5. Growth of Alzheimer/vascular dementia diseased neurons on chip and measurement of neuronal degradation for different citicoline dosages.

This methodology will allow for the sub-cellular resolution (micro-pixel) within neurobiological preparations for example neuron-neuron interfaces and indeed later, entire neuronal networks. This proposed methodology has potential application in all areas of neuroscience, medical diagnostics and pharmacology.

REFERENCES

1. Rapp P.E. An atlas of cellular oscillators, J. Exp. Biology 1979; 81: 281-306.
2. Hierlemann A., Frey U., Hafizovic S., Heer F. Growing cells atop microelectronic chips: Interfacing electrogenic cells in vitro with CMOS-based microelectrode arrays introduction, Proc. of IEEE 2011; 99: 249-251.
3. Kruse K. and Jülicher F. Oscillations in cell biology, Opinion in Cell Biology 2005; 17: 20–26.
4. Hodgkin A. and Huxley A. A quantitative description of membrane current and its application to conduction and excitation in nerve, J. Physiol. 1952; 117: 500-544.
5. Borresen J. and Lynch S. Neuronal computers, Nonlinear Anal. Theory, Meth. & Appl. 2009; 71:2372-2376.
6. Lynch S. and Borresen J. Binary half adder using oscillators, International Publication Number WO 2012/001372 A1, 1-57.
7. Lynch S. and Borresen J. Binary half-adder and other logic circuits, UK Patent Number 2012; GB 2481717 A, 1-57.
8. James CD, Davis R., Meyer M. Aligned microcontact printing of micrometer-scale poly-L-lysine structures for controlled growth of cultured neurons on planar microelectrode arrays, IEEE Trans. on Biomedical Engineering 2000; 47: 17-21.
9. Delivopoulos E, Murray AF, MacLeod N.K. and Curtis JC. Guided growth of neurons and glia using microfabricated patterns of parylene-C on a silicon dioxide background, Biomaterials 2009; 30: 2048-2058.
10. Xu F.L., Fakas S., Korbeek S. et al. Mercury-induced toxicity of rat cortical neurons is mediated through N-methyl-D-Aspartate receptors, Molecular Brain (2012); 5: 1-14.
11. Fromherz P., Eick S. and Hofmann B. Neuroelectronic Interfacing with Semiconductor Chips, Nanoelectronics and Infromation Technology, Ed. R Waser, 2nd Edition. 2012.
12. Stephens C.L., Toda H., Palmer T.D. Adult neural progenitor cells reactivate superbursting in mature neural networks, Experimental Neurology 2012; 234: 20-30.
13. Arthur J.V., Merolla P.A., Akopyan F. Building block of a programmable neuromorphic substrate: A digital neurosynaptic core, International Joint Conference on Neural Networks 2012.

14. Jiang HB., Ren Y., Yuen EY. Parkin controls dopamine utilization in human midbrain dopaminergic neurons derived from induced pluripotent stem cells, Nature Communications 2012; 3: Article number 668.
15. Krupinski J., Abudawood M., Matou-Nasri S. Citicoline induces angiogenesis improving survival of vascular/human brain microvessel endothelial cells through pathways involving ERK1/2 and insulin receptor substrate-1, Vascular Cell 2012; 4: 20.
16. Borresen J. and Lynch S. Oscillatory threshold logic, PLoS ONE 2012; 7: e48498.
17. Talbot K, Wang HY, Kazi H, Han LY, Bakshi KP, Stucky A, Fuino RL, Kawaguchi KR, Samoyedny AJ, Wilson RS, Arvanitakis Z, Schneider JA, Wolf BA, Bennett DA, Trojanowski JQ, Arnold SE. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline.J Clin Invest. 2012 Apr 2;122(4):1316-38. doi: 10.1172/JCI59903.
18. O'Neill C, Kiely AP, Coakley MF, Manning S, Long-Smith CM Insulin and IGF-1 signalling: longevity, protein homoeostasis and Alzheimer's disease.Biochem Soc Trans. 2012 Aug ;40(4):721-7. doi: 10.1042/BST20120080.
19. Krupinski J, Abudawood M, Matou-Nasri S, Al-Baradie R, Petcu E, Justicia C, Planas A, Liu D, Rovira N, Grau-Slevin M, Secades J, Slevin M.Citicoline induces angiogenesis improving survival of vascular/human brain microvessel endothelial cells through pathways involving ERK1/2 and insulin receptor substrate-1.Vasc Cell. 2012 Dec 10;4(1):20. [Epub ahead of print]
20. Biron KE, Dickstein DL, Gopaul R, Jefferies WAPLoS One. 2011;6(8):e23789. doi: 10.1371/journal.pone.0023789. Epub 2011 Aug 31.Amyloid triggers extensive cerebral angiogenesis causing blood brain barrier permeability and hypervascularity in Alzheimer's disease.
21. Grammas P, Sanchez A, Tripathy D, Luo E, Martinez J. Vascular signaling abnormalities in Alzheimer disease.Cleve Clin J Med. 2011 Aug;78 Suppl 1:S50-3. doi: 10.3949/ccjm.78.s1.09.
22. Jantaratnotai N, Ryu JK, Schwab C, McGeer PL, McLarnon JG.Comparison of Vascular Perturbations in an Aβ-Injected Animal Model and in AD Brain. Int J Alzheimers Dis. 2011;2011:918280. doi: 10.4061/2011/918280. Epub 2011 Sep 29.
23. Ma QL, Yang F, Rosario ER, Ubeda OJ, Beech W, Gant DJ, Chen PP, Hudspeth B, Chen C, Zhao Y, Vinters HV, Frautschy SA, Cole GM.Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin.J Neurosci. 2009 Jul 15;29(28) :9078-89. doi: 10.1523/JNEUROSCI.1071-09.2009.

GENTAMICIN INDUCED NEURODEGENRATIVE CHANGES IN AUDITORY CORTEX OF ADULT ALBINO RATS

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ABSTRACT

***Background**: Aminoglycoside-induced nephrotoxicity and ototoxicity is a major clinical problem. Aminoglycosides have good activity against many multi-drug resistant Gram negative bacilli and are therefore important for treating serious infections due to these organisms in adults and children including neonates. Gentamicin, due to it cost effectiveness has been used in most of the trials as compared to other aminoglycosides. Most studies documented the peripheral toxicities of gentamicin without any concern of central neurotoxicity. **Objective**: To observe Gentamicin induced neurodegenerative changes in auditory cortex of adult albino rats. **Methods**: It was an experimental study. Twenty rats were randomly divided in two groups; Group I (Experimental: n = 10) received intramuscular injection of Gentamicin for twenty one days and Group II (Control: n =10) received normal saline intramuscularly. Histological preparations were done on sections obtained from the area around lateral sulcus of rat cortex. The photomicrographs of the relevant stained sections were taken with the aid of a light microscope. **Results**: Light microscopic examination of the auditory cortex sections obtained from gentamicin injected rats (Group I) revealed severe neurodegenerative changes as compared to the rats in (Group II). **Conclusion**: Exposure of rats to Gentamicin for three weeks showed severe neurodegenerative changes. Keywords: Aminoglycosides, Auditory Cortex, Nephrotoxicity, Ototoxicity*

ملخص: يعتبر تسمم الكلى وتسمم الاذن الناتج من الأمينوجليكوزايد من المشاكل الاكلينيكية الرئيسية. للامينوجليكوزايد خاصية جيدة في القضاء علي كثير من العصيات سلبية الجرام المقاومة لأكثر من عقار، وبالتالي فهي مهمة لعلاج الالتهابات الخطيرة الناتجة من هذه العصيات في البالغين والأطفال بما في ذلك حديثي الولادة. ويستخدم الجنتاميسين في معظم التجارب بالمقارنة مع الأمينوجليكوزايد الأخرى نظرا لقلة تكلفته. معظم الدراسات اهتمت بالتسمم الطرفي للجنتاميسين دون أي تركيز علي التسمم العصبي المركزي. **الهدف**: ملاحظة التلف الذي يسببه الجنتاميسين للأعصاب في القشرة السمعية للجرذان البالغة. **منهج الدراسة**: دراسة تجريبية، حيث تم تقسيم عشرون فأر عشوائيا الي مجموعتين، المجموعة الأولى (التجريبية وعددها = 10) وتم حقنها في العضل بالجنتاميسين لمدة واحد وعشرون يوما. والمجموعة الثانية (للمقارنة وعددها = 10) وحقنت بمحلول ملح بالعضل. وقد أخذت عينات نسيجية من المنطقة المحيطة بالتلم الخارجي للقشرة المخية للفئران. تم التصوير المجهري من الأقسام ذات الصلة بمساعدة المجهر. **النتائج**: كشف الفحص المجهري لنسيج القشرة السمعية التي تم الحصول عليها من الفئران التي حقنت بالجنتاميسين (المجموعة الأولى) كشف عن تلف شديد للأعصاب بالمقارنة مع الفئران في (المجموعة الثانية). **الاستنتاج**: تعرض الفئران للجنتاميسين لمدة ثلاثة أسابيع أدي الي تلف شديد للأعصاب

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INTRODUCTION

Gentamicin is a member of aminoglycoside family of antibiotics produced by micrmonospora pupurea. It can be used in different type of infections, including gram positive and gram negative bacteria. In addition, it has significant effect against pseudomonas. Gentamicin works by inhibiting protein synthesis. It binds very strongly to ribosome's (30 S) sub unit and interferes with Protein synthesis. Gentamicin enters the cell by binding to negatively charged phospholipids and enters the cytosol via electron transport linked system and thus need oxygen and ATP to enter cytosol and be effective. Therefore Gentamicin antibiotics are effective only in aerobic bacteria. The structure of Gentamicin is consistent with the aminoglycoside structural activity relationship (SAR), except with a few minor changes. Specifically ring one have methylated amine and one axial hydroxyl group. The methylation of amine will retain its activity and will lower the susceptibility to transferase, which are the enzyme that probably causes inactivation.

Clinically, Gentamicin is used for some urinary tract infection, burns some pneumonia and bone and joint infection caused by gram negative bacteria. The most common clinical application (either alone or as part of combination therapy) of the Gentamicin is in the treatment of serious infections caused by aerobic gram-negative bacilli. Gentamicin has also been used for the treatment of selected staphylococcal and enterococcal infections. Gentamicin is the usual all-purpose agent of choice[11]. Gentamicin is more active against serratia marcescens. Gentamicin has been shown to destabilize the outer membrane of Pseudomonas aeruginosa and form holes in the cell wall, independent of its action on ribosomes (Kadurangamuwa et al, 1993). This action of the aminoglycosides may be the most important.

Ototoxicity is the most important adverse effects clinically, and had dominated attempts to rationalize aminoglycoside dosing[2]. A well-known factor i.e. hearing loss occurred as a result of degeneration of the hair cells of the cochlea, beginning at the basal coil and progressing towards the apex. High frequency hearing loss was followed by loss of lower frequency. According to Takada and Schacht, (1982) disequilibrium and ataxia were main symptoms of vestibulotoxicity. Both acute (reversible) and chronic (irreversible) ototoxicity had been observed. Ganesan et al, (1983) described that chronic toxicity was related to aminoglycoside-phosphoinositol binding, leading to altered membrane structure and permeability. According to Kahlmeter and Dahlager[10] gentamicin toxicity was the most common single known cause of bilateral vestibulopathy. In pathologic studies, severe aminoglycoside toxicity was associated with death of inner ear hair cells[13]. Oei et al described doses that were not enough to kill hair cells but damaged their motion sensitive hairs (sterocilia), making them unable to respond to motion, at least for some months[13]. Guan et al[8] described that the mechanism of toxicity was through reduction of mitochondrial protein synthesis and the interference with mitochondrial function would be expected to cause cellular disruption through reduction in ATP production. Gentamicin is equally vestibulotoxic and ototoxic (Schacht, 1993).

Neuromuscular blockade is also commonly reported side effect. Patients with neuromuscular blockade may present clinically numbness, twitching of muscles and seizures. Said et al[14] had studied that aminoglycoside antibiotic blocked the transmurally elicited twitches of ileum in a concentration manner. According to

Santos et al[15] gentamicin enhances neuromuscular impairment and death of botulinum toxin-exposed mice. Aminoglycosides potentiate neuromuscular weakness caused by botulinum toxin.

Ototoxicity, nephrotoxicity and neuromuscular blockade are well known side effect but there are few studies that elaborated neurotoxic effect of Gentamicin. Aminoglycoside antibiotics are known to cross blood brain barrier and whole nervous system is exposed to these drugs. Evidence is available suggesting central neurotoxicity of aminoglycosides[6]. Exact mechanism of action on central nervous system is still unclear. Based on the literature we planned this study to observe the neurodegenerative effects of Gentamicin on adult albino rats.

MATERIAL AND METHODS

It was an Experimental study. Twenty adult albino rats weighing 130±20 grams were obtained from Central Animal House, J. N Medical College, AMU, Aligarh. They were divided into two groups. Group I: Experimental (n = 10) received an injection of 135 mg/kg body weight of Gentamicin intramuscularly for twenty one days (Gentamicin WHO food Additives series 34, www.inchem.org\documents). Group II: Controls (n = 10) received normal saline in same volume by intramuscular route for twenty one days.The rats were kept in plastic cages in a room 12:12 light/dark photoperiod, temperature of 20-30C and relative humidity of 50-60%. Ethical approval was sought and received from the Department of Anatomy, JN Medical College, AMU, Aligarh, UP, India.

The rats were decapitated on 22nd day of the experiment. The skin as well as soft tissues surrounding the cranium was removed. Sections were obtained from the area around lateral sulcus of rat cortex. The area around the lateral sulcus of rat cerebral cortex is the site of primary auditory area. Sections of auditory cortex to were obtained from both sides of cerebrum to observe neurodegenerative changes. After obtaining samples from the auditory area of cerebral cortex (control and experimental), tissue samples are weighed on digital weighing pan (error of weighing pan is calculated about 0.022 grams). Accurate weight of the samples has been calculated by deducting standard error from estimated weight.

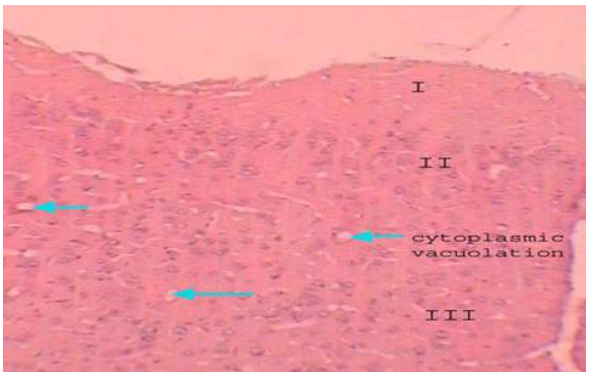

Fig.1 Photomicrograph of the auditory cortex of adult albino rat (Experimental animal) showing edema and cytoplasmic vacuolation in II (external granular) and III (pyramidal) layers (Depicted by Arrow). H&E X100.

The slides with mounted section from Group I and Group II were dried in an incubator at 45^0C for 4 hour for the proper attachment of the sections on the slides. The mounted sections were stained by Haematoxylin & Eosin[3] and Thionin stain. The photomicrographs of the relevant stained sections were taken with the aid of a light microscope.

RESULTS

Auditory cortex of adult albino rat (Experimental) animal showed oedema, cytoplasmic vacoulation in II (External granular) and III (pyramidal) layers [Fig.1].

Photomicrograph of the auditory cortex of adult albino rat (Experimental) animal showing neuronal (Pyramidal and Stellate) cells with cytoplasmic swelling and ill-defined cytoplasmic margins due to Gentamicin toxicity [Fig.2].

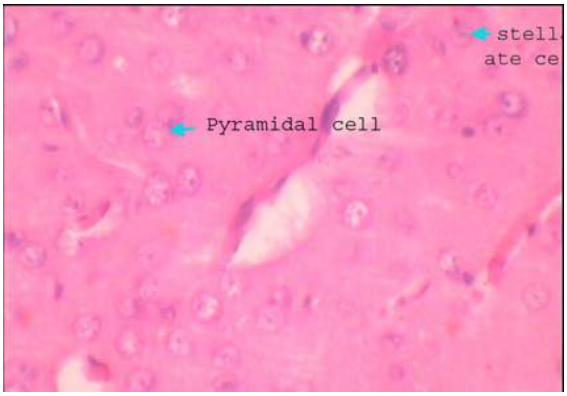

Fig.2 Photomicrograph of auditory cortex of adult albino rat (Experimental) showing neuronal cells with cytoplasmic swelling and ill-defined cytoplasmic margins due to gentamicin toxicity

Photomicrograph of the auditory cortex of adult albino rat (Experimental) animal shows signs of mild degeneration i.e., cytoplasm swelling and eccentric nucleus in II (External granular) and III (Pyramidal cell l) layers [Fig.3].

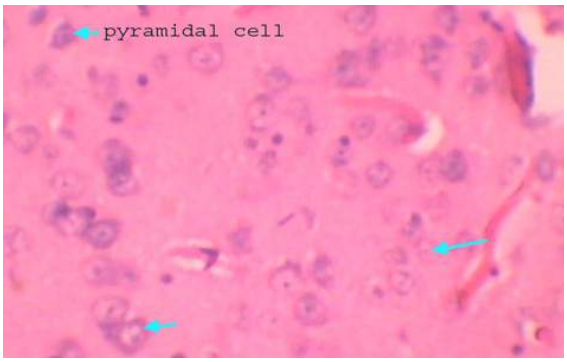

Fig. 3 Photomicrograph of the auditory cortex of adult albino rat (Experimental) cytoplasmic swelling and eccentric nucleus with mild degenerative changes (depicting by arrow). H&E X400

Generalized dispersion of Nissl substance with swollen cells is present in Photomicrograph of the auditory cortex of adult albino rat (Experimental animal) [Fig.6]

Photomicrograph of the auditory cortex of adult albino rat (Experimental animal) shows cytoplasm vacuolation, mild degree of degenerative change and lymphocytic infiltration [Fig.4].

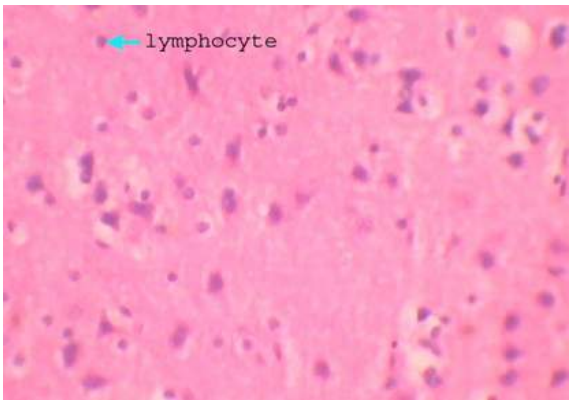

Fig. 4 Photomicograph of the auditory cortex of Albino rat (Experimental) showing cytoplasmic vacuolation, mild degree of degenerative change and lymphocytic infiltration. H&E X 400

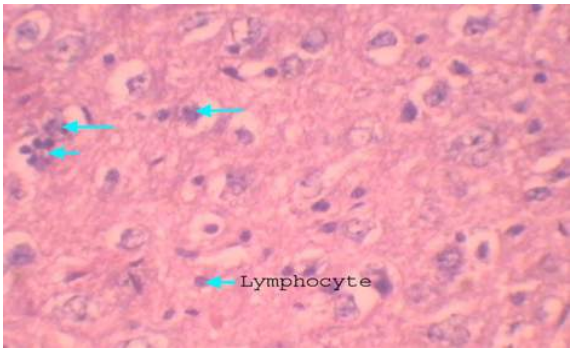

Fig. 5 Photomicrograph of the auditory cortex of adult albino rat (Experimental group) showing nuclear (irregular margins, chromatin clumping and karyorrhexis) and cytoplasmic (vacoulation) degenerative changes. H&E X400.

Photomicrograph of the auditory cortex of adult albino rat (Experimental animal) shows signs of nuclear (irregular margins, chromatin clumping and karyorrhexis) and cytoplasmic (vacuolation) degenerative changes [Fig.5].

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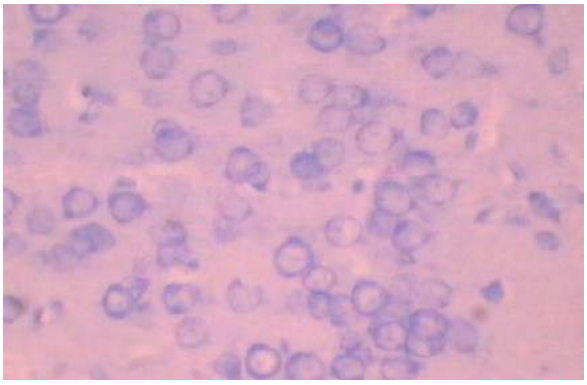

Fig. 6 Photomicrograph of the auditory cortex of an Albino rat showing cells which are swollen and their nissl substance showing generalized dispersion. Thionin stain X 400

DISCUSSION

The present study was designed to observe the neurodegenerative effects of Gentamicin on auditory cortex of adult albino rats. Findings in the literature are available showing ototoxicity, neuromuscular blockade and neurotoxicity caused by aminoglycosides.

Histological findings in present study were suggestive of degenerative changes in experimental group. Oedema and cytoplasmic vacuolation [Fig.1] were present in layer I (external granular layer) and layer II (pyramidal cell layer). Neuronal cells show cytoplasmic swelling with ill-defined cytoplasmic margins [Fig.2]. Pyramidal cells of layer II (pyramidal cell layer) show eccentric nuclei with mild degree of degenerative changes [Fig.3]. Lymphocytic infiltration was also found [Fig.5]. Cytoplasmic vacuolation [Fig.5] was also found in pyramidal cells of layer V (ganglionic layer). Irregular nuclear margins, chromatin clumping, karyorrhexis and cytoplamic vacuolation [Fig.5] were present in neuronal cells of layer V (ganglionic layer). Neuronal cell swelling with generalised dispersion of Nissl substance was found in Thionin staining [Fig.6]. Neurotoxic injury induces changes in nerve cell body which present as swelling and vacuolization[(1)]. Prominent nuclear changes with increased size, irregular outline and dispersion of chromatin are characteristic features of neurotoxic injury[(5)].

Histological findings of the present study were in conformity with neurohistological study on the effect of kanamycin on central auditory auditory pathway conducted by Faruqi *et al* which showed degenerative changes in the cochlear nucleus, inferior colliculus and auditory cortex[(5)]. Decreased staining of Nissl substance of neurons was found in the auditory cortex of kanamycin intoxicated rats. It was explained by Hotz et al that aminoglycoside therapy affects both inner ear and central auditory pathways[(9)].

Histochemical study of gentamicin intoxicated rats showed increased activity of acetylcholinesterase in cochlear nucleus[(4)]. Gentamicin might produce central toxicity by altering concentration of acetylcholine. Watanabe et al reported distinctive lesions occurred in brain stem of patients who were treated with parenteral and intrathecal gentamicin sulfate for Pseudomonas aeruginosa meningitis [(16)].

In an experimental study conducted by Wantabe *et al*, it was reported that a single intracisternal injection of 0.4 ml of 1.25 and 2.5 percent gentamicin sulfate with preservative to healthy adult rabbits produce multiple, minute, disseminated, spongy lesions with cytoplasmic vacuolation of nerve cells [(16)].

This finding is similar with cytoplasmic vacuolation found in neuronal cells of auditory cortex in present study. Convulsions, encephalopathy, confusion, hallucinations, mental depression and sometimes pleocytosis observed in

cerebrospinal fluid of humans, are clinical side effects of gentamicin on central nervous system[7].

CONCLUSION

Exposure of rats to Gentamicin for three weeks showed severe Neurodegenerative changes at microscopic level.

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REFERENCES

1. Aschners M and Costa LG. The reactive astrocytes. The role of Glia in Neurotoxicity, 2nd edition, 2004, 74.
2. Begg EJ and Barclay ML (). Aminoglycosides--50 years on. Br J Clin Pharmacol. 1995; 39(6): 597-603.
3. Drury RAB, Wallington EA, Cameron R. Carleton's Histological Techniques: 4th ed., Oxford University Press NY, U.S.A 1967; 279-280.
4. Faruqi NA, Aslam M, Baitullah and Hasan SA. Acetylcholineesterase activity in cochlear nucleus after kanamycin and Gentamicin intoxication. Pakistan Journal of otorhinolaryngology. 1992; 8: 209-212.
5. Faruqi NA, Hasan M, Hasan SA, Khan MA and Ikramullah. Neurohistological study on the effect of kanamycin on central auditory pathway. Current medical practice 1986; 30(11): 289-294.
6. Faruqi NA, Khan HS. Effect of streptomycin and kanamycin on Central nervous system: An Experimental study. Indian Journal of Experimental Biology 1986; 24: 97-99.
7. Fernando R and Jayakodi RL. Gentamicin Sulfate. IPCS INCHEM HOME 1994.
8. Guan MX, Fischel-Ghodsian N, Attardi G. A biochemical basis for the inherited susceptibility to aminoglycoside ototoxicity. Hum Mol Genet 2000; 9:1787–1793.
9. Hotz MA, Allum JHJ, and Kauffman G. Shift in barin stem latencies following plasma level controlled animogylcosides therapy. European archives of otorhinolaryngology 1990; 4:27.
10. Kahlmeter G, Dahlager JI. Aminoglycoside toxicity: a review of clinical studies published between 1975 and 1982. J. Antimicrob. Chemother 1984; 13 (suppl.A): 9-22.
11. Kumana CR and Yuen KY. Parenteral aminoglycoside therapy: Selection, administration and monitoring. Drugs 1994; 47(6):902–913.
12. Oei Markus LYM, Segenhout Hans M, Dijk Freark, Stokroos Ietse, van der Want, Johannes J. L, Albers Frans WJ. Otology & Neurotology 2004; 25 (1): 57-64 Vestibular Problems.
13. Polgar and others. Anatomic and morphometric changes to gerbil posterior cristas following transtympanic administration of gentamicin and streptomycin. JARO 2001; 02:147-158.
14. Said AA, Matsuki N, Kasuya Y. Effects of Aminoglycoside Antibiotics on Cholinergic Autonomic Nervous Transmission. Pharmacology & Toxicology 1995; 76 (2) 128–132.
15. Santos JI, Swenson P, and Glasgow LA. Potentiation of clostridium botulinum toxin by aminoglycoside antibiotics. Clinical and laboratory observations. Pediatrics 1981; 68:50-54.

16. Wantabe I, Hodges GR, Dworzack, DL. Chemical injury of the spinal cord of the rabbit after intracisternal injection of gentamicin. J.Neuropath. Exp.Neurol 1979; 38(2):104-13.

THE PREVALENCE OF VITAMIN D DEFICIENCY IN TYPE 2 DIABETIC PATIENTS

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ABSTRACT

Background: *Recently, there is accumulating evidence to suggest that altered vitamin D and calcium homeostasis may play a role in the development and control of type 2 DM. Objective: The aim of the current study was to estimate the prevalence of vitamin D deficiency in type 2 DM.* ***Material and Methods***: *This is a cross-sectional study through screening of a random sample of patients with type 2 DM who recruited from Diabetes Clinics in Family Medicine and Primary Health Care at Health Care Specialty Clinic (HCSC)-King Abdul-Aziz Medical City in Saudi Arabia, Riyadh. For eligible patients, who matched the selection criteria, the following laboratory tests were performed; vitamin D level in form of (25 OHD), HbA1c, fasting blood glucose and lipid profile.* ***Results***: *In the current study, 248 type 2 diabetic patients had been screened for vitamin D deficiency. The great majority of diabetic patients had suboptimal level of vitamin D (98.4%). Almost three-quarters of female diabetic patients (73.6%) compared to less than half of male diabetic patients (46.9%) had vitamin D deficiency while approximately half of male patients (50.8% and one quarter of female patients (25.6%) had vitamin D insufficiency. This difference between them was statistically significant (chi-sq.=18.5, P<0.001).* ***Conclusions***: *The results of our study show that the great majority of type 2 diabetic patients having suboptimal vitamin D level. The majority of female diabetic patients (73.6%) while 46.9% of male diabetic patients were vitamin D deficient. Key words: vitamin D, vitamin D deficiency, diabetes mellitus*

ملخص : في الآونة الأخيرة تزايدت الأدلة التي تشير إلى أن توازن مستوى فيتامين د والكالسيوم في الجسم قد يلعب دوراً في الإصابة بداء السكري أو التحكم في مستوى السكر. **الهدف من الدراسة** :هدفت هذه الدراسة إلى معرفة معدل انتشار نقص فيتامين د بين مرضى النوع الثاني من داء السكري. **منهج الدراسة** :هذه دراسة مسحيه تم فيها أخذ عينة عشوائية من مرضى السكري وذلك في عيادات السكر التابعة لمدينة الملك عبدالعزيز الطبية للحرس الوطني في مراكز الرعاية الاولية بالرياض .وقد تم عمل الفحوصات التالية للمرضى الذين انطبقت عليهم شروط البحث: مستوى فيتامين د , المعدل التراكمي للسكر , معدل السكر أثناء الصيام ومستوى الكوليسترول في الدم . **النتائج** :تم عمل الفحوصات لـ 248 مريض حيث وجد أن غالبية المرضى لديهم نقص في مستوى فيتامين د وذلك بنسبة 98.4% من المرضى . كما وجدت الدراسة أن نسبة نقص فيتامين د عند النساء أكبر منها عند الرجال حيث بلغت نسبة النساء الذين يعانون من نقص معدل فيتامين د 73.6% مقارنة بالرجال 46.9% . **الخاتمة** : أظهرت هذه الدراسة أن غالبية مرضى النوع الثاني من السكر لديهم نقص في معدل فيتامين د . كما أظهرت أن نسبة النقص في فيتامين د عند النساء أعلى منه عند الرجال.

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INTRODUCTION

The prevalence of Diabetes Mellitus in Saudi Arabia is one of the highest reported in the world, reaching up to 30% in a recent study[1].

Recently, researchers have shown an increased interest in the vitamin D deficiency. The major and most well-known function of vitamin D is to maintain calcium and phosphorus homeostasis and promote bone mineralization. More recently there is accumulating evidence to suggest that altered vitamin D and calcium homeostasis may also play a role in the development of type 2 DM[2, 3]. In most,[4-7] but not all,[8,9] case-control studies, patients with type 2 DM or glucose intolerance are found to have lower serum 25-OHD concentration compared with controls without diabetes. Hypovitaminosis D, owing to depletion or relative vitamin D resistance, has long been suspected to be a risk factor for glucose intolerance. A report from Martins and colleagues on data from over 15,000 adults in the Third National Health and Nutrition Examination Survey is perhaps the best recent evidence on vitamin D and the general population[21]. The 25(OH)-vitamin D levels were lower in diabetics, women, the elderly, and racial minorities, groups that are at increased risk of having chronic kidney disease (CKD)[21].

In type 2 diabetes, vitamin D may improve the cellular transfer of insulin message. Vitamin D may also contribute to survival of the islets and inhibit inflammatory processes. Some authors[10] report a relationship between low vitamin D levels in humans and reduced glucose stimulated insulin secretion. In some trials improvement of (glucose-stimulated) insulin release after vitamin D supplementation has been found but other studies have not confirmed this[11, 12] Most prospective studies are short term and give variable outcomes about the relationship between vitamin D levels and the development of diabetes[13, 14].

No local published researches have been found that surveyed the prevalence of vitamin D deficiency in type 2 DM patients.

The aim of the current study was to investigate the prevalence of vitamin D deficiency in diabetic people.

SUBJECTS AND METHODS

This is a case-control study included screening of 248 diabetic patients to estimate the prevalence of suboptimal vitamin D level.

A random sample of patients with type 2 DM were recruited in the period from July to the end of September 2009, from Diabetes Clinics in Family Medicine and Primary Health Care at Health Care Specialty Clinic (HCSC)-King Abdul-Aziz Medical City in Saudi Arabia-Riyadh. HCSC is a primary care and family medicine center, located at northeastern part of Riyadh. It services the soldiers and their dependents that belong to its catchments areas. We excluded diabetic patients with renal insufficiency, gestational diabetes and those taking vitamin D supplements.

For eligible patients, who matched the selection criteria, the following laboratory tests were performed; vitamin D level in form of (25 OHD), HbA1c and fasting blood glucose.

In order to identify diabetic patients with suboptimal vitamin D levels, the subjects were given appointment after two to three weeks to check their vitamin D level results. Blood samples were obtained from 248 patients who received blood work up requests. Total serum 25(OH) vit D levels were measured using the LIAISON ® 25 OH Vitamins D TOTAL assay, from

DiaSorin, USA. With following ranges for the classifications of vitamin D status:

Vitamin D status	25 OH Vitamin D
Deficiency	<25 nmol/L
Insufficiency	25-75 nmol/L
Sufficiency	75-250 nmol/L
Toxicity	>250 nmol/L

STATISTICAL ANALYSIS

Vitamin D level was treated as an independent variable and A1C, FBS, lipid profile, Body Mass Index and blood pressure were treated as dependent variables in statistical analysis. Data management and analysis was performed using Statistical Package for Social sciences (SPSS) software, version 16.

The study was conducted on human participants. All data was maintained in a secure and confidential manner. All participants' identification and associated data were separated. All data was analysed as total population in a manner that individual privacy was maintained. All records, results and progress, both electronic and written will be maintained with the researcher for a minimum period of two years in case of review. This statement was approved by the hospital research committee. A written informed consent taken from the participants in the intervention group clarifying the main purpose of the study, the importance of the respondent's views, the researchers name. Also, open letters explaining the steps of the study were distributed to all participants.

RESULTS

In the current study, 248 type 2 diabetic patients had been screened for vitamin D deficiency.

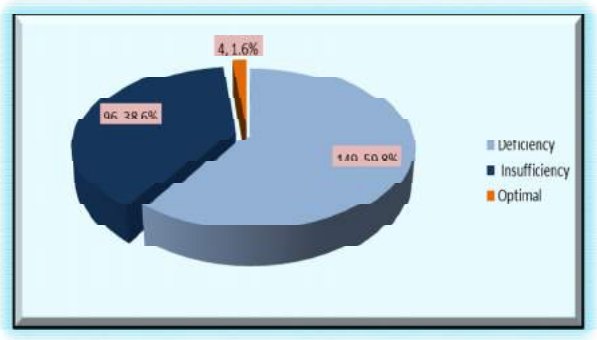

Figure 1: prevalence of vitamin D deficiency in type 2 diabetic patients of the study sample.

Figure (1) illustrates that more than half of them (149; 59.8%) were deficient in vitamin D (< 25 nmol/L), 96 patients (38.6%) had insufficient vitamin D level (25, 1-74.9 nmol/L) while only 4 patients (1.6%) had optimal vitamin D level (> 75 nmol/L). Thus, the great majority of diabetic patients had suboptimal level of vitamin D (98.4%).

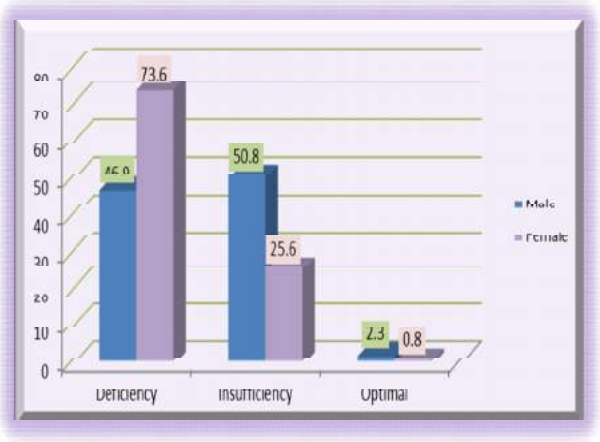

Figure 2: Prevalence of vitamin D deficiency among type 2 diabetic patients according to gender.

From figure 2, it is obvious that almost three-quarters of female diabetic patients (73.6%) compared to less than half of male diabetic patients (46.9%) had vitamin D deficiency while approximately half of male patients (50.8% and one quarter of female patients (25.6%) had vitamin D insufficiency. This difference between them

was statistically significant (chi-sq.=18.5, P<0.001).

DISCUSSION

Vitamin D deficiency or insufficiency is now recognized as a worldwide problem for both children and adults. [3] According to several studies, 40 to 100% of U.S. and European elderly men and women still living in the community (not in nursing homes) are deficient in vitamin D.[15] However, even in the sunniest areas, vitamin D deficiency is common when most of the skin is shielded from the sun. Studies in Saudi Arabia, the United Arab Emirates, Australia, Turkey, India, and Lebanon, 30 to 50% of children and adults had 25-hydroxyvitamin D levels under 50 nmol/L[16-18]. Moreover, The prevalence of low serum 25-hydroxyvitamin D (<50 nmol/l) is more common in diabetics compared with non-diabetics 83% vs. 70%; p = 0.07.[19] The results of our study show that 98.4% of our participants having suboptimal vitamin D level. This study produced results which corroborate the findings of a great deal of the previous work in this field. The majority of female patients 73.6% were vitamin D deficient (<25 nmol/L) while 46.9% of male patients. This result could be attributed to less sun exposure in female patients relative to male patients in our community.

It is not clear what levels of vitamin D are sufficient. It may be that levels of vitamin D within the normal range for an effect on bone formation and calcium metabolism are too low to reduce the emergence of diabetes mellitus and to improve glucose homeostasis, but a clear minimum level of 25(OH)D3 needed for slowing the development of diabetes mellitus has not been established. The prescription of extra vitamin D during the early phase of diabetes is still experimental[20].

Our study has considerable strength as the first local study, up to our knowledge, to estimate the prevalence of vitamin D deficiency among type 2 diabetic patients. Also, the measurements of vitamin D was performed in one laboratory, hence comparison of serum 25(OH) D levels was valid, we included a considerable large group of subjects and the response rate was high (91.5%).

CONCLUSION

The results of our study show that the great majority of our participants having suboptimal vitamin D level. The majority of female patients (73.6%) while 46.9% of male patients were vitamin D deficient.

REFERENCES

1. Alqurashi KA, Aljabri KS, Bokhari SA. Prevalence of diabetes mellitus in a Saudi community. Ann Saudi Med. 2011 Jan-Feb;31(1):19-23.
2. Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006; 84:18–28.
3. Holick MF. High prevalence of vitamin D inadequacy and implications for health. Mayo Clin Proc 2006; 81:353–373.
4. Cigolini M, Iagulli MP, Miconi V, Galiotto M, Lombardi S, Targher G. Serum 25-hydroxyvitamin D3 concentrations and prevalence of cardiovascular disease among type 2 diabetic patients. Diabetes Care 2006; 29:722–724.
5. Hypponen E, Power C. Vitamin D status and glucose homeostasis in the 1958 British birth cohort: the role of obesity. Diabetes Care 2006; 29:2244–2246.
6. Aksoy H, Akcay F, Kurtul N, Baykal O, Avci B. Serum 1,25 dihydroxy vitamin D (1,25(OH)2D3), 25 hydroxy vitamin D (25(OH)D) and parathormone levels in diabetic retinopathy. Clin Biochem 2000; 33:47–51.

7. Isaia G, Giorgino R, Adami S. High prevalence of hypovitaminosis D in female type 2 diabetic population. Diabetes Care 2001; 24:1496.
8. Ishida H, Seino Y, Matsukura S, Ikeda M, Yawata M, Yamashita G, et al. Diabetic osteopenia and circulating levels of vitamin D metabolites in type 2 (noninsulin-dependent) diabetes. Metabolism 1985; 34:797–801.
9. Lambert PW, Service FJ, Arnaud SB. Calcium homeostasis in diabetes mellitus. J Clin Endocrinol Metab 1979; 49:462–466.
10. Baynes KC, Boucher BJ, Feskens EJ, Kromhout D. Vitamin D, glucose tolerance and insulinaemia in elderly man. Diabetologia1997, 40:344-7.
11. Nyomba BL, Auwers J, Bormans V, Peeters TL, Pelemans W, Reynaert J, et al. Pancreatic secretion in man with subclinical vitamin D deficiency. Diabetologia 1986, 29:34-8.
12. Orwoll E, Riddle M, Prince M. Effects of vitamin D on insulin and glucagon secretion in non-insulin-dependent diabetes mellitus. Am J Clin Nutr 1994; 59:1083-7.
13. Teegarden D, Donkin SS. Vitamin D emerging new roles in insulin sensitivity. Nutr Res Rev 2009; 22:82-92.
14. Sue Penckofer, JoAnne Kouba, Diane E. Wallis, Mary Ann Emanuele. Vitamin D and Diabetes: Let the Sunshine In. The Diabetes Educator 2008; 34; 939.
15. Nesby-O'Dell S, Scanlon KS, Cogswell ME. Hypovitaminosis D prevalence and determinants among African American and white women of reproductive age: Third National Health and Nutrition Examination Survey, 1988-1994. Am J Clin Nutr 2002; 76: 187-192.
16. Sedrani SH. Low 25-hydroxyvitamin D and normal serum calcium concentrations in Saudi Arabia: Riyadh region. Ann Nutr Metab 1984; 28:181-5.
17. Marwaha RK, Tandon N, Reddy D, et al. Vitamin D and bone mineral density status of health schoolchildren in northern India. Am J Ckin Nut 2005; 82:477-82.
18. El-Hajj Fuleihan G, Nabulsi M, Choucair M, et al. Hypovitaminosis D in healthy schoolchildren. Pediatrics 2001; 107:E53.
19. Tahrani AA, Ball A, Shepherd L. The prevalence of vitamin D abnormalities in South Asians with type 2 diabetes mellitus in the UK. Int J Clin Pract, February 2010; 64, 3, 351–355.
20. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003 326 469–475.
21. Martins D, Wolf M, Pan D, et al. Prevalence of cardiovascular risk factors and the serum levels of 25-hydroxyvitamin D in the United States: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2007;167:1159-1165.

KNOWLEDGE, ATTITUDE AND PRACTICE OF PARENTS TOWARDS CHILDHOOD VACCINATION

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ABSTRACT

Background: *The prevention and treatment of hypertension are a high priority in medicine Background: It has been recently reported by WHO that a large proportion of children fail to complete their immunization schedule. System weaknesses, low public awareness, fears and misconceptions about vaccines were responsible for that. Despite nearly 100% vaccination rate in Saudi Arabia, often parents delay vaccination and do not fully understand the value of immunization, except that it is mandatory for birth certification and admission in school.* ***Objectives:*** *To assess parental knowledge and attitude regarding vaccination and their effects on vaccination practice.* ***Methodology:*** *A cross-sectional study was conducted using a self-administered Arabic questionnaire, including 20 questions related to parental knowledge, attitude, and practice regarding childhood vaccination. It was distributed in PHC settings.* ***Results:*** *The study included parents of 390 children. Factors significantly associated with better knowledge score and positive parental attitude regarding child vaccination were source of information about child vaccination from TV, internet and journals/newspapers, parents with first child, younger age, and higher level of education. There was a moderate positive correlation between total knowledge score and total attitude score of child vaccination ($r=0.382$, $p<0.001$).* ***Conclusion:*** *Positive attitude towards immunizations was remarkably high in this study group of parents. Knowledge on childhood immunizations, however, was not significantly higher in those who reportedly receive information from health professionals.*

ملخص: الاحصاءات الحديثة من منظمة الصحة العالمية تبين أن نسبة كبيرة من الأطفال لا تستطيع الوصول إلى الخدمات الخاصة بالتطعيم أو أن تكمل جدول التطعيم المقرر , و بينت أيضا أن فقدان خدمات التطعيم سببه ضعف النظام الصحي، قلة وعي الآباء, الخوف و بعض الاعتقادات الخاطئة عن التطعيم. على الرغم من أن المملكة العربية السعودية حققت ما يقرب من 100٪ في معدل تطعيمات الأطفال ، إلا أن الآباء في كثير من الأحيان لا يتبعون الجدول الزمني المقرر للتطعيمات ، و بعضهم لا يعرفون من أهمية التطعيم إلا أنه إلزامي للحصول على شهادة الميلاد والقبول في المدارس. **هدف البحث:** يهدف البحث إلى استطلاع مدى معرفة الآباء و توجهاتهم نحو تطعيم الأطفال و أثر ذلك على ممارساتهم .**طرق البحث:** تم إجراء دراسة مقطعية باستخدام استمارة استبيان باللغة العربية تشتمل على 20 سؤالا تتعلق بمعرفة الآباء و التوجهات و الممارسات في مجال تطعيم الأطفال. تم اعتماد الاستبيان المحتوي على 20 بندا بعد أخذ الإذن من المؤلف. **نتائج البحث:** ضمت الدراسة آباء 390 طفلاً، العوامل التي ارتبطت بمعرفة أفضل لدى أولياء الأمور كانت مصادر المعلومات عن تطعيم الأطفال (تليفزيون، انترنت، صحف و مجلات)، وجود طفل أول في ترتيب العائلة، الأمهات الصغيرات في السن، الأمهات العاملات، ارتفاع مستوى تعليم الأمهات و الآباء. أما العوامل التي ارتبطت باتجاه إيجابي لأولياء الأمور نحو تطعيم الأطفال فكانت مصادر المعلومات (تليفزيون، انترنت، صحف و مجلات)، الآباء الصغار و الأمهات الصغيرات في السن، ارتفاع مستوى تعليم الآباء والأمهات. كان هناك ارتباط ايجابي ذو دلالة معنوية بين المعرفة و الاتجاه نحو تطعيم الأطفال (معامل الارتباط =0.382 و مستوى الدلالة (<0.001)**الخلاصة:** معدل الاتجاه الايجابي نحو تطعيم الأطفال كان ممتازا في هذه المجموعة من أولياء الأمور ، لكن مستوى المعرفة عن تطعيم الأطفال لم يكن مرتفعا ارتفاعا ذا دلالة معنوية بين من تلقوا معلوماتهم من الأطباء.

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INTRODUCTION

Immunization of children against serious communicable diseases is the most cost effective strategy to decrease overall morbidity and mortality among children.[1,2] In order to accomplish this strategy, high coverage of vaccination is essential to be maintained.[1,3]

When the Expanded Programme on Immunization (EPI) was launched in 1974, less than 5% of the world's children were immunized during their first year of life against six killer diseases; Polio, Diphtheria, Tuberculosis, Pertussis (Whooping Cough), Measles and Tetanus.[4] From 1984 onward, the EPI has been implemented in Saudi Arabia as an integral and essential element of primary health care.[5]

Over 1.5 million children die from vaccine preventable diseases as reported by WHO. Previous estimated number of all deaths in children under five in 2008 was 8.8 million, and 17% of all deaths in children under five are preventable by vaccination.[6] The WHO estimates that current immunization programs save more than 3.2 million lives each year and the full utilization of existing vaccines could save an additional 1.7 million lives per year.[7]

Recent analysis from WHO showed failure of a large proportion of children to access immunization services or to complete their immunization schedule. Lack of services due to system weaknesses, low public awareness, or fears and misconceptions about vaccines were some of the influencing factors.[8]

Vaccination coverage can be affected by many other factors like low socioeconomic status and low education level. These factors can play a role in delay or finishing full set of vaccination.[9] Despite notable improvement, still around three million children are permanently disabled each year.[10, 11] Studies suggest that parents and health care providers are uncomfortable with multiple injections in single visits.[12-14] Even in areas with high coverage, it is important to know attitudes and behaviours toward immunizations in order to improve services and maintain high coverage rate.[15]

Since 1979, the government has supported the practice of tying the issuing of birth certificates for successful completion of first two years of life primary immunizations against diseases which are targeted by available vaccines. The National Immunization Program has achieved eradication of neonatal tetanus and polio. Still efforts are needed to eradicate measles, rubella and mumps, and to reduce the incidence of the remaining communicable diseases.[16]

The recent data issued by WHO Office for the Eastern Mediterranean Region, reported that twenty countries in the region are free from polio. As for the regular immunizations against the diseases targeted by childhood vaccination, the rate of immunization reached over 97% in Saudi Arabia over the past five years.[17, 18]

Despite nearly 100% childhood vaccination rate in Saudi Arabia, often parents do not follow the schedule in a timely manner, and do not fully understand the value of immunization except that it is mandatory for birth certification and admission in school. Thus, this study aimed at assessing parental knowledge, attitude and practice toward vaccination of their children.

METHODS

This cross-sectional study was conducted at two primary care centers (Health Care Specialized Centre [HCSC -Khashm Alaan] and King Abdulaziz Housing Clinic [Iskan]), National Guard Health Affairs, Riyadh, Saudi Arabia. These two clinics serve a total population of over 150,000

patients of which at least one third are children.

All parents visiting the primary care with their children were enrolled for interview if they agreed to participate.

The sample size was estimated based on the assumption that 93% of the parents would have a positive attitude based on the UAE study,[19] with a margin of error ± 3%. Using a confidence interval of 98% a sample size of 380 was obtained, which was adjusted up to 400 for data losses. By convenient non-random sampling, parents who visited the two primary care clinics with their children were recruited to participate in the study after their agreement. The appointment schedule was not influenced by the recruitment process during the study period.

Eligible participants were asked to fill a self-administered questionnaire including 20 statements related to knowledge, attitude and practice of parents visiting the clinic with their children. The 20-item Arabic Questionnaire was adopted after permission from validated questionnaire in Iraq. [20]

The questionnaire included the demographic data for child (age, birth weight, gender, feeding, number of preschool children and child order) and demographic data for parents (age, employment and education), knowledge related questions [14], attitude questions [5] and one practice Question. For knowledge questions, scores were summed up for correct answers. No negative marking was done and higher score indicated higher knowledge level. For attitude, Scores were summed up for correct answers. No negative marking was done and higher score indicated more positive attitude.

The collection and interview parts were supervised by assigned staff nurse, to ensure good compliance while collecting the data and help during filling of the questionnaire.

DATA ENTRY AND ANALYSIS

Data were analysed by using SPSS software statistical program, version 18. Summarization of the data was presented using tables and graphs. The following statistics were applied: Continuous variables (total knowledge and attitude scores) were presented as mean and standard deviation (SD). Categorical variables were presented as frequency and percentage. Significance was determined at p value < 0.05. Chi square test was applied to test for the association between categorical variables while t-test was used to test for the difference in the means of two continuous variables.

Ethical committee approval was obtained from the Family Medicine Research Committee of the Department of Family Medicine & Primary Health Care in King Abdulaziz medical city. Verbal Consent was taken from respondents, clarifying the main purpose of the study, the importance of the respondent views, thanking in advance and assuring strict confidentiality of the information with consent statement on the Questionnaire. All data were maintained in a secure and confidential manner. Data were analysed as cumulative in a manner that individual privacy was maintained.

RESULTS

The study included parents of 390 children. Response rate was 96%. Table (1) presents the children characteristics. Over 43% of the children were below 1 year old. More than one-third of them (36.4%) were between one and three years old. More than half of them were males (56%). Majority of children (69.7%) had a birth weight of above 2.5 kg. Breast feeding was reported among only 24% of them while bottle and mixed feeding were reported among 34%

and 42% of them, respectively. Regarding birth order, most of them were second or more (72.4%). Mothers represent 60.2% of the participants. The majority of them (86.2%) were not employed and 29.7% of them were university/college graduates. Fathers represent 39.8% of the participants. Most of the fathers were employed (96.1%) but only 18.8% of them had university degree.

Characteristic	*Frequency (%)*
Child age: (385)	
< one year	166 (43.1)
(1 – 3) years	140 (36.4)
≥ 4 years	79 (20.5)
Child gender: (389)	
Male	218 (56)
Female	171 (44)
Child birth weight: (386)	
≤ 2.5 kg	117 (30.3)
> 2.5 kg	269 (69.7)
Child feeding: (388)	
Breast Feeding	93 (24)
Bottle Feeding	132 (34)
Both	163 (42)
Preschool children: (279)	
One	165 (43.5)
02-Mar	163 (43)
≥ 4	51 (13.5)
Child order: (387)	
First child	107 (27.6)
Second or more	280 (72.4)
Parent participating: (384)	
Father	153 (39.8)
Mother	231 (60.2)
Mother employment: (390)	
Employed	54 (13.8)
Not Employed	336 (86.2)
Mother education: (390)	
Primary	89 (22.8)
Intermediate	65 (16.7)
Secondary	120 (30.8)
College/university	116 (29.7)
Father employment: (389)	
Employed	374 (96.1)
Not Employed	15 (3.9)
Father education: (389)	
Primary	33 (8.5)
Intermediate	86 (22.1)
Secondary	197 (50.6)
College/university	73 (18.8)

Figure (1) shows that physicians were the main source of information (77.7%) for the parents about immunization, followed by TV (37.6%), Internet (21.7%) and newspapers (13.3%).

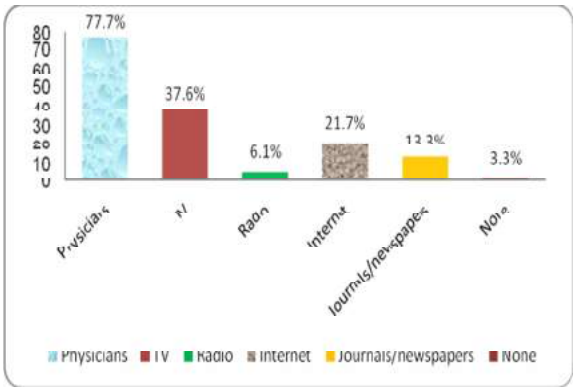

Figure (1): Source of parent information about childhood vaccination

Table (2) shows that fever was the most commonly reported adverse effect of vaccination by parents (74.2%) followed by pain (48.6%). Skin rash and convulsions were reported by only 4.9% and 4.1% of the participants, respectively. Less than half of the parents (46.5%) reported that the maximum limit for vaccines per visit should be recommended by physicians.

More than half of the participants (60.2%) believed that vaccine is for all ages. The majority of them recognized correctly that vaccination prevents diseases (82.6%), that there are different types of vaccines (87.4%), a uniform schedule for children under the age of 2 years (83%), vaccination enhances immunity (89.2%) and healthy child need vaccination (85.9%). More than half of the parents recognized that there are situations in which vaccine cannot be given (58.5%). The majority of the parents did not accept that harm of the vaccine is more than benefits (92.8%) or multiple vaccines in one visit decrease immunity (85.6%).

Parents` total knowledge score ranged between 1 and 11.4 (out of 11) with a mean of 8.08 and SD of 1.8

Table 2: Parental knowledge about vaccination (right answers).

N	*Item*	*Frequency (%)*
1	Adverse effects of vaccines*:	
	Fever	290 (74.2)
	Pain	190 (48.6)
	Skin rash	19 (4.9)
	Diarrhoea	42 (10.7)
	Convulsions	16 (4.1)
	Don't know	49 (12.5)
2	Maximum limit of vaccines per visit:	
	1-2 vaccines	149 (38.1)
	3-4 vaccines	57 (14.6)
	5 or more	3 (0.8)
	Recommend by physician	182 (46.5)
3	Vaccine for all ages	234 (60.2)
4	Vaccination prevent disease	323 (82.6)
5	Different types of vaccines	339 (87.4)
6	Uniform schedule less than 2 years	322 (83)
7	Vaccination start first week of life	279 (71.7)
8	Situations you can't give the vaccine	227 (58.5)
9	Harm of vaccines more than benefits	28 (7.2)
10	Vaccination enhance immunity	348 (89.2)
11	Healthy child need vaccination	335 (85.9)
12	Multiple vaccines in one visit decrease immunity	56 (14.4)

Table (3) presents the significant factors associated with better parents` knowledge of child vaccination. Regarding their source of information about child vaccination, those whose source was TV showed higher significant total knowledge score (8.5±1.69 versus 7.83±1.83), p<0.001. Similarly, those whose source was internet showed higher significant total knowledge score (8.68±1.3 versus 7.91±1.89), p<0.001. Parents whose source of information was journals/newspapers showed higher significant total knowledge score (8.54±1.54 versus 8.01±1.83), p<0.049.

Variables	***Total knowledge score***		***t-value* (p-value)***
	Mean	SD	
TV(source of information)			
No (242)	7.83	1.83	3.62
Yes (146)	8.5	1.69	(<0.001)
Internet			
No (303)	7.91	1.89	3.53
Yes (85)	8.68	1.3	(<0.001)
Journals/newspapers			
No (336)	8.01	1.83	1.97
Yes (52)	8.54	1.54	-0.049
Child birth order			
First (107)	8.42	1.78	2.24
Second or more (277)	7.97	1.79	-0.026
Mother`s age			
≥30 (203)	7.79	1.91	3.45
<30 (181)	8.42	1.63	-0.001
Mother`s employment status			
Employed (54)	8.9	1.55	3.63
Not employed (333)	7.95	1.81	(<0.001)
Mother`s education			
School education (271)	7.77	1.79	5.27
College degree (116)	8.79	1.64	(<0.001)
Father`s education			
School education (313)	7.91	1.8	3.77
College degree (73)	8.78	1.66	(<0.001)

Parents with first order children showed higher significant total knowledge score about vaccination than those with second or more child birth order (8.42±1.78 versus 7.97±1.79), p<0.026. Younger mothers (<30 years) showed higher significant total knowledge score about vaccination than order (≥30 years) (8.42±1.63 versus 7.79±1.91), p=0.001. Employed mothers showed higher significant total knowledge score about vaccination than non-employed (8.9±1.55 versus 7.95±1.81), p<0.001. Higher educated mothers had significant higher total knowledge score about child vaccination than less educated (8.79±1.64 versus 7.77±1.79, p<0.001). Higher educated fathers had significant higher total knowledge score about child vaccination than less educated (8.78±1.66 versus 7.91±1.80, p<0.001.

Table (4). Parental attitude and practice of child vaccination.

	Item	Frequency
Practice	Regular vaccination	304 (77.7)
Attitude	Barriers against vaccination:	
	a) Loss of education	172 (44.1)
	b) Vaccine availability	67 (17.2)
	c) Limited service	35 (9)
	d) Fear	61 (15.6)
	e) Don't know	148 (37.9)
	Vaccination not safe	309 (79.4)
	Prefer to vaccinate your child	367 (93.9)
	Recommend vaccination to others	378 (96.9)
	In favour of vaccination program	337 (96.7)

As illustrated in Table (4), regular child vaccination was reported by 77.7% of the parents. Missing school due to clinic visit for vaccination (44.1%), vaccine non-availability (17.2%), limited service (9%) and fear (15.6%) were the reported barriers against vaccination. Almost one-fifth of the parents (20.6%) believed that vaccination is not safe. The great majority of them preferred to vaccinate their child (93.9%), recommend vaccination to others (96.9%) and in favour of vaccination program (96.7%).

Parents` total attitude score ranged between zero and 4 (out of 4) with a mean of 3.67 and SD of 0.68.

Table (5). Factors significantly affect total parents` attitude score towards child vaccination

Variable	Total Attitude score		t-value* (p-value)
	Mean	SD	
TV (source of information)	3.57	0.78	3.68
No (243)	3.83	0.43	(<0.001)
Yes (146)			
Internet	3.60	0.74	3.71
No (304)	3.91	0.29	(<0.001)
Yes (85)			
Journals/newspapers	3.64	0.71	2.04
No (337)	3.85	0.36	(0.042)
Yes (52)			
Mother`s age	3.58	0.76	2.73
≥30 (203)	3.77	0.56	(0.007)
<30 (182)			
Father`s age	3.60	0.75	2.19
≥35(216)	3.75	0.58	(0.029)
<35 (167)			
Mother`s education	3.62	0.69	2.25
School education (272)	3.79	0.64	(0.019)
College degree (116)			
Father`s education	3.62	0.72	2.93
School education (314)	3.88	0.41	(0.004)
College degree (73)			

Table (5) presents the significant factors associated with positive parents` attitude towards child vaccination. Regarding their source of information about child vaccination, those whose source was TV showed higher significant total attitude score (3.83±0.43 versus 3.57±0.78), p<0.001. Similarly, those whose source of vaccination information was internet showed higher significant total attitude score (3.91±0.29 versus 3.6±0.74), p<0.001. Parents whose source of information was journals/newspapers showed higher significant total attitude score (3.85±0.36 versus 3.64±0.71), p<0.042. Younger mothers (<30 years) showed higher significant total attitude score towards vaccination than order (≥30 years) (3.77±0.56 versus 3.58±0.76), p=0.007. Younger fathers (<35 years) showed higher significant total attitude score towards vaccination than order (≥35 years) (3.75±0.58 versus 3.60±0.75), p<0.029. Higher educated mothers had significant higher total attitude score towards vaccination than less educated (3.79±0.64 versus 3.62±0.69, p=0.019. Higher educated fathers had significant higher total attitude score towards vaccination than less educated (3.88±0.41 versus 3.62±0.72, p=0.004.

Figure (2) shows that there was a significant positive correlation between total knowledge score and total attitude score of child vaccination (r=0.382, p<0.001).

DISCUSSION

It is widely accepted that childhood immunization programs have played a great part in the prevention of many diseases; hence, vaccination coverage is an indirect way to assess child health care from the point of view of public health.[21]

The results of the survey offer insight into the knowledge, attitude and practices with regards to immunization among the parents and their source of information and can be utilized to conduct larger community based survey in order to intervene and maintain high vaccination status of the population as the key issue in the maintenance of the existing high vaccination coverage in the KSA.

As expected, on the basis of high vaccination coverage for infants for the vaccine-preventable diseases in KSA, the attitude towards vaccination was generally positive in the present study. Over 80% of respondents were in favour of vaccination and believed that it prevents disease. This finding is in line with those reported in other countries.[22, 23] in which majority of respondents acknowledged the importance of Immunization.(24) It is also promising when one notes that the majority of the respondents were confident enough to recommend immunization to others.

It is particularly important to note that 20% of the respondent in our study believes immunization is not safe. Respondents were noted to be not well informed about possible side effects of immunization with the exception of fever and pain. Concerns about immunization safety are widely prevalent [25] as well as concerns regarding the adverse impact of possible side effects on immunization coverage have been reported earlier.[26] It is to be noted that physicians are a main source about immunization for these patients.

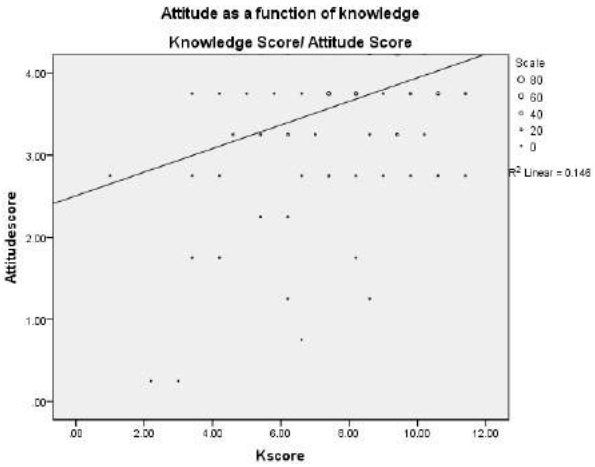

Figure (2): Correlation between total knowledge and total attitude scores

It is heartening to note that doctors are responsible for informing a majority of respondents about immunization but a need exists to work further in this area. There is a need to educate physician in this area since they are found to be deficient in knowledge about immunization.[27] The role of physician is also very important in promotion of immunization among the population.[28]

The media is noted to be a strong source for providing awareness among the respondents about immunization in the current survey where 43.7% of the respondents reported TV/radio as their source of information about child vaccination. There again exists a need for further improvement in this area. Television can be a good source to promote immunization and results of our study point out a need to further utilize this source for this purpose as better knowledge and attitude towards child immunization was reported among those depend on TV as a source of their information. The important role that media can play in promotion of immunization has been highlighted by earlier reports.[29]

A further important issue arising from the results is that 77.7% reported that a health professional was the main source of information regarding childhood immunizations. This is in contrast to

finding of UAE study where a large proportion of mothers seem to obtain information on side effects from other sources such as the media or the internet where opponents of vaccinations may invariably publish biased or unreliable interpretations of proven scientific results.[30] Unless properly addressed, this erroneous information on side effects, together with a possible diminishing perception of the lethality of vaccine preventable diseases, could adversely affect vaccine coverage.

Older mothers were less likely to have knowledge and positive attitude towards child vaccination. Perhaps, in older women, this reflects a higher prevalence of traditional nihilistic views, such as destiny being the cause of disease. The same finding has been reported in other gulf countries (UAE).[19]

It was found that the knowledge score was lower in those women with a compromised educational standard. It is a truism that knowledge increases with education. It is however, questionable whether those more informed women actually received their information from health professionals. This observation could be due to recall bias: someone who remembers being well informed also knows more about the program. For some women, the information provided may not have been targeted to their level of understanding or to their specific questions and concerns. It seems that having information from health professionals was not significantly related to knowledge level in contrast to having information from TV, internet or journals/newspapers.

In accordance with what has been reported In Iraqi study,[20] the level of knowledge among parents was positively correlated with their attitude to and practices of immunization.

Among limitations of the current research is that it was conducted in localized centres (King Abdulaziz Medical City in Riyadh, Saudi Arabia). So the generalizability of the results over Saudi community is questionable. However, adequate sample size provided enough statistical power to detect associations and yielded estimates of percentages with sufficient precision.

In conclusion, the prevalence of a positive attitude towards immunizations was excellent in this study group of parents, and satisfaction with the service was high. Knowledge on childhood immunizations however was not significantly higher in those who reportedly receive information from health professionals while it was higher among those received information from TV, internet and newspapers, although a larger percentage of the parents got their information from physicians. The knowledge of child vaccination was insufficient in some important points as side effects, situations you can't give the vaccine and that vaccination should be given for all ages. In order to maintain the current high vaccination coverage in the KSA, it is recommended that health education activities should focus particularly on parents of a compromised education and older in age and should also target their information to appropriate levels of each parent's understanding

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REFERENCES

1. Boëlle PY. Theoretical epidemiology and vaccine. Rev Med Interne 2007; 28: 161-5.
2. Nicoll A, Elliman D, Begg NT. Immunization: causes of failure and strategies and tactics for success. BMJ 1989; 299(30): 808-12.
3. Farag MK, Al-Mazrou YY, Al-Jefry M, Al-Shehri SN, Baldo MH, Farghali M. National immunization coverage Saudi Arabia. Journal of Tropical Pediatrics 1995; 41:59-67.
4. Novelli VM, Khalil N, Metarwah B, El-Baba F, Nahar R, Abu- Nahya M. Childhood immunization in the state of Qatar: Implications for improving coverage. Annals of Saudi Medicine 1991;11(2):201-4.
5. Al-Shehri SN, Al-Shammari SA, Khoja TA. Missed Opportunities for Immunization. Canadian Family Physician 1992; 38:1087-91.
6. World Health Organization. Global immunization data. [Cited at 2012 march 12], Available from: http://www.who.int/immunization_monitoring/Global_Immunization_Data.
7. Tufenkeji H, Kattan H. Childhood immunization in the Kingdom of Saudi Arabia. Annals of Saudi Medicine 1994; 14(2):91-3.
8. Global immunization vision and strategy (Progress report and strategic direction for the Decade of Vaccines), [Cited at 2012 march 12], available from: http://apps.who.int/gb/ebwha/pdf_files/WHA64/A64_14-en
9. Schwarz NG, Gysels M, Pell C, Gabor J, Schlie M, Issifou S et al. Reasons for non-adherence to vaccination at mother and child care clinics (MCCs) in Lambaréné, Gabon. Vaccine 2009; 27: 5371-5.
10. Novelli VM, Khalil N, Metarwah B, El-Baba F, Nahar R, Abu- Nahya M. Childhood immunization in the state of Qatar: Implications for improving coverage. Annals of Saudi Medicine 1991;11(2):201-4.
11. Harunur Rashid AKM. Childhood immunization status related to social and educational status of parents in a peripheral northern town of Saudi Arabia. Annals of Saudi Medicine 1993; 13(4):335-9.
12. Orenstein WA, Rodewald LE, Hinman AR. Immunization in the United States. In: Plotkin S, Orenstein WA, eds. Vaccines, 4th ed. Philadelphia: Elsevier; 2004:1357–1386.
13. Hinman AR, Orenstein WA, Rodewald L. Financing immunizations in the United States. Clin Infect Dis. 2004;38:1440–1446.
14. Langmuir AD. Medical importance of measles. Am J Dis Child. 1962; 103:224–226.
15. Gust DA, Strine TW, Maurice E, Smith P, Yusuf H, Wilkinson M et al. Under immunization among children: effects of vaccine safety concerns on immunization status. Pediatrics 2004; 114: e16-22.
16. Ministry of health, Saudi Arabia. [Cited at 2012 march 12], Available from: http://www.moh.gov.sa/en/Ministry/MediaCenter/News/Pages/NEWS-2011-5-3-001.aspx
17. World Health Organization (WHO). [Cited at 2012 march 12], Available from: http://apps.who.int/immunization_monitoring/en/globalsummary/timeseries/tscoveragebycountry.cfm?C=SAU.
18. World Health Organization (WHO). [Cited at 2012 march 12], Available from: http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileresult.cfm
19. Bernsen RM, Al-Zahmi FR, Al-Ali NA, Hamoudi RO, Ali NA, John Schneider J, et al. Knowledge, Attitude and Practice towards Immunizations

among Mothers in a Traditional City in the United Arab Emirates Journal of Medical Sciences 2011; 4(3): 114-121.
20. Al-lela OQB, Bahari MB, Al-abbassi MG, Basher AY. Development of a questionnaire on knowledge, attitude and practice about immunization among Iraqi parents. J Public Health published online March, 2011
21. Tang CW, Huang SH, Weng KP, Ger LP, Hsieh KS. Parents' Views About the Vaccination Program in Taiwan. Pediatrics and Neonatology 2011; 52: 98-102.
22. Vannice KS, Salmon DA, Shui I, Omer SB, Kissner J, Edwards KM, et al. Attitudes and beliefs of parents concerned about vaccines: Impact of timing of immunization information Pediatrics 2011;127: S120–S126
23. Qidwai W, Ali SS, Ayub S, Ayub S. Knowledge, Attitude and practice regarding immunization among family practice patients. JDUHS 2007; 1 (1): 15-19.
24. Mansuri FA, Baig LA. Assessment of immunization service in perspective of both the recipients and the providers: a reflection from focus group discussions. J Ayub Med Coll. 2003; 15:14-8.
25. Smith PJ, Kennedy AM, Wooten K, Gust DA, Pickering LK. Association between health care providers' influence on parents who have concerns about vaccine safety and vaccination coverage. Pediatrics 2006; 118:1287-92.
26. Buttery J, La Vincente S, Andrews R, Kempe A, Royle J. Adverse events following immunization: desperately seeking surveillance. Lancet Infect Dis 2006; 6: 680-1.
27. Kumar R, Taneja D K, Dabas P, Ingle G K, Saha R. Knowledge about tetanus immunization among doctors in Delhi. Indian J Med Sci 2005;59:3-8
28. Nowalk MP, Bardella IJ, Zimmerman RK, Shen S. The physician's office: can it influence adult immunization rates? Am J Manag Care 2004; 10:13-9.
29. Speers T, Lewis J. Journalists and jabs: media coverage of the MMR vaccine. Commun Med. 2004; 1:171-81.
30. Wolfe RM, Sharp LK. Vaccination or immunization? The impact of search terms on the internet. J Health Commun 2005; 10: 537-51.

PARENTAL KNOWLEDGE, ATTITUDE AND PRACTICE ON ANTIBIOTIC USE FOR UPPER RESPIRATORY TRACT INFECTIONS IN CHILDREN

[1*]Khaled Al-Dossari

ABSTRACT

Background: *Several factors are evidently associated with the overuse of antibiotics both at the doctor`s level and the parents of children level.* ***Objectives:*** *To assess the level of knowledge and practice of parents about antibiotics use for upper respiratory tract infection (URTI) in their children as well as to determine the contributing factors for inappropriate use.* ***Material and Methods:*** *A cross-sectional study was carried out in two PHC centres in National Guard Health Affairs, Riyadh, between 1 January 2012 and 29 February 2012. It included parents of children (age from birth to 12 years) presenting with URTI symptoms.* ***Results:*** *The study included 352 parents of Saudi children. Most of the parents (71%) reported doctors as their source of antibiotic information. Only 1.4% of the participants identified correctly all antibiotics while 35.8% of them did not identify any antibiotic correctly. Factor analysis showed that the three common underlying factors responsible for antibiotics overuse were: parental self-prescribing tendency, parental tendency of asking for antibiotics from doctor and parental carefree attitude regarding over use and the three common underlying factors responsible for cautious approach to antibiotics use were: parental cautious nature, parental preference of advice over antibiotics and parental belief that URTI are mostly self-limiting.* ***Conclusions:*** *Parents are self-prescribing because of their easy access of antibiotics without prescription and their indifferent attitude toward microbial resistance.* ***Keywords***: *Antibiotics. Saudi Arabia, knowledge, URTI*

معرفة الوالدين وتوجهاتهم وممارساتهم في استخدام المضادات الحيوية لالتهابات الجهاز التنفسي العلوي عند الأطفال

ملخص: تشترك عوامل عدة في الاستخدام المفرط للمضادات الحيوية منها ما يخص الطبيب و منها ما يخص أولياء الأمور. **أهداف الدراسة:** تهدف هذه الدراسة إلى تقدير مستوى المعرفة و الممارسة بين أولياء الأمور فيما يتعلق بالمضادات الحيوية و العوامل التي تشترك في الاستخدام الخاطئ لها في علاج الأطفال المصابين بعدوى الجهاز التنفسي العلوي. **طريقة البحث:** تم إجراء دراسة مقطعية بمركزين صحيين تابعين للشئون الصحية للحرس الوطني بالرياض خلال المدة من 1 يناير حتى 29 فبراير للعام 2012. شملت الدراسة أولياء أمور الأطفال منذ الولادة و حتى سن الثانية عشر المصابين بأعراض عدوى الجهاز التنفسي العلوي. **النتائج:** ضمت هذه الدراسة 352 ولي أمر لأطفال سعوديين أكثر من نصفهم كانوا إناثا (59.4%). أقر معظم المشاركين (71%) أن مصدر معلوماتهم عن المضادات الحيوية كان الأطباء. من بين المشاركين، استطاع 1.4% فقط التعرف على كل المضادات الحيوية التي عرضت عليهم بينما 35.8% منهم لم يستطيعوا التعرف على أي مضاد حيوي. أكثر من ثلثي المشاركين (69.9%) استطاعوا التعرف على كل الأدوية غير المنتمية لفصيلة المضادات الحيوية. التحليل الإحصائي العاملي أوضح أنه يوجد ثلاثة عوامل رئيسية مؤثرة في الاستخدام المفرط للمضادات الحيوية وهي : ميل أولياء الأمور لوصفها بأنفسهم، ميلهم لطلب وصفها من الطبيب و اعتقادهم بأنها الأفضل. كما وجدت ثلاثة عوامل مؤثرة في استخدام المضادات الحيوية بحذر و هي : الطبيعة الحذرة لأولياء الأمور، و تفضيل سمع النصائح عن المضادات الحيوية و أخيرا اعتقاد أولياء الأمور أن عدوى الجهاز التنفسي تشفى تلقائيا . **الخلاصة:** يقوم الوالدان بصرف الدواء بأنفسهم بسبب الوصول السهل للمضادات الحيوية دون وصفة طبية، وموقفهم غير المبالي تجاه مقاومة الميكروبات للمضادات الحيوية , وأشار أولياء الأمور إلى أن هناك حاجة إلى مزيد من التعليم لكل من الأطباء والآباء والأمهات لاستخدام المضادات الحيوية بالطريقة المناسبة.

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INTRODUCTION

During the winter period, the majority of cases visiting the primary health care centres are due to upper respiratory tract symptoms[1]. Literature reports have shown that upper respiratory tract infectious diseases worldwide include: common cold, influenza, rhinorrhea, and bronchitis[2]. Despite the predominantly viral cause, with no need for antibiotic therapy[3,4], antibiotics, in practice, are frequently prescribed to children with symptoms of acute respiratory tract infection (URTI)[4-8]. Children aged 0 to four years received 53% of all antibiotics prescribed to the pediatric population[9]. This misuse of antibiotics is currently one of the major public health issues worldwide[10-13].

Problems associated with the overuse of antibiotics include development of antibacterial resistance, increasing the burden of chronic disease, raising costs of health services, and the development of side effects (e.g. adverse gastrointestinal effects)[14]. In addition, antibiotics may reduce the duration of fever in children with influenza which could reflect an increased risk of secondary bacterial infection for such children[8].

Several contributing factors are evidently associated with the overuse of antibiotics both at the doctor`s level[15-21] and the parents of sick children level and[22-24], namely: cultural factors, behavioral characteristics, socio-economic status, and level of education[25-27]. Furthermore, doctors usually relate their pattern of over prescribing to parents` pressure[28]. Also, lack of health education is one of the major contributing factors in the overuse of antibiotics[29]. Thus, Pediatricians acknowledge prescribing antimicrobial agents when they are not indicated[15]. Pediatricians believe educating parents is necessary to promote the judicious use of antimicrobial agents[16]. Self-medication is also a behaviour that contributes to the misuse of antibiotics[30,31].

Thus, the current parental knowledge, attitude and practice on antibiotic use in common childhood URTI is a matter of great interest and importance, and this study is trying to address these issues in particular

MATERIAL & METHOD

This was a cross-sectional descriptive study carried out in two PHC centers [King Abdulaziz Housing Clinic (Iskan) and Health Center for Specialized Care (HCSC Kashm Alaan) , National Guard Health Affairs, Riyadh, Saudi Arabia between 1 January 2012 and 29 February 2012.

Parents having children, aged from 0 to 12 years, presenting with URTI symptoms (nasal congestion, cough, fever and sore throat) were included in this study. Children having fever lasting more than 7 days, or chronic diseases, or symptoms such as earache, or those who came without one of their parents and children with symptoms of lower respiratory tract symptoms such as wheezing, stridor and breathing difficulty were excluded.

The sample size of 352 was estimated based on 34% of parents giving their children antibiotics for URTI without physician's advice, in the Egyptian study[36], with a desired precision of + 5%, alpha of 0.05 (CI of 95%) and power of 0.8. Participants of the study were selected by convenient sampling as they visited the clinic during the study period, and presented with inclusion criteria. Participants' selection comes from the random order by which they visited the clinic.

A pre-tested questionnaire was used in this survey adopted from a similar Greek

study[32]. Permission was taken by email from the researchers, who used this questionnaire in Greece, to translate it in Arabic language and use for local study. The questionnaire contains demographic characteristics, knowledge of antibiotics, sources of information, practice of antibiotic use in URTI and awareness of first-aid resources. The KAP-questionnaire was structured in three main sections which displayed the Knowledge (Section A), Attitudes (Section B) and Practices (Section C) of parents regarding antibiotics use in URTI of their children.

Section (A) included questions regarding parental knowledge concerning antibiotics. They were asked to mark antibiotic names out of seven commonly used medications and to answer questions relevant to antibiotics indications, side effects and their use in viral infections. Section (B) studied the parental attitudes regarding URTIs, antimicrobial agents' use and the doctors' role. Parents where asked which symptoms and what duration would lead them to seek medical attention for their children, as well as their expectations regarding antibiotics prescription. Other questions included reasons for antibiotic use without medical advice (over the counter acquisition of antibiotic, use of leftover antibiotic from previous illness, etc.) or whether they would seek for a doctor who is more lenient with antibiotic administration. Finally, (Section C) looked into parental practices and whether the parent-doctor relation is influenced by the latter's attitude on antibiotic prescription. Parents were asked whether their doctor spends enough time explaining the illness and suggested antibiotic treatment for their child, whether he is influenced by their demand to prescribe antibiotics, as well as whether their doctors gives them instructions over the phone (without previous examination) for antibiotic administration to their sick child.

Each question (apart from those included in the demographic data section) was in a format of five possible answers (accepting only one right answer), according to the 5-point Likert scale: 1 = strongly agree, 2 = agree, 3 = uncertain, 4 = disagree and 5 = disagree strongly or 1 = always, 2 = most of the times, 3 = often, 4 = sometimes and 5 = never.

To verify parent's responses consistency and exclude random completion, three couples of similar questions (where each couple included the same statement expressed in a different way) and three pairs of contradictory questions (where each question included the reverse statement requiring the opposite answer) were entered in the questionnaire's structure. All these questions were randomly placed in the questionnaire to minimize parents' awareness. Questionnaires with discordant responses to two or more of these paired questions were removed.

After we received written permission from King Abdullah Research Centre, the questionnaires were distributed by nurses to all parents attending the PHC with their children with URTI symptoms and before entering the doctor's room. In order to increase compliance, all nurses were personally informed by the researcher about the study nature and its importance. They were asked to distribute the questionnaires to parents, collect and mail them back to the researcher. An informed verbal consent was obtained from every parent before participation in the study. Participants were assured that collected data will be strictly confidential, and will not be disclosed for any reason, and will be used only for research purposes. Professional advice was provided regarding appropriate use of antibiotics in URTI in children

RESULTS

The data were verified manually, entered in computer and IBM-SPSS software statistical program version 19 was utilized for data entry and analysis. Categorical variables were presented as frequencies and percentages. Spearman's Rho was used to measure correlation between two variables. P-value of less than 0.05 was considered significant. Principle Component Analysis was carried out on the items in the questionnaire to find the main underlying factors; beliefs and behavioural that parents are influenced by in prescribing or avoiding antibiotics.

The study included 352 parents of Saudi children. Table (1) presented their baseline characteristics. (59.4%) of them are female. Almost one-third of the mothers were high school educated (35.2%) while 29.3% were university educated.

Table 1: Demographic characteristics

	Frequency	*Percent*
Gender		
Male	143	40.6
Female	209	59.4
Mother's educational level		
Primary	76	21.6
Secondary	49	13.9
High school	124	35.2
College	103	29.3
Father's educational level		
Primary	39	11.1
Secondary	59	16.8
High school	188	53.4
College	66	18.8
Family income		
Low	28	8.0
Middle	296	84.0
High	28	8.0
Relation of the patient to treating physician	17	4.8
Relative/family friend /formal relationship	335	95.2

More than half of the fathers were high school educated, while 18.8% were university educated. Family income was middle in most of the participants (84%). In majority, formal relationship to the treating physician was reported (95.2%).As obvious from figure (1), the access to health care system was described as good by 61.4% of the parents, while it was described as bad by 3.4% of them.

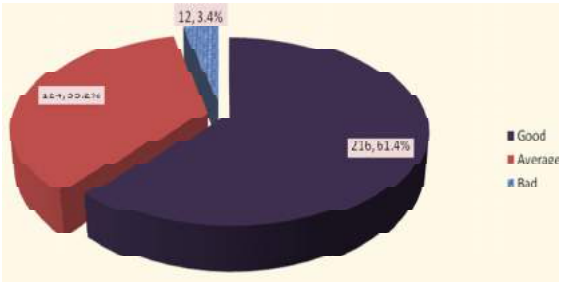

Fig. 1: Distribution of the parents according to their perceived access to health care system.

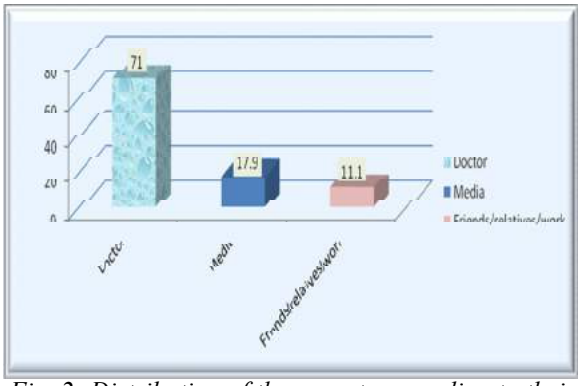

Fig. 2: Distribution of the parents according to their source of information about antibiotics.

Most of the parents (71%) reported doctors as their source of antibiotic information, while media and friends/relatives were reported by 17.9% and 11.1% of them respectively, as sources of antibiotic information (Fig. 2).

Parental knowledge about commonly used antibiotics: As shown in table (2), amoxicillin and Augmentin were recognized by 44.6% and 38.9% of the parents, respectively as antibiotics compared to clarithromycin that reported by 16.5% of them as an antibiotic. On the other hand, histop (antihistamine) was reported as an antibiotic by 21.6% of the

parents while normal saline nasal drops, flagyl and oral rehydration solution were reported as antibiotic by 9.9%, 6.3% and 4.5% of the participants, respectively.

Table 2: Knowledge about commonly used medications (n=352).

Common Medications	*Yes (%)*	*No (%)*
Augmentin	38.9	61.1
Clarithromycin	16.5	83.5
Histop	21.6	78.4
Amoxicillin	44.6	55.4
Flagyl	6.3	93.7
Normal saline nasal drops	**9.9**	**90.1**

URTI and practice of parents: As shown in table (4), 79% of the parents expected prescription of paracetamol and analgesics by their physicians to treat URTI, while 47.4% of them expected prescription of antibiotics. Antitussives, normal saline nasal drops and antihistamine were expected to be prescribed by physicians for URTI treatment among 31.8%, 31.3% and 19.3% of parents, respectively.

Table (5): Responses of the participants to the questions about their likelihood of antibiotic prescription to their child by doctors (n=352).

Childs Symptoms	*Always*	*Most of the time*	*Usually*	*Sometimes*	*Never*
Cold	47 (13.4)	53 (15.1)	50 (14.2)	111 (31.5)	91 (25.9)
Runny nose	24 (6.8)	48 (13.6)	46 (13.1)	100 (28.4)	134 (38.1)
Sore throat	93 (26.4)	80 (22.7)	63 (17.9)	94 (26.7)	22 (6.3)
Cough	56 (15.9)	56 (15.9)	62 (17.6)	99 (28.1)	79 (22.4)
Vomiting	57 (16.2)	86 (24.4)	38 (10.8)	78 (22.2)	93 (26.4)
Fever	97 (27.6)	84 (23.9)	36 (10.2)	67 (19.0)	68 (19.3)
Ear pain	109 (31.0)	92 (26.1)	34 (9.7)	63 (17.9)	54 (15.3)

Likelihood of antibiotic prescription to their child by doctors: On descriptive analysis, parents were more likely (always or most of the time) to request antibiotic for ear pain (57.1%), fever (51.5%), sore throat (49%) while less likely to request antibiotic for vomiting (40.6%), cough (31.8%), cold (28.5%) and runny nose (20.4%).

Antibiotic use without the doctor's advice: Non-serious status of the child (23.6%), lack of time or money (20.8%) were the reason for giving antibiotics to the child without physician's advice.

Table 4: Parental reasons for giving their child antibiotics without physician's advice. (n=352).

Reason	*Always*	*Most of the time*	*Usually*	*Sometimes*	*Never*
Lack of time or money to visit physician	39 (11.1)	34 (9.7)	38 (10.8)	66 (18.8)	175 (49.7)
Child's condition did not seem serious enough.	28 (8.0)	55 (15.6)	40 (11.4)	73 (20.7)	156 (44.3)
Knowledge of antibiotics for the same symptom so self-prescribed	34 (9.7)	33 (9.4)	44 (12.5)	47 (13.4)	194 (55.1)
Pharmacist recommended the antibiotic.	24 (6.8)	29 (8.2)	39 (11.1)	86 (24.4)	174 (49.4)
Friend or relative recommended the antibiotic.	12 (3.4)	16 (4.5)	29 (8.2)	41 (11.6)	254 (72.2)
Lack of time or money to visit physician	39 (11.1)	34 (9.7)	38 (10.8)	66 (18.8)	175 (49.7)
Child's condition did not seem serious enough.	28 (8.0)	55 (15.6)	40 (11.4)	73 (20.7)	156 (44.3)

Similarly physician`s prescription (19.1%), pharmacist recommendation (15%) and friend/family relative recommendation (7.9%) were the reasons for giving antibiotics to the child without physician's advice, respectively.

Parental believes and practice for appropriate use of antibiotics: The majority of the parents (84%) agreed that parents and doctors should be informed about judicious antibiotic use. Almost two-thirds of them (66.4%) agreed that

overuse and inappropriate use of antibiotics reduces efficacy.

More than half of the parents (50.2%) agreed that antibiotics are used unnecessarily while more than one-third of them (39.5%) agreed that most of URTI are of viral origin. Thirty percent of the parents agreed that they may change their doctors because of prescribing antibiotics to their children to treat URTI. Slightly less than half of the parents (49.1%) agreed that most of URTI are self-limited.

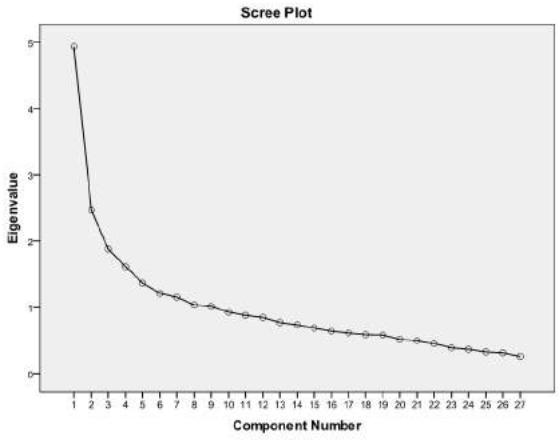

Fig. 3: Scree Plot for Principal Component Analysis.

Around half of the participants (49.2%) are well informed about judicious antibiotic use. Almost two-thirds of the parents (63.5%) asked their doctor to prescribe antibiotics to treat URTI of their children. Most of the participants (82.9%) mostly followed doctors` instruction and 43.3% of them appreciated the doctors who did not prescribe antibiotics.

Parental believes and practice for in-appropriate use of antibiotics: Table (8) shows that more than half of the parents (53.4%) agreed that children with flu like symptoms get better with antibiotics and 44.3% agreed that antibiotics can prevent URTI complications. Almost one-third of them (32.8%) agreed that new antibiotics that can kill resistant bacteria can be produced by scientists.

Table (8): Parental beliefs, attitudes & practices regarding antibiotic use.

Beliefs and attitudes (Practices)	*Strongly agree (Always)*	*Agree (Mostly)*	*Not sure (Usually)*	*Disagree (Sometimes)*	*Strongly Disagree (Never*
Lack of time and resources	39 (11.1)	34 (9.7)	38 (10.8)	66 (18.8)	175 (49.7)
child condition is not seriousness	28 (8.0)	55 (15.6)	40 (11.4)	73 (20.7)	156 (44.3)
Similar prescription	34 (9.7)	33 (9.4)	44 (12.5)	47 (13.4)	194 (55.1)
Pharmacist recommendation	24 (6.8)	29 (8.2)	39 (11.1)	86 (24.4)	174 (49.4)
Friend/relative recommendation	12 (3.4)	16 (4.5)	29 (8.2)	41 (11.6)	254 (72.2)
Phone antibiotic recommendation	11 (3.1)	13 (3.7)	22 (6.3)	20 (5.7)	289 (81.3)
Ask antibiotic prescription directly	14 (4.0)	32 (9.1)	26 (7.4)	62 (17.6)	218 (61.9)
Insist prescribing antibiotics	11 (3.1)	33 (9.4)	30 (8.6)	45 (12.9)	231 (66.0)
Doctor prescription only because you asked him	14 (4.0)	22 (6.3)	25 (7.1)	58 (16.5)	233 (66.2)

Almost one-quarter of the parents (26.1%) agreed that they would use any leftover antibiotics whenever their child presented with similar URTI symptoms, 17.1% of them agreed that antibiotics have no side effects while 20.5% agreed that they would change their doctors because of non-prescription of antibiotics as they think appropriate.

Only 19.7% of the parents were much dissatisfied with antibiotic non-prescription. The common reported reasons for inappropriate antibiotic use always or most of the time were non-seriousness of the child status (23.6%), lack of time and resources (20.8%),

pediatrician has prescribed the same antibiotic in the past for the same symptoms. (19.1%), pharmacist recommendation (15%) and friend/relatives recommendation (7.9%).

Table (9): Underlying Factors prompting parents to prescribe or avoid antibiotics for their children.

	*Rotated Factor Loadings**					
	Self-Prescribing	Asking for antibiotics	Cautious about use	Antibiotics are good	Prefer advice only	Disease self-limiting
Faster recovery with antibiotics	-	-	-	0.547	-	-
Scientists can produce new antibiotics.	-	-	-	0.504	-	-
Inappropriate use reduces efficacy	-	-	-	0.534	-	-
Antibiotic use prevents complications of URTI.	-	-	-	0.732	-	-
Not enough time or money for doctor visit.	0.751	-	-	-	-	-
Thought child's condition was not serious enough	0.708	-	-	-	-	-
Same antibiotic prescribed in past, for same symptoms	0.586	-	-	-	-	-
Because a pharmacist recommended the antibiotic.	0.78	-	-	-	-	-
Because a friend/ relative recommended the antibiotic	0.694	-	-	-	-	-
Would reuse any leftover antibiotics for URTI symptoms	0.412	-	-	-	-	-
Antibiotics are used too much and unnecessarily	-	-	0.462	-	-	-
Will change doctor as he prescribes antibiotics a lot	-	-	0.549	-	-	-
Parents & doctors should be informed on antibiotic use	-	-	0.65	-	-	-
Consider antibiotic adverse reactions when using them	-	-	0.584	-	-	-
Antibiotics have no side- effects.	-	-	-0.552	-	-	-
Ask doctor if antibiotics is necessary	-	-	-	-	0.767	-
Glad if doctor does not prescribe antibiotics	-	-	-	-	0.692	-
Doctor recommends antibiotics on the phone	-	0.771	-	-	-	-
Ask directly your doctor to prescribe antibiotics	-	0.784	-	-	-	-
Insist on prescribing antibiotics as a precaution	-	0.711	-	-	-	-
Doctor prescribes antibiotic only because you ask	-	0.776	-	-	-	-
Most URTI are viral, not requiring antibiotics	-	-	-	-	-	0.75
Most URTI are self-limiting, not needing antibiotics	-	-	-	-	-	0.577
Eigen Value	3.06	2.96	2.08	1.54	1.52	1.48
% of Variance	11.35	10.95	7.72	5.71	5.62	5.46
Cumulative % of Variance	11.35	22.3	30.02	35.73	41.35	46.81

* values > 0.4 only shown

KMO and Bartlett's Test*		
Kaiser-Meyer-Olkin Measure of Sampling Adequacy.		.77
Bartlett's Test of Sphericity	Approx. Chi-Square	2236.97
	Df	351
	p-value	<0.001

* KMO > 0.5 suggest sample size adequacy for analysis, and statistically significant Bartlett's test for Sphericity suggest correlations between items were sufficiently large for Principal Component Analysis.

Antibiotic recommendation by physician via phone was reported always or most of the time by 6.7% of parents, 13.1% of the parents asked antibiotic prescription directly from their physicians, 12.5% of parents insisted prescribing antibiotics and 10.3% of them have mentioned that their doctors prescribed antibiotics mostly only because they asked them.

Parental belief that antibiotics were being used excessively was found to be significantly correlated to parental consideration of antibiotic side effects before use (Spearman's rho 0.339, p-value 0.01).

Parents who believed that antibiotics are used excessively also thought that physicians and patients should be informed well about the judicious use of antibiotics (Spearman's rho 0.179, p-value 0.01).

Parental belief that most URTI were viral in origin correlated with non-use of antibiotics for URTI as these would be self-limiting (Spearman's rho 0.187, p-value 0.01)

Parental belief that antibiotics have no side effects was found to be correlated with the behavior of insisting on antibiotic prescription on unconfirmed diagnosis (Spearman's rho 0.266, p-value 0.01).

Parental behavior of reusing leftover antibiotics was found be correlated to self-prescribing antibiotics without physician's advice based on old knowledge for similar symptoms (Spearman's rho 0.377, p-value 0.01) and to the belief that scientists can discover antibiotics against resistant microbes (Spearman's rho 0.105, p-value 0.049).

Six factor combinations (components) based on screen-plot and having Eigen values higher than Kaiser criterion of 1, were included here for interpretation, although rotated components, 7-9 could also be considered for inclusion as Eigen values were also higher than 1, but these were single items and the Scree plot appears to smooth out after 6.

These six common underlying factors were responsible for overuse or cautious approach to antibiotics: Inappropriate Use; Parental self-prescribing tendency, Parental tendency of asking for antibiotics from doctor and parental carefree attitude regarding over use while for appropriate Use; Parental cautious nature, Parental preference of advice over antibiotics and parental belief that URTI are mostly self-limiting.

DISCUSSION

This is not the first study indicating public misconceptions with regards to antibiotic use for common URTIs. In our study, although parents believed that most URTIs are self-limiting, they expected to receive antibiotics when this diagnosis was made. Similarly, in a web-based questionnaire among a sample of the general Dutch population, Cals et al showed that nearly half of the responders (47%) incorrectly identified antibiotics as being effective in treating viral infections [38]. In the same study, the term "acute bronchitis" raised an immediate expectation for an antibiotic prescription similar to "ear ache-otitis", as shown in the current study.

Almost half of parents believed that URTIs are mostly self-limited although approximately two-thirds of them asked physicians to prescribe antibiotics for treating URTI. Slightly less than half of parents (47%) expected to possibly receive antibiotics when such a diagnosis was given. However, it is incorrect to assume that 47% of the parents desired only antibiotic therapy because the

majority of them also preferred other drugs given for symptomatic therapy as paracetamol and analgesics.

Ear ache, fever and sore throat were the most common diagnosis for which parents always or usually expect to receive antibiotics. Comparable results have been reported in a study conducted among Greek parents[32].

Approximately 15-35% of parents gave antibiotics to their children without consulting their physician and almost two-thirds of them appreciated that unnecessary antibiotic use reduces its efficacy.

Saudi parents also reported that information regarding unnecessary antibiotic use and resistance came from their physicians, which is similar to what has been reported by Greek parents[32] while it is different from findings of a public survey published by Hawkings et al where respondents reported that most information regarding antibiotic resistance was derived from the media[39]. In the same study, patients had a low sense of personal ability to help contain this problem. It is possible that many parents might have endorsed their physicians as their primary health influence and derived most of their opinions regarding antibiotics from them.

These different responses between studies are possibly a reflection of the difference in health care systems. In western countries, the great majority of children have regular follow-up by private consultant pediatricians who are accessible either on the phone or with a home/office visit. This leads to a close and trusted relationship between the parent-child and the physician.

In KSA, parents have free access to all types of antibiotics despite a specific legislation forbidding antibiotic use without a prescription.

It is not uncommon that many parents believe weather change to be the main cause of URTI. Many think their children are more vulnerable to URTI, especially after being exposed to colder weather or the rainy season. This health belief may be derived from their past experience or cultural belief. In the current study, only 40% of parents recognizes that URTI mostly of viral origin.

In this study, almost 53% of parents felt that their child with flu like symptoms needed antibiotics, which was not prescribed by the doctor. There is a widespread perception that for every symptom, there is a specific remedy or drug, and antibiotics are viewed as wonder drugs capable of healing a wide variety of illnesses ranging from gastrointestinal disorders to headaches[40]. Parents may feel that antibiotics could help ease their anxiety and worry if it is given to their sick child. In addition, they do not need to come back again to ask for an antibiotic after one to two days of "poor improvement" of the illness.

Principal component analysis reveals that parents can be grouped as over-users and proper-users of antibiotics. The over-users have a tendency to self-prescribe perhaps due to easy availability of antibiotics without the need of a doctor's prescription, coupled with a carefree indifferent attitude regarding antibiotic resistance or irrespective of whosoever may be giving the condoning advice and even demanding or having no shyness in demanding the antibiotics from physician in case his/her advice is sought.

The proper users / under-users of antibiotics for their children have some common characteristics as well: these tend to be cautious in nature regarding

antibiotic use, believe that most URTI are self-limiting or viral in nature, therefore are better informed and take their doctor's advice seriously, giving it value and that supersedes their personal preference.

It appears that the parents can be given more health education regarding proper use of antibiotics, as many parents also feel that it is needed. In addition, physicians need to be educated not be pressured by the parents, however, tighter regulation of pharmacies may be the solution to curb easy access to antibiotics. This would limit influences of self, media, friends and those other than physicians encouraging to initiate antibiotics for lesser than necessarily severe symptoms.

In the current research, data were collected from parents through a self-administered questionnaire with the help of trained nurses. This kind of data collection was preferred versus the pattern of interviewing the parents, taking into account many drawbacks. First, the interviewer might influence the parents' response during their conversation, and secondly interviewees may respond in accordance with what they believe to be the "correct" replies. Additionally, the probability of the responders' embarrassment towards the interviewer would affect the quality of their answers. Moreover, a large number of interviewers would have to be trained to be sent to interview the parents, which was impractical. Finally, the variability among the interviewers could not be excluded. Using the questionnaires on the other hand, each responder received the same set of questions phrased in exactly the same way, so the answers were derived in a more objective way. Questionnaires may, therefore, yield data more precise than information obtained through an interview[41-42].

Among limitations of the current research, first: the study was associated with a poor recall of an URTI experience and antibiotic use. Therefore, parents' knowledge, attitude and practices may not always be consistent with their actual behavior. Invalid answers may also have occurred because of embarrassment. Second: the language and phrasing used in writing the questions may not have been fully understood by parents of low socioeconomic status (because of the use of medical terms), leading to inaccurate answers. Finally, subjective appreciation of URTI symptoms (cough, runny nose, and ear ache) may have influenced the responses.

In conclusion, this study has documented many areas in which parental knowledge on antibiotic use for acute URTI is considerably lacking, resulting in inappropriate attitudes and practices. Half of the parents attending the physicians for their children with URTI expected to get antibiotics. Factors responsible for inappropriate use were parental self-prescribing tendency, parental tendency of asking for antibiotics from doctor and parental carefree attitude regarding over use. Parents are self-prescribing because of their easy access of antibiotics without prescription and their indifferent attitude toward microbial resistance. Parents pointed out that more education is needed for both doctors and parents for appropriate antibiotic use.

From the results of the current study, we recommend implementation of educational programs on antibiotic use for parents, helping reduce their misuse. It is essential to establish evidence-based clinical practice guidelines of acute URTI for doctors with regular medical audit of treatment for acute URTI to ensure that patients receive the best quality of care. The Saudi parents and physicians should have a trusted relationship because most parents will be happy with the information

provided to them and they would not change their private physician if antibiotics were used too much or too little. Strict enforcement of over-the-counter sale of antibiotics should be implemented.

It is hoped that by identifying weak areas in parents' knowledge and attitude, better planned educational and behavioral modification efforts can be made to reduce unnecessary prescription of antibiotics and curtail the still burgeoning problem of bacterial resistance in children specifically and in the community at large.

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REFERENCES

1. Bauman KA. The family physician's reasonable approach to upper respiratory tract infection care for this century. *Arch Fam Med.* 2000;9:596–7. doi: 10.1001/archfami.9.7.596.
2. West J. Acute upper airway infections: childhood respiratory infections. British Medical Bulletin. 2011;61(1): 215-230.
3. Orr PH, Scherer K, Macdonald A, Moffatt ME. Randomized placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. *J FamPract.* 1993;36:507–12
4. Gonzales R, Malone DC, Maselli JH, Sande MA. Excessive antibiotic use for acute respiratory infections in the United States. *Clin Infect Dis.* 2001;33:757–62. doi: 10.1086/322627.
5. Mangione-Smith R, McGlynn EA, Elliott MN, McDonald L, Franz CE, Kravitz RL: Parent expectations for antibiotics, physician-parent communication, and satisfaction. Arch PediatrAdolesc Med 2001, 155:800-6.
6. Watson RL, Dowell SF, Jayaraman M, et al: Antimicrobial use for pediatric upper respiratory infections: reported practice, actual practice, and parent beliefs. Pediatrics 1999, 104:1251-7.
7. McCaig LF, Besser RE, Hughes JM: Trends in antimicrobial prescribing rates for children and adolescents. JAMA 2002, 287:3096-3102.
8. Harnden A, Perera R, Brueggemann AB, Mayon-White R, Crook DW, Thomson A, Mant D: Respiratory infections for which general practitioners consider prescribing an antibiotic: a prospective study. Arch Dis Child 2007, 92(7):594-7
9. Nyquist AC, Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for children with colds, upper respiratory tract infections, and bronchitis. JAMA 1998; 279:875-7.
10. Mangione-Smith R, Elliott MN, Stivers T, McDonald L, Heritage J, McGlynn EA: Racial/ethnic variation in parent expectations for antibiotics: implications for public health campaigns. Pediatrics 2004, 113:e385-e394.
11. Nash DR, Harman J, Wald ER, Kelleher KJ: Antibiotic prescribing by primary care physicians for children with upper respiratory tract infections. Arch PediatrAdolesc Med 2002, 156:1114-1119
12. Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS, Douglas RM: Effect of beta lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. BMJ 2002, 324:28-30.
13. Yagupsky P: Selection of antibiotic-resistant pathogens in the community. Pediatr Infect Dis J 2006, 25:974-76.
14. Alumran A, Hurst C, Xiang-Yu H. Antibiotics overuse in children with upper respiratory tract infections in Saudi Arabia: Risk factors and potential interventions. Clinical Medicine and Diagnostics 2011; 1(1):8-16.
15. Bauchner H, Pelton SI, Klein JO: Parents, physicians, and antibiotic use.Pediatrics 1999, 103:395-398.
16. Elan P, Katzenstein D, Frankish CJ, Herbert CP, Milner R, Speert D, Chambers K: Prescribing practices and attitudes toward giving children antibiotics. Canadian Family Physician 2001, 47.

17. Pechère JC: Patients' Interviews and Misuse of Antibiotics. Clinical Infectious Diseases 2001, 33:S170-S173.
18. Butler CC, Hood K, Verheij T, Little P, Mel bye H, Nuttall J, Kelly MJ, Mölstad S, Godycki-Cwirko M, Almirall J, Torres A, Gillespie D, Rautakorpi U, Coenen S, oossens H: Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. BMJ 2009, 338:b2242.
19. Nasrin D, Collignon PJ, Roberts L, Wilson EJ, Pilotto LS, Douglas RM: Effect of beta lactam antibiotic use in children on pneumococcal resistance to penicillin: prospective cohort study. BMJ 2002, 324:28-30.
20. Yagupsky P: Selection of antibiotic-resistant pathogens in the community. Pediatr Infect Dis J 2006, 25:974-76.
21. Bauchner H, Pelton SI, Klein JO: Parents, physicians, and antibiotic use. Pediatrics 1999, 103:395-398.
22. Stivers T. Participating in decisions about treatment: overt parent pressure for antibiotic medication in pediatric encounters. SocSci Med 2002, 54(7):1111-30.
23. Mangione-Smith R, McGlynn EA, Elliott MN, McDonald L, Franz CE, Kravitz RL. Parent expectations for antibiotics, physician-parent communication, and satisfaction. Arch PediatrAdolesc Med 2001, 155:800-6.
24. Watson RL, Dowell SF, Jayaraman M, et al. Antimicrobial use for pediatric upper respiratory infections: reported practice, actual practice, and parent beliefs. Pediatrics 1999, 104:1251-7.
25. Braun B, Fowles J. Characteristics and experiences of parents and adults who want antibiotics for cold symptoms. Arch Fam Med 2000;9(7):589-595.
26. Kozyrskyj A, Dahl M, Chateau D, Mazowita G, Klassen T, Law B. Evidence-based prescribing of antibiotics foe children: role of socioeconomic status and physician characteristics. Canadian Medical Association Journal 2004; 171(2):139-145.
27. Teng C, Leong K, Aljunid S, Cheah M. Antibiotic prescription in upper respiratory tract infections. Asia Pacific Family Medicine 2004; 3(1-2):38-45.
28. Pech`re J. Patients` interviews and misuses of antibiotics. Clinical Infectious Diseases. 2001; 33(S3): S170-S173.
29. Cebotarenco N, Bush P. Reducing antibiotics for colds and flu: a student-taught program. Health Education Research, Cym008, 2007.
30. Bi P, Tongb S, Partonc K. Family self-medication and antibiotics abuse for children and juveniles in a Chinese city. Social Sciences and Medicine. 2000;50(10):1445-1450.
31. Sarahroodi S, Arzi A, Sawalha A, Ashtarinezhand A. Antibiotics self-medication among southern Iranian university students. International Journal of Pharmacology. 2010; 6: 48-52.
32. Panagakou SG, Spyridis N, Papaevangelou V, Theodoridou KM, Goutziana GP, Theodoridou MN, Syrogiannopoulos GA, Hadjichristodoulou CS. Antibiotic use for upper respiratory tract infections in children: a cross-sectional survey of knowledge, attitudes, and practices (KAP) of parents in Greece. BMC Pediatr. 2011 Jul 5;11:60.
33. Chan GC, Tang SF. Parental knowledge, attitudes and antibiotic use for acute upper respiratory tract infection in children attending a primary healthcare clinic in Malaysia. Singapore Med J. 2006 Apr;47(4):266-70.
34. Shlomo V, Adi R, Eliezer K. The knowledge and expectations of parents about the role of antibiotic treatment in upper respiratory tract infection--a survey among parents attending the primary physician with their sick child. BMC FamPract. 2003 Dec 30;4:20.
35. Belongia EA, Naimi TS, Gale CM, Besser RE. Antibiotic use and upperrespiratory infections: a survey of knowledge, attitudes, and experience inWisconsin and Minnesota. Prev Med. 2002 Mar;34(3):346-52
36. Alumran A, Hurst C, Hou XY. Antibiotics Overuse in Children with Upper Respiratory Tract Infections in Saudi Arabia: Risk Factors and Potential Interventions. Clinical Medicine and Diagnostics 2011; 1(1): 8-16

37. Aboul Fotouh AM, el-Damaty SE, Abdel Megeid FY. Mother's knowledge about antibiotic and role of self prescription. J Egypt Public Health Assoc. 1998;73(1-2):57-69. PubMed PMID: 17249211.
38. Cals JW, Boumans D, Lardinois RJ, Gonzales R, Hopstaken RM, Butler CC, Dinant GJ. Public beliefs on antibiotics and respiratory tract infections: an internet-based questionnaire study. Br J Gen Pract 2007; 57(545):942-7.
39. Hawkings NJ, Wood F, Butler CC. Public attitudes towards bacterial resistance: a qualitative study. J AntimicrobChemother 2007; 59(6):1155-60.
40. Kunin CM, Lipton HL, Tupasi T, Sacks T. Social, behavioral and practical factors affecting antibiotic use worldwide: report of Task Force 4. Rev Infect 1987; 9:S270-85.
41. Questionnaire and interview as data – gathering tools [http://www.okstate.edu/ag/agedcm4h/academic/aged5980a/5980/newpage16.htm]
42. Limitations of survey research [http://www.un.org/popin/books/reprod/chap1.htm]

EFFECT OF AEROBIC EXERCISES ON BLOOD PRESSURE IN MILD AND MODERATE HYPERTENSIVE MIDDLE AGED AND OLDER PATIENTS.

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ABSTRACT

Background: *The prevention and treatment of hypertension are a high priority in medicine and public health. It is well documented that blood pressure reduction with medication significantly reduces cardiovascular risk. Exercise remains a cornerstone therapy for the primary prevention, treatment, and control of hypertension. This study aims at analysing the effect of Aerobic exercises on reduction of Blood Pressure in the subject with Pre and Stage 1 hypertension.* ***Material and Methods:*** *In this study patient with pre hypertension and stage 1 hypertension without any pre medication cardiac therapy were selected. They underwent 6 weeks of aerobic exercise training program. The aerobic exercise program consisted of repetitive, low resistance movements for at least 30 to 45 min, at 50% to 70% of Max heart rate, 3 to 4 times per week. The systolic & diastolic blood pressure were measured at baseline and after 6 weeks of aerobic exercises training program using sphygmomanometer[10,13] and pulse rate was measured by manual method.* ***Results:*** *The result of present study demonstrated a significant difference between group effects in both the Systolic and Diastolic Blood Pressure. It was found that there was significant difference in the mean systolic blood pressure and diastolic blood pressure values for pre and stage hypertensive subjects.* ***Conclusions:*** *In conclusion, the inclusion of Aerobic exercise in daily activities is an efficient way of blunting the blood pressure changes in hypertensive patients and it is of high statistical significance ($p<0.005$). The above mentioned efficiency is more on Stage 1 hypertensive subjects when compared to pre hypertensive subjects.*

Keywords: Hypertension, Aerobic Exercise,

ملخص: الوقاية والعلاج من ارتفاع ضغط الدم من أولويات الطب والصحة العامة. من المؤكد أن خفض ضغط الدم بالأدوية يقلل بشكل ملحوظ من المخاطر القلبية الوعائية. ممارسة الرياضة لا تزال تمثل حجر الزاوية في الوقاية الأولية، والسيطرة والعلاج على ارتفاع ضغط الدم. تهدف هذه الدراسة إلى تحليل أثر التمارين الهوائية على خفض ضغط الدم في مرحلة ما قبل ظهور ارتفاع ضغط الدم و ارتفاع ضغط الدم في المرحلة الاولي. **منهج الدراسة**: تم اختيار مرضي ضغط الدم في مرحلة ما قبل ظهور ارتفاع ضغط الدم ومرحلة ارتفاع ضغط الدم البسيط وغير خاضعين لأي علاج. أخضعوا لبرنامج رياضي لمدة 6 أسابيع . يتألف البرنامج من التمارين الرياضية المتكررة بحركات المقاومة المنخفضة لمدة لا تقل 30 حتي 45 دقيقة، بنسبة 50٪ إلى 70٪ من معدل ضربات القلب, 3 إلى 4 مرات في الأسبوع. تم قياس ضغط الدم الانقباضي والانبساطي قبل البرنامج وبعد 6 أسابيع من التمارين الهوائية كما تم قياس معدل النبض. **النتائج**: أظهرت نتيجة الدراسة فرقا كبيرا ذو دلالة احصائية ($p<0.005$) في ضغط الدم قبل وبعد التمارين الاستنتاجات: إدراج التمارين الرياضية في الأنشطة اليومية هو وسيلة فعالة لخفض ضغط الدم, وتظهر الفعالية اكثر على ارتفاع ضغط الدم في المرحلة الاولي بالمقارنة مع مرحلة ما قبل ارتفاع ضغط الدم.

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INTRODUCTION

Hypertension generally defined as blood pressure persistently above 140/90 mm Hg and is extremely common. Even mild blood pressure elevations are associated with an increased risk of myocardial infarction and stroke, and the risk rises continuously with the severity of the condition[1]. Individuals who have blood pressure that is more than 160/95 mm Hg have an annual incidence of coronary artery disease (CAD), congestive heart failure, intermittent claudication, and stroke that is up to three times higher than normotensive persons[2].They also have an exercise capacity about 30% less[3].

Consequently, the prevention and treatment of hypertension are a high priority in medicine and public health. It is well documented that blood pressure reduction with medication significantly reduces cardiovascular risk. But nonpharmacologic strategies for blood pressure reduction, including weight loss, dietary modification, and exercise, are also effective. Particularly when patients have mild to moderate hypertension, these strategies offer the possibility of reducing blood pressure and cardiovascular risk without any of the adverse side effects associated with medication.

Exercise remains a cornerstone therapy for the primary prevention, treatment, and control of hypertension. Exercise programs that primarily involve endurance activity prevent the development of hypertension and lower blood pressure (blood pressure) in adults with normal blood pressure and those with hypertension[4].

With direct effects on circulation, metabolism, and the nervous system, exercise represents a multipronged assault on cardiovascular risk. Whether used only with other lifestyle changes or in combination with medication, exercise is a particularly attractive tool for hypertension control. Many studies[5] have validated exercise for treating high blood pressure. Exercise not only reduces blood pressure, it also lowers levels of low-density lipoprotein cholesterol, reduces insulin resistance and glucose intolerance, and often is associated with reduced body weight[6].

Influence of gender and weight. There was no significant correlation between weight change and blood pressure reduction. Comparable effects have been seen in adolescents, individuals over 60, and those in between[7].

Generally, it appears that training in the range of 40% to 70% of VO2 max(50% to 70% of maximum heart rate) was as effective as, if not more effective than, a more intense regimen. Blood pressure reductions typically appeared within 3 months of the start of training. Generally, no further blood pressure reduction occurs after 3 months of training, except in rare instances[8]. The program should be at least 1 to 3 months to reach the stable stage, and training should be maintained indefinitely, because the hypotensive effect persists only as long as regular endurance exercise is maintained.

The basic exercise prescription for all groups is similar to that recommended by the ACSM[9] to develop and maintain cardiovascular and muscular fitness in healthy adults: at least a half-hour of endurance exercise at 50% to 75% of maximal oxygen uptake (50% to 70% of maximum heart rate) done at least 3 days a week. Physical activity of moderate intensity involving rhythmic movements with the lower limbs for 50–60 minutes, 3 or 4 times per week reduces blood pressure and appears to be more effective than vigorous exercise[10].

The type of aerobic exercise is largely a matter of patient preference. Walking at a 15-minute/mile pace is ideal for many; it

requires no equipment or special clothing and fits readily into most patients' schedules. Some prefer jogging, biking, or swimming. Exercise machines such as treadmills, stationary cycles, or cross-country ski devices provide an effective workout for individuals who enjoy exercising at home, health club or gym.

The rationale for treating hypertension is the reduction of cardiovascular morbidity and mortality. It is important to note that aerobic exercise has a positive effect on other cardiovascular risk factors, such as blood lipid levels, body weight, and insulin resistance. Overall, more than 40 clinical studies suggest an inverse relationship between physical activity and the incidence of coronary artery disease. With appropriate screening and individualized exercise prescription, regular physical activity can and should be incorporated into the life-style of an individual. Increases in activity among sedentary persons have the potential to bring major benefits in functional capacity, a sense of well-being and other health outcomes[10].

Drug therapy has for long been the mainstay management of hypertension. The commonly used drugs causes adverse effects like bradycardia, bronchospasm, fatigue, deterioration of renal function, adverse metabolic effects like increased serum cholesterol and reduction in HDL cholesterol. Reduction in blood pressure via regular aerobic exercise reduces cost and medication related side effects.

This study aims at analysing the effect of Aerobic exercises on reduction of Blood Pressure in the subject with Pre and Stage 1 hypertension.

METHODOLOGY

In this study patient with pre hypertension and stage 1 hypertension without any pre medication cardiac therapy were selected. They underwent a 6 weeks aerobic exercise program.

After explaining the procedure an informed consent was obtained from all the patients. Prescribed aerobic exercises were given after a brief warm up and the exercise program ends with cool down exercises. The aerobic exercise program consisted of repetitive, low resistance movements for at least 30 to 45 min, at 50% to 70% of Max heart rate, 3 to 4 times per week. The systolic & diastolic blood pressure were measured at baseline and after 6 weeks of aerobic exercises training program using sphygmomanometer[10-13] and pulse rate was measured by manual method.

All the patients were requested to attend the experimental set up daily for the first 2 weeks regularly to participate in the exercise program[14]. Each patient is given the value of their target heart rate and instructed to rest a while if the pulse rate reaches the target heart rate. Once the patients were trained they were asked to continue the program for the remaining 4 weeks at their residence. Patients were taught to measure pulse rate and asked to record their pulse rate and discomfort if any. The blood pressure measurements before and after 6 weeks of exercise program was statistically analysed using descriptive and inferential statistics.

RESULTS

In this study 40 subjects with a mean age of 42.52±5.29 ranging from 35 to 51 years, mean systolic pressure of 147.87 ± 12.52 and mean diastolic pressure 89.8 ± 4.81 were taken. Required statistical test were performed to find out the effect of experiment on the dependent variables, these findings are mentioned below.

Table 1: Effect of aerobic exercises on systolic blood pressure

		Group A *M ± SD* *(n=20)*	*Group B* *M ± SD* *(n=20)*	*Paired t-test*	
				T	P
Pre SBP1		137 ± 1.78	158.75 ± 8.32	-11.43	0.001*
Post SBP45		134.3 ± 2.18	137.75 ± 6.04	-2.41	0.021*
Independent T-test	t	11.711	22.74		
	p	0.001*	0.001*		

Table 2: Effect of aerobic exercises on diastolic blood pressure

		Group A *M ± SD* *(n=20)*	*Group B* *M ± SD* *(n=20)*	**Paired t-test**	
				T	P
Pre DBP1		85.3 ± 2.04	94.25 ± 2.65	-11.9	0.001*
Post DBP45		83.2 ± 1.89	88.1 ± 2.17	-2.17	0.001*
Independent T-test	t	10.3	16.2		
	p	0.001*	0.001*		

Keys: Group A: Pre-hypertensive Subjects, Group B: Stage I hypertensive subjects, SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure, 1- Baseline reading, 45- After 45 day of aerobic exercise training.

The result of present study demonstrated a significant difference between group effects in both the Systolic and Diastolic Blood Pressure (Table 1). To look for the difference between the baseline readings taken on the first day of the study with the post-test readings of systolic blood pressure on the 45th day an independent t-test was performed which showed a significant difference in both group A as well as in group B (Table 2). It was found that the systolic blood pressure decreased 3 mm/hg which was found significant (t=11.71, p<=0.001). A similar decrease of 21 mm/hg in group B was seen which was significant (t=22.74, p<=0.001).

From the analysis of systolic blood pressure and diastolic blood pressure changes after exercise, it was found that there was significant difference in the mean systolic blood pressure and diastolic blood pressure values for pre and stage hypertensive subjects. The objective of this study was to compare the mean difference in systolic blood pressure and diastolic blood pressure for group A and group B subjects to evaluate the effect of aerobic exercise on hypertension. When we analyse the response of group A and group B subjects. It was found that mean systolic blood pressure of 137mmhg (group a) and 158.75mmhg (group b) seen pre-test was reduced to 134.35 (group a) and 137.75 (group b) post-test. Also it was found that mean diastolic blood pressure of 85.35 (group a) and 94.25 (group b) seen pre-test was decreased to 85 (group a) and 88.1(group b) post-test.

DISCUSSION

The physiological basis for this reduction in blood pressure values is that the aerobic endurance training decreases blood pressure through a reduction of vascular resistance,

in which the sympathetic nervous system and the renin-angiotensin system appear to be involved, and favourably affects concomitant cardiovascular risk factors[15-18].

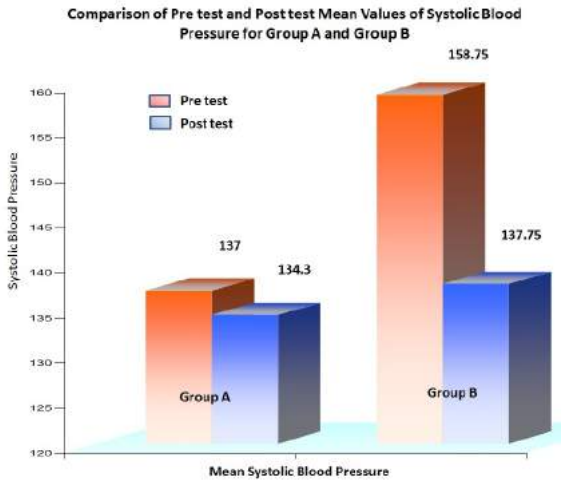

Fig. 1: Comparison of 1st and 45th day's Systolic BP between pre & stage 1 hypertensive patients.

Our results are similar to the study conducted by A Kiyonaga et al (1985)[1] to evaluate the effect of Blood pressure and hormonal responses to aerobic exercise. They selected twelve patients with essential Hypertension (WHO stages I-II) were subjected to mild aerobic exercises for 10 to 20 weeks. A reduction in SBP/DBP (mean) blood pressures by more than 20/10 (13) mm Hg was seen in 50% of patients after 10 weeks and in 78% after 20 weeks of exercise. The results indicate that exercise therapy is a potent non pharmacological tool for the treatment of essential hypertension, especially of the low rennin type. When we analyse the mean difference values of systolic blood pressure and diastolic blood pressure in group A and group B subjects, the results shows that there is a significant difference ($p<0.005$) in the values of systolic blood pressure and diastolic blood pressure. The result shows that the aerobic exercise plays an important role in reducing the blood pressure changes associated with hypertension [19-20].

The results of this study accord with the findings of most recent studies that show moderate intensity aerobic exercise training can lower blood pressure in patients with stage 1 and 2 essential hypertension. The average reduction in blood pressure is 10, 5 mm Hg for systolic and 7, 6 mm Hg for diastolic blood pressure and these reductions do not appear to be gender or age specific [21-24].

The next objective of this study was to compare the role of aerobic exercise on systolic blood pressure and diastolic blood pressure between pre hypertensive (group A) and stage 1 hypertensive (group B) subjects. When we analyze the results it was found that there was significant difference ($p<0.005$) in the values of systolic blood pressure and diastolic blood pressure between group A and group B subjects. Result shows that patients with stage 1 hypertension showed much change in the systolic blood pressure and diastolic blood pressure values when compared with the pre hypertensive subjects [25-26].

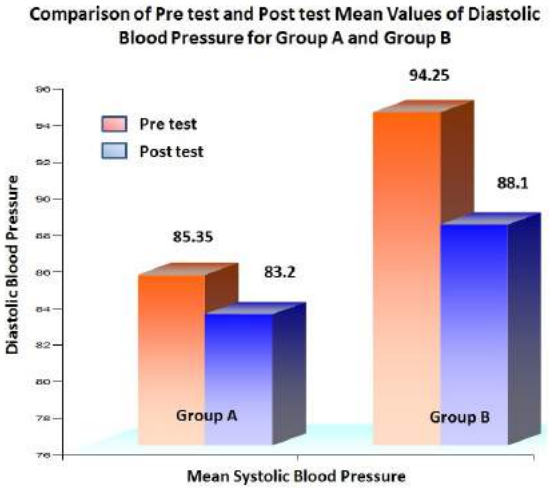

Fig. 2: Comparison of 1st and 45th day's Diastolic BP between pre & stage 1 hypertensive patients.

The results take a strong support from Karen T. Lesniak et al (2001)[27] Hypertensive subjects appear to experience greater reductions than normotensive subjects. Exercise interventions may be

safely and effectively used with mild to moderate as well as severe levels of hypertension. Through this present study it is clear that aerobic exercise plays a major role in the control of hypertension and these beneficial effects are found more in stage 1 hypertensive subjects when compared to pre hypertensive patients [28].

CONCLUSION

In conclusion, the inclusion of Aerobic exercise in daily activities is an efficient way of blunting the blood pressure changes in hypertensive patients and it is of high statistical significance ($p<0.005$). The above mentioned efficiency is more on Stage 1 hypertensive subjects when compared to pre hypertensive subjects.

REFERENCES

1. A Kiyonaga, K Arakawa, H Tanaka and M Shindo; Blood pressure and hormonal responses to aerobic exercise; Hypertension1985; 7; 125-131
2. Darren E.R. Warburton, Crystal Whitney Nicol, and Shannon S.D. Bredin; Health benefits of physical activity: the evidence; CMAJ 2006; 174(6):801-9
3. Kazuko Ishikawa-Takata, Toshiki Ohta, and Hirofumi Tanaka; How Much Exercise Is Required to Reduce Blood Pressure in Essential Hypertensives: A Dose–Response Study; AJH 2003; 16:629–633
4. Linda Pescatello, and Barry Franklin; News release: American College of Sports Medicine; March 2004; vol 36: pp 533-553.
5. Mark A. Booher, and Bryan W. Smith; Physiological effects of exercise on the cardiopulmonary system; Clin Sports Med 22 (2003) 1– 21
6. Darren E.R. Warburton, Crystal Whitney Nicol, and Shannon S.D. Bredin ; Prescribing exercise as preventive therapy; CMAJ 2006; 174(7):961-74
7. Philip B. Mellen, Shana L. Palla, David C. Goff, and Denise E. Bonds; Prevalence of Nutrition and Exercise Counseling for Patients with Hypertension; J Gen Intern Med 2004;19:917–924
8. Jean Cléroux, Ross D. Feldman, and Robert J. Petrella; Recommendations on physical exercise training; CMAJ • MAY 4, 1999; 160 (9 Suppl)
9. Gareth Beevers, Gregory Y H Lip, Eoin O'Brien; ABC of hypertension. Blood pressure measurement Part I-Conventional sphygmomanometry: technique of auscultatory blood pressure measurement; BMJ 2001;322:981-5
10. Gareth Beevers, Gregory Y H Lip, Eoin O'Brien; ABC of hypertension. Blood pressure measurement Part II-Conventional sphygmomanometry: technique of auscultatory blood pressure measurement; BMJ 2001;322:1043-7
11. Ethel M Frese, Randy R Richter, Tamara V Burlis; Self-Reported Measurement of Heart Rate and Blood Pressure in Patients by Physical Therapy Clinical Instructors; Physical Therapy 2002; 82 (12), 1192-1200.
12. Jan A Staessen, Leszek Bieniaszewski, Karel Pardaens, Victor Petrov, Lutgarde Thijs, and Robert Fagard; Life style as a blood pressure determinant; J R Soc Med 1996;89:484-489
13. Norman R.C. Campbell, Ellen Burgess, Bernard C.K. Choi, Gregory Taylor, Elinor Wilson, RN, Jean Cléroux, J. George Fodor, Lawrence A. Leiter, and David Spence; Methods and an overview of the Canadian recommendations; CMAJ • MAY 4, 1999; 160 (9 Suppl)
14. Karen T. Lesniak, and Patricia M. Dubbert; Exercise and hypertension; Current Opinion in Cardiology 2001, 16:356–359
15. Yukihito Higashi, Shota Sasaki, Nobuo Sasaki, Keigo Nakagawa, Tomohiro Ueda, Atsunori Yoshimizu, Satoshi Kurisu, Hideo Matsuura, Goro Kajiyama and Tetsuya; Daily Aerobic Exercise Improves Reactive Hyperemia in Patients with Essential Hypertension; Hypertension 1999; 33; 591-597
16. Véronique A. Cornelissen and Robert H. Fagard; Effects of Endurance Training on Blood Pressure, Blood Pressure–Regulating Mechanisms, and Cardiovascular Risk Factors; Hypertension 2005; 46; 667-675

17. Athanasios J. Manolis; Exercise And Hypertension; European Society of Hypertension Scientific Newsletter: Update on Hypertension Management 2005; 6: No. 23
18. Peter F. Kokkinos; Exercise as hypertension therapy; Hellenic J Cardiol 2001; 42: 182-192,
19. Janet P. Wallace; Exercise in Hypertension - A Clinical Review; Sports Med 2003; 33 (8): 1
20. K. L. D. De Angelis, A. R. Oliveira, A. Werner, P. Bock, A. Belló-Klein, T. G. Fernandes, A. A. Belló, and M. C. Irigoyen; Exercise Training in Aging: Hemodynamic, Metabolic, and Oxidative Stress Evaluations; Hypertension, Sep 1997; 30: 767 - 771.
21. Gang Hu, Noël C. Barengo, Jaakko Tuomilehto, Timo A. Lakka, Aulikki Nissinen, and Pekka Jousilahti; Relationship of Physical Activity and Body Mass Index to the Risk of Hypertension: A Prospective Study in Finland; Hypertension, Jan 2004; 43: 25 - 30.
22. Schwartz RS, Hirth VA; The effects of endurance and resistance training on blood pressure; Intl J Obes Relat Metab Disord 1995; 19(suppl 4):S52-S57
23. Braith RW, Pollock ML, Lowenthal DT, et al; Moderate- and high-intensity exercise lowers blood pressure in normotensive subjects 60 to 79 years of age; Am J Cardiol 1994; 73(15):1124-1128
24. Lim PO, MacFadyen RJ, Clarkson PB, et al; Impaired exercise tolerance in hypertensive patients; Ann Intern Med 1996; 124(1 pt 1):41-55
25. Arroll B, Beaglehole R; Does physical activity lower blood pressure? A critical review of the clinical trials; J Clin Epidemiol 1992; 45(5):439-447
26. Kelley G, McClellan P; Antihypertensive effects of aerobic exercise: a brief meta-analysis review of randomized controlled trials; Am J Hypertens 1994; 7(2):115-119
27. Halbert JA, Silagy CA, Finucane P, et al; The effectiveness of exercise training in lowering blood pressure: a meta-analysis of randomised controlled trials of 4 weeks or longer; J Hum Hypertens 1997;11(10):641-649
28. Kelley G; Dynamic resistance exercise and resting blood pressure in adults: a meta-analysis; J Appl Physiol 1997;82(5):1559-1565

RECENT INSIGHTS INTO NOSOCOMIAL INFECTIONS- A NEGLECTED CONDITION

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ABSTRACT

Nosocomial infections (NI), also known as hospital acquired infection (HAI), is infection whose development is favoured by a hospital environment, such as one acquired by a patient during a hospital visit or one developing among hospital staff. Such infections include fungal and bacterial infections and are aggravated by the reduced resistance of individual patients [(4)]. Nosocomial infections continues to be of major clinical and epidemiologic importance in developing countries [(2,3)] as it constitutes a major source of morbidity, mortality and significant incremental health care expense for the hospitalized patient, despite major advances in clinical sciences. As per the Study on the Efficacy of Nosocomial Infection Control (SENIC) routine surveillance of NI has become an integral part of infection control and quality assurance in US hospitals because its potential of reducing nosocomial infections[(1)]. Studies performed in the United States have demonstrated that an integrated infection control program that includes targeted device-associated surveillance can reduce the incidence of nosocomial infection by as much as 30% and lead to reduced health care costs[(1)].

ملخص: عدوى المستشفيات (NI)، المعروف أيضا باسم عدوى المستشفيات المكتسبة (HAI)، هي العدوى التي يساعدها على النمو بيئة المستشفى، مثل التي يحصل عليها المريض خلال زيارة المستشفى أو أحد العاملين في المستشفى. هذه الأمراض تشمل الأمراض الفطرية والبكتيرية والتي تفاقمت من جراء انخفاض المقاومة من المرضى الفردية (غارنر JS، 1996). عدوى المستشفيات لا تزال ذات أهمية كبرى السريرية والوبائية في البلدان النامية (جيفيك MA، 2005؛ روزنتال VD، 2004) كما أنها تشكل مصدرا رئيسيا للوفيات والمراضة وخاصةالرعاية الصحية المتزايدة على حساب المريض في المستشفى، على الرغم من التقدم الكبير في العلوم السريرية. وفقا لدراسة حول فعالية مكافحة العدوى المكتسبة بالمستشفيات المراقبة الروتينية (SENIC) على(NI) أصبحت جزءا لا يتجزأ من مكافحة العدوى وضمان الجودة في مستشفيات الولايات المتحدة بسبب إمكاناتها للحد من عدوى المستشفيات (هالي RW، 1985). وقد أظهرت الدراسات التي أجريت في الولايات المتحدة أن مكافحة العدوى المتكاملة برنامج يتضمن استهداف جهاز المراقبة المرتبطة يمكن أن تقلل من حدوث العدوى المكتسبة داخلة بنسبة تصل إلى 30٪، وتؤدي إلى خفض تكاليف الرعاية الصحية (هالي RW، 1985).

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INTRODUCTION

Nosocomial are caused by a wide variety of pathogens; including Pseudomonas aeruginosa, Klebsiella spp., Escherichia coli, Enterococci, Staphylococci etc. Staphylococci and Enterococci are major causes of nosocomial infections. They cause superficial skin lesions such as boils, styes and more serious infections such as pneumonia, mastitis, phlebitis, meningitis and urinary tract infections; and deep-seated infections, such as osteomyelitis and endocarditis. Methicillin-resistant S. aureus (MRSA) is a strain of S. aureus which by definition is resistant to the semi- synthetic penicillins (i.e. methicillin, nafcillin, and oxacillin). As such, it is resistant to all other beta-lactam antibiotics (including other penicillins, cephalosporins and cephamycins). Additionally, MRSA is often resistant to other classes of antibiotics including aminoglycosides, macrolides and quinolones. Thus, MRSA is not only methicillin resistant but also multiply-resistant as well[19].

Surveillance of NI is a necessary first step toward reducing the risk of infection among patients treated through trained nurse epidemiologists who should assume increasing responsibility for education of personnel and for performance of studies designed to elucidate the mechanism and prevention of hospital infections. The next step is to apply infection control practices that have been shown to prevent nosocomial infections.

PREVALENCE OF NOSOCOMIAL INFECTION

NI are found to be more prevalent in Hospital Departments & Individual Systems[14,15,16]. In general nosocomial infection rates vary by service and by levels of invasive management of seriously ill patients. Accordingly the incidence of Nosocomial infections are highest in Intensive care Unit (ICU) followed by Coronary care unit (CCU), High dependency Unit, Post-operative ward etc in prevalence to be followed gradually in rank by general surgical and medical departments. Departments with low infection rates include Ophthalmology and Maternity.

Studies on Nosocomial infections show that incidence of HAI is highest in large teaching or academic hospitals, intermediate in small teaching hospitals and lowest is small non-teaching Hospitals. These studies show that immunity of the patient is the major factor in Hospital Acquired infection. In large Hospital, more seriously ill patients are admitted sophisticated therapy is given. These patients are immunocompromised by the disease as well as the treatment (surgery ± chemotherapy + radiotherapy) that is immunosuppressive therapy etc.

As for the sites of infection, Urinary tract infection (UTI) by far, is the commonest infection Pneumonia, Surgical wound infections are the next most common, Skin infection, though relatively un-common in temperate zone, are relatively more prevalent in hot countries. Then comes. Blood stream infection namely septicaemia, bacteraemia , IV infection site infection. Infection of the peritoneal cavity (peritonitis).

CLASSIFICATION OF NOSOCOMIAL INFECTION

NI may be endogenous, arising from an infectious agent present within a patient's body, or exogenous, transmitted from another source within the hospital. In addition to patient-to-patient spread, others may be involved, including staff, students, visitors and voluntary workers[18].

COMMON MODES OF TRANSMISSION

1. Direct Contact: E.g. Direct contact between patients is the most important mode of transmission.
2. Self-infection: From patients own pathognomic floras of skin, nose, mouth, throat periniusn, infected lesions.
3. Indirect Contact: E.g. Indirect contact with contaminated inanimate objects like improperly sterilized instruments, dressing materials; contaminated fomites e.g. bed pans, blankets etc etc.
4. Air Borne Transmission: From outside hospital-With air flow from infected areas like-Dustbins, open morgues.
5. Vector Borne Transmission: E.g. Via. Mosquitoes-malaria, Dengue etc.
6. Transmission by Common Vehicles: e.g. via. Food, blood, Water (contaminated) Medications etc.

PREVENTION OF NOSOCOMIAL INFECTION

The other frustrating fact regarding the natural history of Nosocomial or Hospital Acquired Infections is that they cannot be eradicated entirely; but many of them can be prevented by proper control measures. In places where control programs can be implemented, there had been a proven reduction of morbidity and mortality. Furthermore, the money that can be saved by reduction of nosocomial infections is much more used for infection control[13].

Several approaches have been adopted in order to limit pathogen colonization. Strict hygienic practices by healthcare personnel e such as basic hand washing e along with regular disinfection of the hospital environment are considered by some of basic importance. However, it should be noted that routine disinfection of the hospital environment is controversial [21,22,23]. Since nosocomial infections remain an important problem even for hospitals with well-organized and decisively implemented infection control programs, studies of innovative infection control measures are warranted.

Guidelines on hospital hygiene.
- Disinfection.
- Sterilization.
- Cleaning.
- Laundering.
- Catering.
- Waste-disposal.

Guidelines on procedures:
- Urethral Catheterization.
- Prevention of surgical wound infection.
- Tracheostomy.
- Intravenous fluid administration.
- Prevention of nosocomial Pneumonia
- Hand washing etc.

Guidelines on special issues:
- Prevention of nosocomial H.I.V Infection.
- Hepatitis B immunization.
- Prevention of infection in hemodialysis unit; transplant unit etc.

Three fundamental principles govern the measures that should be taken in order to prevent the transmission of HAI in health-care facilities:

Isolation: Identify and separate/segregate from other patients:

- Known infected patients,
- Patients with certain symptoms or
- behaviors (e.g., poor hygiene),
- Patients with high potential for contamination of the environment (uncontained, draining surgical wound)

Routes of transmission: Eliminate or minimize potential routes of transmission

from sources of microorganisms (e.g., use aseptic technique when inserting IV catheters).

Barrier Techniques: Use basic barrier techniques to eliminate or minimize the risk of transmitting infectious agents from patient to patient, from patient to caregiver, and from caregiver to patient. Presume all patients are infected until proved otherwise.

Guidelines used in other hospitals or countries should be adapted so that they are appropriate to be implemented in the hospital. The guidelines should cover most routine procedures and treatments as follow[17].

Nosocomial infection caused by Methicillin resistant Staphylococcus aureus (MRSA)

The worldwide emergence of multidrug resistant bacterial strains is of growing concern. These infections are difficult to eradicate due to resistance to many antimicrobials, thus major cause of morbidity and mortality, leading directly and indirectly to an enormous increase in cost of hospital stay for the patients and also emergence of new health hazards for the community.

MRSA colonization and infection in acute and non-acute care facilities have increased dramatically over the past two decades, evidenced by the increasing number of reported outbreaks in the medical literature. Because of its resistance to antibiotics, management of MRSA infections requires more complicated, toxic and expensive treatment. It is important for the health care professional to understand the difference between colonization and infection. Colonization indicates the presence of the organism without symptoms of illness. S. aureus permanently colonizes the anterior nares of about 20% to 30% of the general population. Hospital workers are more likely to be colonized than persons in the general population, presumably because of increased exposure[20].

IMPROVED HAND HYGIENE-REDUCTION IN NOSOCOMIAL INFECTION

Hand hygiene is a fundamental aspect of infection control, with several studies showing a decline in nosocomial infection rates when compliance with hand hygiene is enhanced[5,6,7]. Despite universal acknowledgement of the pivotal role that hand hygiene plays in reducing nosocomial infection, compliance among health care workers remains poor, with rates ranging from 16% to 81% [8,9,10].

Pittet et al studied predictors of noncompliance with hand hygiene in an observational study and found that, in multivariate analysis, physicians and nursing assistants had lower compliance rates than nurses. Of concern, compliance was lower in ICUs and during procedures that carried a high risk of contamination[11]. Dubbert et al found that, although education alone improved compliance rates transiently, performance feedback resulted in a more sustained improvement in compliance[9]. In a pre- and post-intervention study in an inpatient rehabilitation unit, McGuckin et al used a patient education model consisting of patients asking HCWs coming into contact with them whether they had washed their hands. Compliance (measured through soap/sanitizer usage per resident-day) improved to 94% during the 6-week intervention. However, adherence to hand hygiene fell to 40% in the follow-up period[12].

REFERENCES

1. Haley RW, Culver DH, White JW, Morgan WM, Emori TG, Munn VP, et al. The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. Am J Epidemiol 1985;121:182-205.
2. Cevik MA, Yilmaz GR, Erdinc FS, Ucler S, Tulek NE. Relationship between nosocomial infection and mortality in a neurology intensive care unit in Turkey. J Hosp Infect 2005;59:324-30.
3. Rosenthal VD, Guzman S, Crnich C. Device-associated nosocomial infection rates in intensive care units of Argentina. Infect Control Hosp Epidemiol 2004;25:251-5.
4. Garner, J.S., W.R. Jarvis, T.G. Emori, T.C. Horan and J.M. Hughes, 1996. CDC definitions for nosocomial infections. In: APIC infection Control and Applied Epidemiology: Principles and Practice. Ed., Olmsted, R.N., St. Louis: Mosby, pp: A1-A20.
5. Doebbeling BN, Stanley GL, Sheetz CT, Pfaller MA, Houston AK, Annis L, et al. Comparative efficacy of alternative hand-washing agents in reducing nosocomial infections in intensive care units. N Engl J Med 1992;327:88-93.
6. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, Perneger TV. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene: Infection Control Programme. Lancet 2000;356:1307-12.
7. Fendler EJ, Ali Y, Hammond BS, Lyons MK, Kelley MB, Vowell NA. The impact of alcohol hand sanitizer use on infection rates in an extended care facility. Am J Infect Control 2002;30:226-33.
8. Pittet D. Improving adherence to hand hygiene practice: a multidisciplinaryvapproach. Emerg Infect Dis 2001;7:234-40.
9. Dubbert PM, Dolce J, Richter W, Miller M, Chapman SW. IncreasingvICU staff handwashing: effects of education and group feedback. InfectvControl Hosp Epidemiol 1990;11:191-3.
10. Donowitz LG. Handwashing technique in a pediatric intensive carevunit. Am J Dis Child 1987;141:683-5.
11. Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital. Infection Control Program. Ann Intern Med 1999; 130:126-30.
12. McGuckin M, Taylor A, Martin V, Porten L, Salcido R. Evaluation of a patient education model for increasing hand hygiene compliance in an inpatient rehabilitation unit. Am J Infect Control 2004;32:235-8.
13. Sudsukh U, The control of nosocomial infections in Thailand in the future, J Med Assoc Tahi 1989 72; (supp l 2) 44-5.
14. Danchaivijitr S, Mortensen N. Use of prevalence data, In: Hospital Infection Prevalence Survey and Program Guidea WHO Manual (Unpublished).
15. Mayon-White RT, Dual G, Kereselidze T, Tikhomirov E. An international survey of the prevalence of hospital acquired infection. J Hosp Infect 1988: 11: S43-8.
16. Britt MR, Burk JP, Nordguist AG, et al. Infection control in small hospital: prevalence surveys in 18 institutions. JAMA 1976; 236: 1700-3.
17. S.A. Khan. Nosocomial infection: general principles & the consequences, importance of it's control and an outline of the control policy - A Review Article. Bangladesh Medical Journal 2009; 38(2): 60-64
18. Boyce JM. Infect Control Hosp Epidemiol 1992, 13:725.
19. Shrestha B, Pokhrel B, Mohapatra T. Nepal Med Coll J. 2009; 11:123
20. Van Hal SJ, Stark D, Lockwood B, Marriott D, Harkness J. J Clin Microbiol 2007; 10: 1128
21. Dettenkofer M, Wenzler S, Amthor S, Antes G, Motschall E, Daschner FD. Does disinfection of environmental surfaces influence nosocomial infection rates? A systematic review. Am J Infect Control 2004;32:84-89.
22. Dettenkofer M, Spencer RC. Importance of environmental decontamination e a critical view. J Hosp Infect 2007;65: 55-57.
23. Kramer A, Schwebke I, Kampf G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. BMC Infect Dis 2006;6:130.

ANIMAL MODELS OF NON CIRRHOTIC PORTAL HYPERTENSION (NCPH)

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ABSTRACT

Portal hypertension (PHT) is a common and serious clinical syndrome often associated with chronic liver diseases. Portal hypertension may be defined as portal pressure gradients of 12 mmHg or more in the veins of the portal system caused by obstruction in the liver from intrahepatic or extrahepatic portal venous compression or occlusion (often associated with chronic liver disease), causing enlargement of the spleen and collateral veins. In the western world, hepatic cirrhosis related to chronic hepatitis C and B and alcoholic cirrhosis are the conventional rationale for the development portal hypertension. Besides cirrhosis, a number of disorders collectively called as non-cirrhotic portal hypertension (NCPH) can also result in portal hypertension. Evaluation of non-cirrhotic portal hypertension is more difficult than cirrhotic portal hypertension, both from clinical and pathological perspectives.

ملخص: ارتفاع ضغط الدم البابي هو متلازمة سريرية شائعة وخطرة وغالبا ما ترتبط مع أمراض الكبد المزمنة. ويمكن تعريف ارتفاع ضغط الدم البابي عندما يصل الضغط في اوردة النظام البابي الي 12 ملم زئبق أو أكثر والناتج عن انسداد او الضغط علي الاوردة البابية داخل الكبد (والمصاحب عادة لأمراض الكبد المزمنة) ، مما يسبب في تضخم الطحال والأوردة الجانبية. في العالم الغربي، تشمع الكبد المتصل بالتهاب الكبد المزمن C و B وتليف الكبد الناتج عن الكحول من الاسباب التقليدية لارتفاع ضغط الدم البابي. بالإضافة الى تليف الكبد، هنالك اضطرابات اخري تسمى مجتمعة باسم ارتفاع ضغط الدم المدخل الغير مرتبط بتليف الكبد يؤدي أيضا إلى ارتفاع ضغط الدم البابي. تقييم ارتفاع ضغط الدم البابي الغير مرتبط بتليف الكبد هو أكثر صعوبة من تقييم ارتفاع ضغط الدم البابي الناتج من التليف الكبدي، من وجة النظر السريرية والمرضية

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INTRODUCTION

Non-cirrhotic portal fibrosis (NCPF) and extra-hepatic portal vein obstruction (EHPVO) are very common in developing countries and almost always present only with characteristic features of portal hypertension. Non-cirrhotic portal fibrosis (NCPF), the equivalent of idiopathic portal hypertension in Japan and hepatoportal sclerosis in the United States of America, is a common cause of portal hypertension in India and accounts for 15-40% [8,21,37]. Its etiopathogenesis is still obscure, as patients present late when bleeding has already occurred from the varices. The disease is common in the lower or lower–middle socio-economic strata of society. Improved hygienic standards of living could explain the relative rarity of the disease in the West and declining incidence in Japan.

Table 1: General considerations in choosing animal models (modified from Mullen & McCullough)[4]

Reproducibility:	Rate of reproducing the model should be high with the Consistent time frame to attain desired state.
Specificity:	The model should bear only the characteristic anomalies without other complicating problems.
Costs:	Consider not only the direct costs, but also indirect costs such as animal housing (and, therefore, the time to achieve the desired state). An expensive but reliable model could be cheaper than a cheap but inconsistent model.
Safety:	Animal handling should involve no risk both to the person engaged in as well as the animal.
Size:	The size should be appropriate enough to have great deal of vascular study. The size also determines drug spending.
Ethics:	Different ethics committees can have different opinions about the acceptability of one model
Feasibility:	Whether the laboratory has the expertise, manpower facilities, etc, to generated or hand the model.

EXPERIMENTAL MODEL OF PORTAL HYPERTENSION

The inability to solve the enigma of portal hypertension shoots essentially from not being able to produce the disease experimentally in animals. Animal models, mimicking the human situation, have helped us in exploring the pathophysiology of portal hypertension as ethical considerations limit experimental procedures in humans. The use of animal models as an alternative source has allowed researchers to investigate the state of disease in ways which is inaccessible in a human patient. According to the Animal Care guidelines high-degree resemblance to human condition, high reproducibility and homogeneity and a low mortality, are the basic criteria for animal model of portal hypertension (Table1).

MODELS OF INTRAHEPATIC PORTAL HYPERTENSION

Several models of intrahepatic portal hypertension in animals have been developed.. The most common are models of cirrhosis from any causes, secondary biliary cirrhosis, idiopathic portal hypertension and schistosomiasis.

Table 2: Effect of arsenic exposure on serum albumin and aspartic lactic transaminase (ALT)

Experimental details	Albuin (g/dl)	ALT (IU/l)
Control	3.40±0.06	51±27
120 ppm for 3 months	3.32±0.50	101±56*
240 ppm for 3 months	3.02±0.30	136±82*
360 ppm for 3 months	3.24±0.90	56±49
360 ppm for 6 months	3.3±0.60	183±84*
500 ppm for 1.5 months	2.72±0.20*	56±12.2

*P <0.05; Values are expressed as mean ± SE

Table 4: Effect of oral arsenic feeding on liver histopathology of mice of different groups

Group (ppm)	Duration (months)	Fibrosis (%)	Inflammation (%)	Kupffer cell hyperplasia (%)	Normal (%)
Control	---	---	---	---	100
120	1.5	---	25	42	29
120	3.0	---	18	---	82
120	6.0	---	25	---	75
240	1.5	---	44	---	56
240	3.0	---	25	38	37
360	1.5	---	40	13	47
360	3.0	---	44	---	56
360	6.0	---	40	---	60
500	1.5	30	23	---	46

Whole liver compression – Dog model: Yamana et al[38] produced a unique model of whole liver compression in dogs where whole of the liver was wrapped and compressed with a tense ligature of polypropylene mesh or gauze. Both the intrahepatic resistance and portal venous pressure were raised without development of hepatorenal collaterals for nine weeks after the surgery. Since this whole liver compression method requires no complicated surgical maneuver, the experimental animals survived well.

Cirrhosis induced by carbon-tetrachloride (CCl_4): Currently, the carbon-tetrachloride (CCl_4) hepatotoxin-induced model of cirrhosis, mimicking human non-biliary cirrhosis, is considered the 'gold standard' for cirrhosis [22]. However, it is associated with major drawbacks such as low reproducibility resulting from a mortality rate averaging 30% during induction, poor homogeneity and a rather low resemblance to human cirrhosis, as typical features of human cirrhosis, such as nuclear atypia, mitoses and nodular parenchymal regeneration, resulting in a more typical distorted architecture, are not so prominent. Additionally, inhalation with CCl_4 seems to be the sole way of achieving a high yield of cirrhosis, which might pose potential health hazards for its investigator[6,7,22].

Secondary billiary cirrhosis induced by bile duct ligation: Chronic cholestasis produces secondary biliary cirrhosis in animals as it does in man. The chronic bile duct-ligated rat model (CBDL) is commonly used model of PHT [6]. This surgically induced model of cirrhosis can be used after 3–5 weeks and is therefore less costly than a hepatotoxin-induced liver damage model[10]. There are, however, several disadvantages: high mortality (> 40%), haemodynamic instability owing to the toxic effect of the cholestasis on renal function, and higher susceptibility for sepsis owing to the absence of bile in the digestive tract, exaggerated dilatation of the extrahepatic bile duct causing extrinsic compression on portal vascular structures, and the fact that CBDL rats do not show elevated portal venous inflow when studied under pentobarbital anaesthesia [6, 22].

Table:3 Collagen and 4-hydroxyproline (4-HP) levels in liver following different dosage of arsenic at 1.5, 3 and 6 months of treatment.

Duration (months)	Experi-mental group (ppm)	Hepatic collagen (µg/mg protein)	Hepatic 4-HP (µg protein)
1.5	Control	11.3±1.47	23.5±4.36
	120	24.3±0.71[a]	102.8±6.50[c]
	240	13.6±1.60	152.0±18.80[c]
	360	17.7±1.30[a]	70.5±1.30[b]
	500	87.8±8.90c	132.5±9.81[c]
3	Control	12.0±1.11	22.3±4.00
	120	26.4±2.90[a]	320.0±15.10[c]
	240	63.1±7.00[c]	193.0±11.80[c]
	360	71.8±5.80[c]	200.0±10.10[c]
6	Control	14.1±2.50	29.9±5.50
	120	595.4±130.0[a]	242.0±79.80[a]
	240	397.7±129.4[a]	164.8±9.80[a]
	360	159.3±3.90[a]	373.0±14.40[a]

P values: a <0.05; b<0.01; c<0.001; Values are expressed as mean ± SE

Table 5 Liver function Tests in Control and Arsenic-Exposed Mice at the End of Different Study Periods

Month	Group	T. Protein (g/dL)	Albumin (g/dL)	ALT (IU/L)	AST (IU/L)	ALP (IU/L)
3	Control (n = 5)	6.46±0.34	3.24±0.35	22.80±2.77	23.40±4.44	107.6±5.02
	Experimental (n = 6)	6.23±0.46	3.08±0.29	23.83±2.99	24.10±4.57	109.8±6.99
6	Control (n = 10)	6.58±0.58	3.42±0.45	24.30±3.80	23.50±2.27	108.6±8.03
	Experimental (n = 10)	6.50±0.73	3.17±0.48	26.30±4.49	26.00±5.29	111.7±5.83
9	Control (n = 5)	6.52±0.54	3.40±0.60	22.80±2.78	22.60±1.67	113.4±8.64
	Experimental (n = 5)	6.40±1.32	3.08±0.68	31.20±9.65	26.80±4.29	116.8±11.62
12	Control (n = 9)	6.36±0.91	3.06±0.45	25.00±4.27	23.50±2.78	121.5±6.8
	Experimental (n = 14)	6.66±0.86	3.03±0.61	34.60±6.93**	32.80±8.21*	128.4±12.02
15	Control (n = 8)	6.05±0.26	3.11±0.12	27.50±4.10	25.50+6.63	123.7±5.02
	Experimental (n = 6)	5.95±0.32	2.71±0.24*	40.80±5.60**	38.16±6.79*	164.6±10.94**

*p<0.01; **p<0.001

Cirrhosis induced by hepatotoxin thioacetamide (TAA): A potential alternative to these above-mentioned problems is the induction of cirrhosis in the rat with the hepatotoxin thioacetamide (TAA), which is suggested to have more in common with human cirrhosis[1]. To date the problem with TAA has been the heterogeneous production of cirrhosis (varying from 3 to 7 months [28]) when administered orally. To overcome these inconveniences, Li et al.[23] recently suggested an intoxication protocol over 12 weeks which adapts the dose of TAA in drinking water according to the weekly body weight, as originally described for intragastric administration of CCl_4 by Proctor[29]. W. Laleman in 2006 concluded that thioacetamide, adapt to weekly weight changes, leads to a homogenous, reproducible model of cirrhosis in the rat in 18 weeks, which is associated with all the typical characteristics of portal hypertension, including endothelial dysfunction[36].

Periportal fibrosis: Other cirrhosis or precirrhosis induced by alcohol have been described in the literature. It has been shown that portal hypertension develops in alcohol-fed baboons[24]. These baboons developed fatty liver and perivenular fibrosis. Cirrhosis and portal hypertension also developed in some monkeys with a

Table 6: Hepatic Glutathione and other Enzymes of the Antioxidant Defense system in Control and Arsenic-Exposed Mice at the End of Different Study Periods

Month	Group	G6PDH (nmole NADP reduced/min/ mg/protein	GR (umole of NADPH oxidation/min /mg protein)	GST (nmole produced/min/ mg protein)	Catalase (umole H202 reduced/min/mg protein	GSH-Px (umole NADPH oxidation/min /mg protein)
3	Control (n = 5)	10.32±0.230	24.38+0.89	118.02±1.12	6.78±0.22	8.28±0.38
	Experimental (n = 6)	11.04±0.56	27.39±2.66	130.05±11.04**	7.26±0.59	9.19±0.67^
6	Control (n = 10)	10.46±0.84	24.92±0.37	118.42±2.04	6.68±0.33	8.27±0.28
	Experimental (n = 10)	8.39±0.62#	25.43±1.31	121.85±7.30	6.34±1.05	7.49±0.94^
9	Control (n = 5)	10.05±0.41	24.99±0.83	117.41±1.87	6.78±0.27	8.29±0.20
	Experimental (n = 5)	7.02±0.29**	24.24±2.21	113.92±4.70	6.06±0.48*	7.01±0.61#
12	Control (n = 9)	9.80±0.25	25.04±0.44	117.73±2.24	6.74±0.29	8.03±0.24
	Experimental (n = 14)	6.39±0.64**	20.86±1.88**	102.68±6.90**	5.45±0.50**	5.95±1.01**
15	Control (n = 8)	9.94±0.26	24.93±0.79	122.28±4.22	6.47±0.26	8.02±0.55
	Experimental (n = 6)	5.02±0.87**	18.43±2.02**	88.72±18.0**	4.55±0.85**	5.20±1.12**

*p<0.05; ^p<0.02; #p<0.01; **p<0.001

diet for a period of 16 months lacking choline, low in protein (5%), and rich in cholesterol. In dogs it has been demonstrated that the repeated intraportal injection of a polyvinyl alcohol suspension over a 2-6 months period produces portal hypertension [2].

MODELS OF EXTRAHEPATIC PORTAL HYPERTENSION:

Portal Vein Stenosis Model: The most common animal model of prehepatic portal hypertension currently used is partial portal vein ligation. This model has been developed in the rats [4,5,35], mice [9, 14] and rabbits[3]. Neuhof in 1912 first consummate the production of portal hypertension in animals by partial constriction of the portal vein. This study was carried out in dog with the degree of constriction of portal vein up to 50%. After a period of recovery, the portal vein was further stenosed to 25% of its original diameter and finally after 6 days the portal vein was completely ligated. Neuhof clearly described anastomoses between the hepatic and diaphragmatic vessels, the gastric and esophageal veins, and the portal system and vena cava in the postmortem report at 34 days. Splenomegaly was also present but the remaining portal tract appeared to be normal. Later, Reynell stenosed the portal vein in rats with a 50% mortality rate[30]. Most of the surviving rats had portal hypertension. Between 1973-75 it was shown that the diameter of the stenosis and the body weight or age of the rat were critical in determining survival[25].

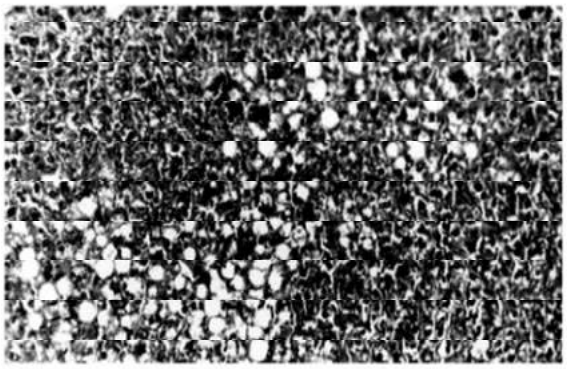

Fig 1: Liver histology of mice exposed to arsenic for 12 months. The histology shows fatty changes in the liver (hematoxylin-eosin, magnification X 100).

Portal vein occlusion using microspheres: A new experimental animal model for portal hypertension was developed by an intraportal injection of DEAE-cross-linked dextran microspheres (100±25 microns in diameter) in the female Japanese white rabbit characterized by elevation in portal pressure and portal systemic collateral (Komeichi H, 1991). Histology of the liver revealed portal obstruction by the injected microspheres in almost all portal triads, resulting in a foreign body granuloma. Since this model appears to show the two main conditions characteristic of portal hypertension, persistent elevation of portal pressure and both extra- and intrahepatic portal collaterals, mimicking those in humans, portal obstruction by injecting DEAE-cross-linked dextran microspheres into the portal vein of the rabbit could provide a versatile model for portal hypertension.

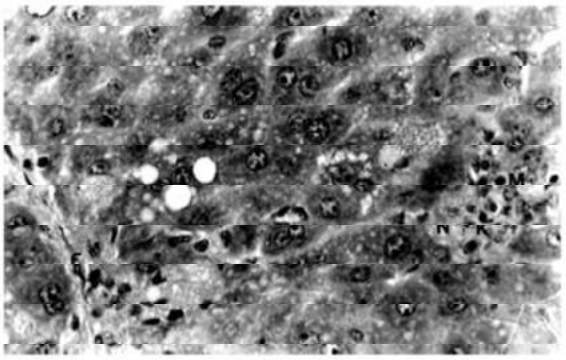

Fig 2. Liver histology of mice exposed to arsenic for 15 months. The histology shows hepatocellular degeneration and necrosis characterized by collections of mononuclear cells and Kupffer cells associated with injured hepatocytes. Streaky fibrosis is seen at one end of the liver lobule (hematoxylin-eosin, magnification X 400)

MODELS OF PRESINUSOIDAL PORTAL HYPERTENSION:

The exact mechanism for the development of idiopathic portal hypertension has not been clarified but the pathomorphological changes caused by this syndrome have been widely studied in animals. These lesions have been attributed to intra-abdominal infection.

MODELS OF IDIOPATHIC PORTAL HYPERTENSION (IPH):

Prolonged sensitization with egg albumin: Okabayashi and Suzuki produced idiopathic portal hypertensive models in rabbits characterized by splenomegaly and portal hypertension. They emphasized chronic antigenic stimulation as being the cause of splenomegaly with prolonged intravenous administration of egg albumin. Later, the experiment was conducted on dogs as the rabbit could not tolerate more than three intraportal injections. However, they could not provide the mechanism whereby the spleen reacts to chronic antigenic stimulation. The histological changes that occurred in these animals were characterized by early portal inflammation immediately followed by portal fibrosis, aberrant vasculature and disappearance of portal venules and were very similar to those in human IPH.

Prolonged sensitization with non-pathogenic E. coli: In rabbits, killed nonpathogenic E. coli were administered intraportally. The animals that received an intraportal mixture of killed E. coli and rabbit antiserum (aggregated E. coli) developed histological changes in the liver and portal hypertension[19]. Early inflammatory reactions in the portal area and parenchyma were followed by the development of portal fibrosis. Three intraportal challenges with aggregated E. coli were enough to produce marked portal fibrosis, splenomegaly, and portal hypertension. In dogs, repeated intraportal injections of a mixture of killed nonpathogenic E. coli and dog anti-E. coli serum induced portal fibrosis and intrahepatic presinusoidal portal hypertension[33].
However, these investigators have used repeated cannulation of the portal vein which may itself cause damage to the portal vein intima, portal pyemia and altered hemodynamic and histological picture in the animal. Another limitation of the model is the use of E. coli and anti-E. coli aggregate, which is not only unphysiological, but also the large aggregate can block the hepatic sinusoid causing a situation akin to portal vein thrombosis. Accordingly, alternative routes of introducing E. coli into the portal circulation have been proposed[17].

Schistosomiasis japonica models: Since schistosomiasis japonica and idiopathic portal hypertension share similar histological changes of the liver, Masayoshi K et al produced rabbit model by infecting with 200-300 Schistosoma cercariae percutaneously and subcutaneously. The angioarchitecture of chronic schistosomiasis japonica is characterized by narrowing, obstruction and obtuse angles of bifurcation of the peripheral portal veins and this disease is quite similar to IPH in both histological and angioarchitecture strongly suggest that portal change is the primary lesion of the hepatic disorder in IPH. However, splenomegaly invariably noted in IPH is not necessarily observed in chronic schistosomiasis japonica, suggesting that the portal system may be more extensive in IPH than in schistosomiasis japonica.

MODELS OF NON-CIRRHOTIC PORTAL HYPERTENSION (NCPH)

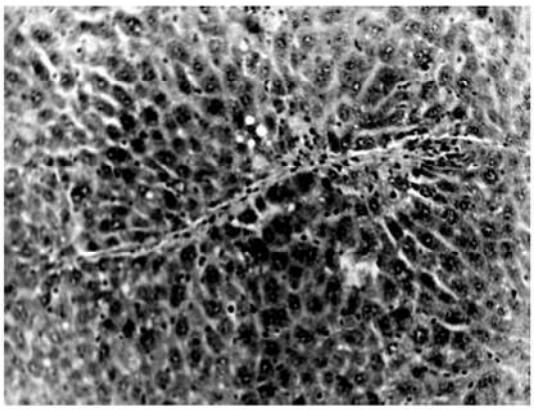

Fig 3: Liver histology of mice exposed to arsenic for 15 months. The histology shows streaky fibrosis in the liver (hematoxylin-eosin, original magnification x 100).

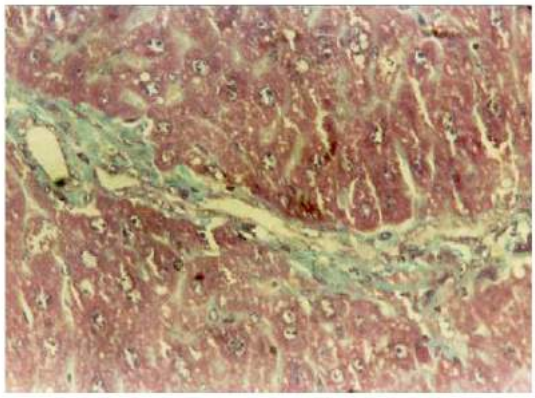

Fig 5: Liver histology of mice exposed to arsenic for 15 months. The histology shows mature collagen deposition spreading from the portal tracts through the liver lobules (Masson Trichrome x 400).

Chronic arsenic ingestion: Despite the establishment of an association of non-cirrhotic portal fibrosis with drinking of arsenic-contaminated water in several districts of West Bengal, India, elucidation of the mechanism of this disorder has remained conjectural. Chronic arsenic toxicity is a form of hepatic fibrosis that causes portal hypertension, but does not progress to cirrhosis. Hepatotoxic effects of arsenic in humans have been reported [14,26,32,34]. Injury to intrahepatic portal vein and even development of cirrhosis have been alleged to occur with prolonged usage of Fowler's solution containing sodium arsenite.

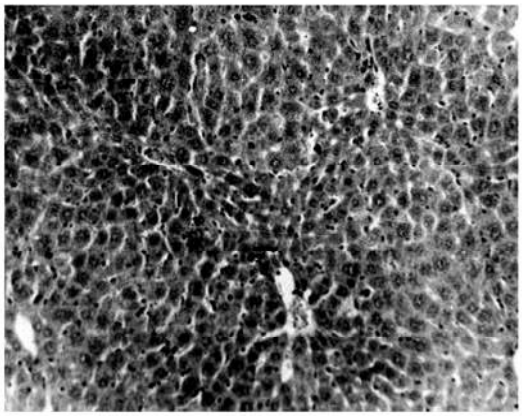

Fig 4 Normal liver histology of control mice at the end of 15 months of feeding As-free water (hematoxylin-eosin, magnification x 100).

Sarin SK et al in 1999 produced a reproducible and homogenous murine model of hepatic fibrogenesis and fibrosis without significant hepatocellular necrosis and inflammation through chronic arsenic feeding (Table 2). In addition they investigated the fibrogenic potential of chronic ingestion of different dosages of arsenic in mice. The study pointed that fibrogenesis could be induced within six weeks by arsenic. There was relatively more fibrosis with extended arsenic exposure associated with increased hepatic collagen deposition much more than hydroxyproline levels (Table 3-4). This fact was also supported by the histopathological studies which showed that the fibrosis and collagen deposition was more at 6 months. This result was specially obtained with arsenic dosage of 120 ppm. The fibrogenesis and fibrosis produced with this dosage at 6 months was near maximum that could be produced by feeding arsenic to mice. The mortality rate with 120 ppm dosage was near to the ground. Higher dosages of arsenic given for a short period of 6 weeks did enhance collagen synthesis and deposition; but there was no dose dependent increase with prolonged exposure.

The main conclusions of the study were: (i) prolonged oral arsenic ingestion in mice leads to significant hepatic fibrogenesis

and collagen synthesis with minimal hepato-cellular injury; (ii) arsenic ingestion alone is unlikely to cause non-cirrhotic portal fibrosis or cirrhosis of liver. This murine model of arsenic feeding could be used for the evaluation of new antifibrotic agents for the liver.

Guha Mazumdar et al described in a population from West Bengal that chronic arsenic toxicity leads to the development of hepatic fibrosis with portal hypertension in the absence of cirrhosis [12,13]. The group also demonstrated for the first time hepatic fibrosis due to long-term arsenic toxicity in a murine model of NCPF. In this study the mice received drinking water contaminated with arsenic (3.2 mg/L) or arsenic-free (0.01 mg/L, control) *ad libitum* till 3, 6, 9, 12, and 15 months. The result demonstrated that after 12 months of arsenic feeding, the liver weights increased significantly consistent with raised ALT and AST (Table 5). Arsenic feeding after 6 months showed significant decrease in hepatic glutathione and the enzymes glucose-6-phosphate dehydrogenase and glutathione peroxidase than the control group. Also, the plasma membrane Na^+/K^+ ATPase activity was reduced while lipid peroxidation increased significantly after 6 months of arsenic feeding. Hepatic catalase activity was significantly reduced at 9 months in the arsenic-fed group, while glutathione-S-transferase and glutathione reductase activities were also significantly reduced at 12 and 15 months (Table 6). Histopathology of the liver (Fig 1-5) remained normal for the initial 9 months, but showed fatty infiltration after 12 months of arsenic feeding. Fibrosis was only evident after 15 months. The main findings of the study were (i) long term arsenic toxicity produced hepatic fibrosis in murine model. (ii) Initial biochemical evidence of hepatic membrane damage, probably due to reduction of glutathione and antioxidant enzymes, may be seen by 6 months. (iii) Continued arsenic feeding resulted in fatty liver with serum aminotransferase and alanine aminotransferase elevated at 12 months and hepatic fibrosis at 15 months.

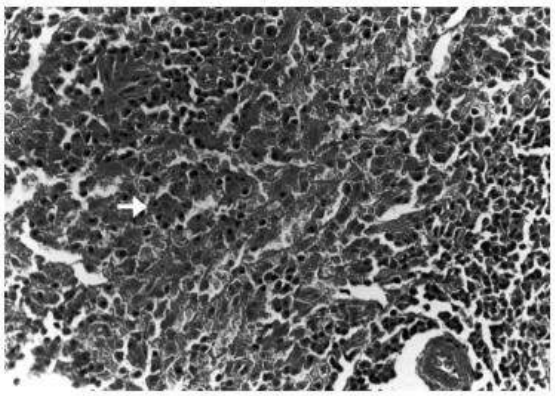

Fig 6: Photomicrograph showing a section from spleen with medullary congestion and (→) hemosidrin pigment (H&E x 160).

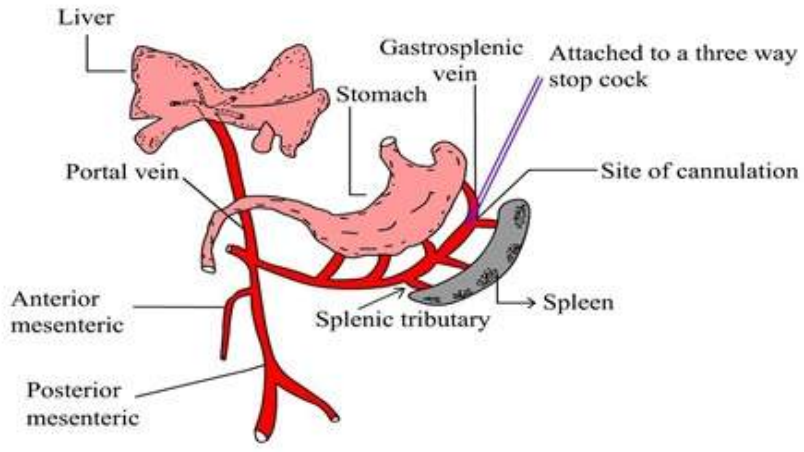

Fig 7: Indwelling cannula placed in gastrosplenic[27]

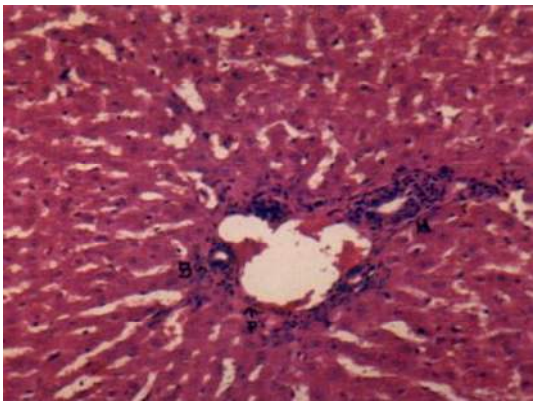

Fig 8: Photomicrograph of a section of liver showing normal hepatic parenchyma in NCPF[27]

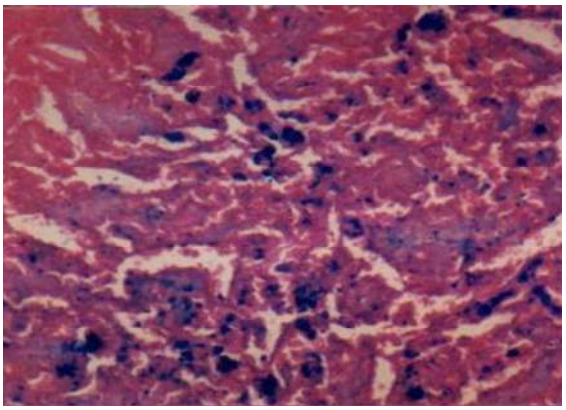

Fig 9: Photomicrograph showing a section from spleen with medullary congestion and hemosidrin pigment[27]

Repeated immunosensitization by rabbit splenic extract: A rabbit model of NCPF was developed by an intramuscular injection of splenic extract[15]. Six milligrams of the splenic protein thus prepared was mixed with Freund's complete adjuvant in a 1:1 ratio and injected intramuscularly into the experimental rabbits every 2weeks for 3 months. The control group of animals was sensitized by normal saline mixed with Freund's complete adjuvant in an equal ratio in the same manner. This animal model showed significant splenomegaly at one (0.63±0.19 vs 0.23±0.04 g; $p<0.05$), three (0.73±0.24 vs 0.38±0.10 g; $p<0.05$) and six (0.51±0.17 vs 0.23±0.04 g; $p<0.05$)

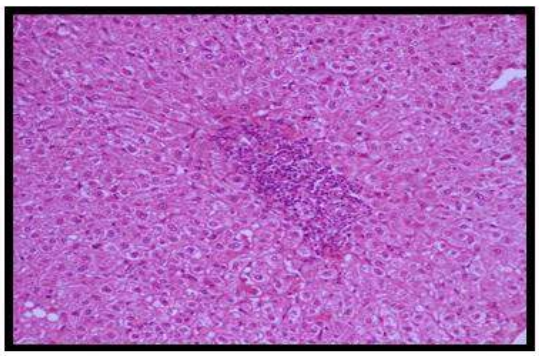

Fig 10: Small portal vein-obstructed with mild portal inflammation (+), H&E

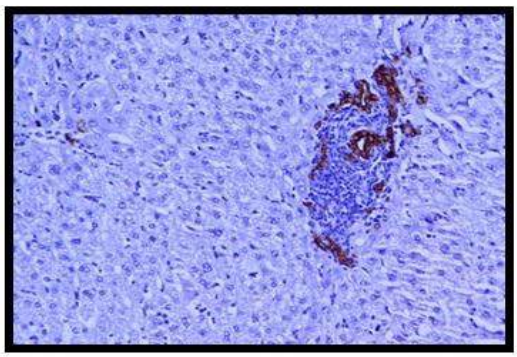

Fig 11: Small portal vein obstructed with mild portal inflammation (+), CK7, immunohistochemistry (IHC)

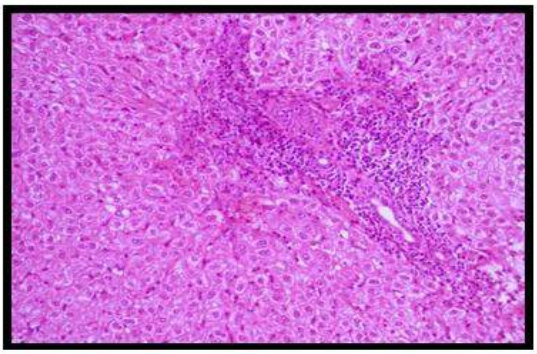

Fig 12: Medium portal vein with moderated portal inflammation (++), & compromised portal vein lumen,,H&E

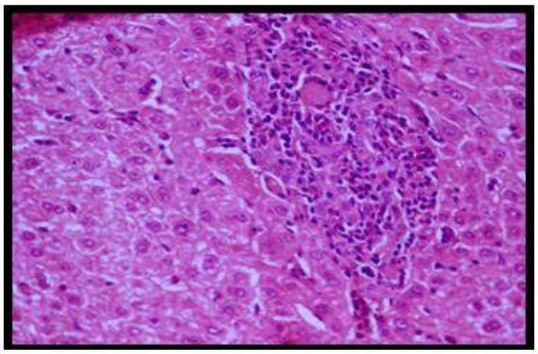

Fig 13: Small portal vein-obstructed with portal inflammation and giant cell, H&E

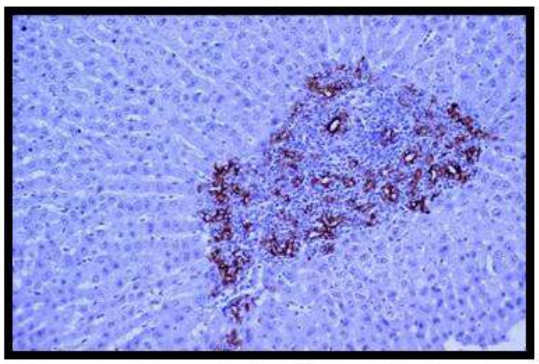

Fig 18: Small portal vein with completely obstructed portal vein showing Bile Duct proliferation

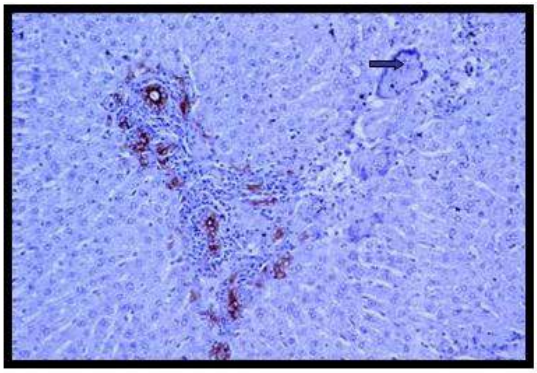

Fig 19: Portal tract with moderated portal inflammation (++) and giant cell (arrow)

with persistent rise in portal pressure at one (19.4±2.9 *vs* 10.4±2.2 mmHg; $p<0.05$), three (16.7±1.1 *vs* 7.2±3.6 mmHg; $p<0.05$), and six (20.3±5.4 *vs* 10.3±4.8 mmHg; $p<0.05$) months without hepatic parenchymal injury, quite akin to NCPF seen in humans. The histological examination of the liver specimen from NCPF rabbits showed mild portal and lobular inflammation, along with Kupffer cell hyperplasia. The major histological changes observed in the spleen from NCPF rabbits were fibrocongestive sp lenomegaly, that is, medullary congestion, thick-walled vessels and hemosidrin-laden macrophages (Fig 6). This study also proposes that repeated immunostimulation may have an important role in the pathogenesis of NCPF.

Repeated low dose endotoxinemia of portal circulation: Portal pyelephlebitis due to repeated abdominal infections and thrombosis in the portal circulation lead to obstruction of small and middle branches of portal vein and development of NCPF. Based on this hypothesis, Omanwar S et al[27] developed an animal model of NCPF by repeated low dose endotoxemia by injecting E. coli (heat killed) into the portal system of the animal through an indwelling cannula (placed in gastrosplenic vein) to understand the etiology and pathophysiology of this disease. Heat killed *E. coli* (LPS, 4 mg/kg b. wt) was injected through an indwelling cannula into the gastrosplenic vein (Fig 7) in pre-sensitized (1.5 mg E. coli protein/kg b. wt + Freund's complete adjuvant; 1:1 ratio; IM) rabbits. The control group of rabbits received normal saline in the same manner. The mean portal pressure in NCPF rabbits was significantly ($p<0.05$) higher compared to the control group at one (17.5 ± 3.4 Vs 10.4 ± 2.2 mmHg), three (17.8 ± 1.3 vs 7.2±3.6 mm Hg), and at 6 (19.8 ± 3.1 vs. 10.3 ± 4.8 mmHg) months. Similarly, the splenic weight in NCPF rabbits was significantly

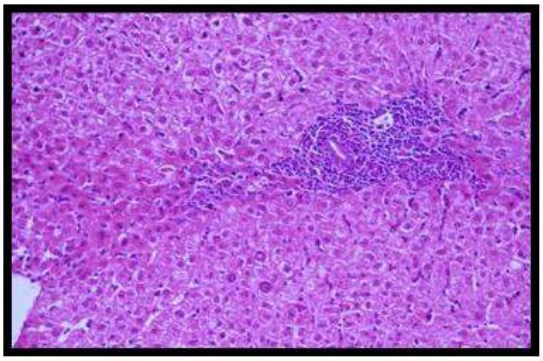

Fig 16: Medium portal vein with small lumen showing mild portal inflammation

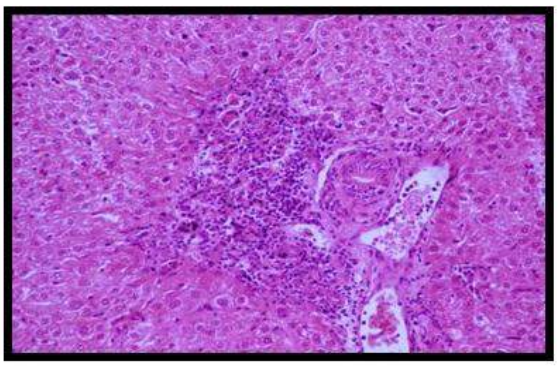

Fig 17: Medium portal vein with normal lumen showing mild portal inflammation

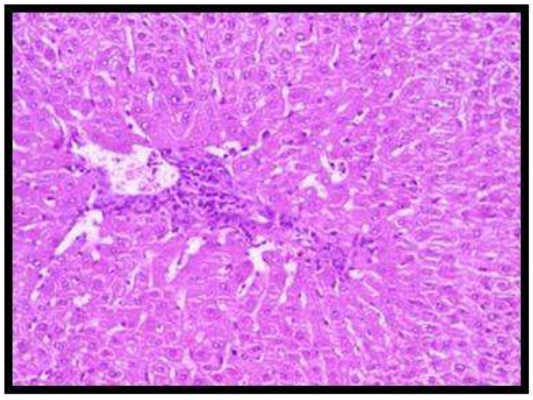

Fig 22: Dilated PV with dilated sinusoids (H&E)

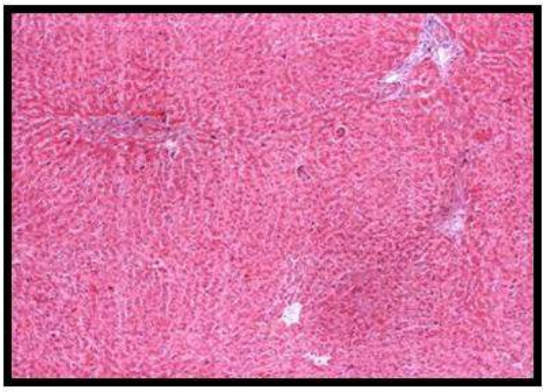

Fig 23: No significant fibrosis

($p<0.05$) greater than the control rabbits at one, three and six months. Absence of hepatic parenchymal injury and persistently elevated portal pressure makes this model ideal to investigate the vascular reactivity to various agents (Fig 8-9).

More recently, Sakhuja P et al[31] studied the liver histology in rabbit model of NCPF (induced by injecting LPS) especially with respect to the changes in portal veins. Five micron thick sections were stained with routine H & E and with Masson's Trichrome stain. Immunohistochemical staining with antibodies to Cytokeratin 7 using DAB as chromogen was also performed in all cases to identify bile ducts and portal tracts. Portal tracts (PT) were divided into small, medium and large based on size of accompanying bile duct. Portal veins (PV) in each PT were counted as normal if lumen was seen, or obstructed if PV was not identified or completely obscured by inflammatory cells. Number of obstructed Portal veins was then expressed as a percentage of total PTs. The model was characterized with splenomegaly and portal hypertension with normal liver function tests. Obstructed PVs were seen in 25-80% (mean = 54.12%) of small PTs in the experimental group in comparison to 15 – 26% (mean = 19.75%) in the control group. 5 of 8 rabbits in the experimental group showed greater than 50% obstructed PVs in the small PTs. Several PTs showed mononuclear inflammation with accompanying giant cells and granulomatous reaction causing obstruction to portal veins. Similar inflammation was observed focally in the lobular parenchyma. One animal showed active granulomatous inflammation in the medium sized portal veins. No significant fibrosis or cirrhosis was seen in any case. No significant inflammation or fibrosis was observed in the control group. The main conclusion of the study was that E.Coli induced portal hypertension is associated with obstructive

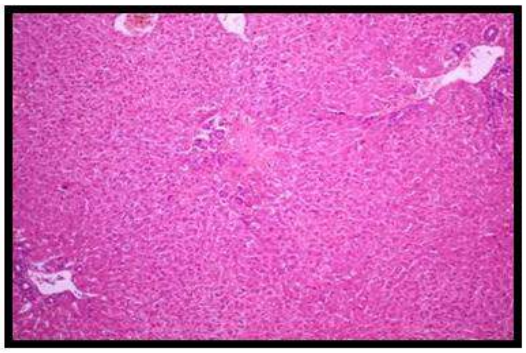

Fig 20: Dilated PV with dilated sinusoids and focal LI with giant cells (H&E)

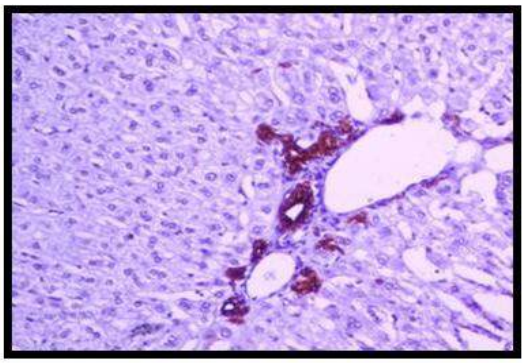

Fig 21: Dilated PV with dilated sinusoids (CK7, IHC)

venopathy in small portal veins, without accompanying fibrosis[31].

REFERENCES

1. Ariosto F, Riggio O, Cantafora A, Colucci S, Gaudio E, Mechelli C et al. Carbon tetrachloride-induced experimental cirrhosis in the rat: a reappraisal of the model. Eur Surg Res 1989;21:280–6.
2. Burgener FA, Gutierrez OH, Logsdon GA. Angiographic, hemodynamic, and histologic evaluation of portal hypertension and periportal fibrosis induced in the dog by intraportal polyvinyl alcohol injections. Radiology 1982; 143: 379-385.
3. Cahill PA, Foster C, Redmond EM, Gingalewski C, Wu Y, Sitzmann JV. Enhanced nitric oxide synthase activity in portal hypertensive rabbits. Hepatology 1995; 22: 598-6
4. Castaneda B, Debernardi-Venon W, Bandi JC, Andreu V, Perez-del-Pulgar S, Moitinho E, Pizcueta P, Bosch J. The role of portal pressure in the severity of bleeding in portal hypertensive rats. Hepatology 2000; 31: 581-586
5. Colombato LA, Albillos A, Groszmann RJ. Temporal relationship of peripheral vasodilatation, plasma volume expansion and the hyperdynamic circulatory state in portalhypertensive rats. Hepatology 1992; 15: 323-328
6. Colombato LA, Robin M, Pomier-Layrargues G, Huet PM. Animal models of portal hypertension. In: Holstege A, Hahn EG, Scholmerich J, editors. Portal Hypertension – Proceedings of the 79th Falk Symposium. Germany: Kluwer Academic Publishers, 1995.pp. 3–14.
7. Dashti H, Jeppsson B, Hägerstrand I, Hultberg B, Srinivas U, Abdulla M et al. Thioacetamide- and carbon tetrachlorideinduced liver cirrhosis. Eur Surg Res 1989;21:83–91.
8. Dhiman RK, Chawla Y, Vasishta RK, Kakkar N, Dilawari JB, Trehan MS, Puri P, Mitra SK, Suri S. Non-cirrhotic portal fibrosis (idiopathic portal hypertension): experience with 151 patients and a review of the literature. J Gastroenterol Hepatol. 2002;17 (1):6-16.
9. Fernandez M, Vizzutti F, Garcia-Pagan JC, Rodes J, Bosch J. Anti-VEGF receptor-2 monoclonal antibody prevents portalsystemic collateral vessel formation in portal hypertensive mice. Gastroenterology 2004; 126: 886-894
10. Franco D, Gigou M, Szekely AM, Bismuth H. Portal hypertension after bile duct obstruction: effect of bile diversion on portal pressure in the rat. Arch Surg 1979;114:1064–7.
11. Gaisford WD, Zuidema GD. Nutritional Laennec's cirrhosis in the macaca mulatto monkey. J Surg Res, 1965;5: 220-235.
12. Guha Mazumder DN, Chakraborty AK, Ghosh A, et al. Chronic arsenic toxicity from drinking tubewell water in rural west Bengal. Bull Wld Health Org 1988;66:499–504.
13. Guha Mazumder DN, Das Gupta J, Santra A, *et al.* Noncancer effects of chronic arsenicosis with special reference to liver damage. In: Arsenic Exposure and Health Effects. Abernathy CO, Calderon RL, Chappell WR, eds., London: Chapman & Hall 1997;112–123.
14. Huet PM, Guillaume E, Cote J, Legare A, Lavoie P, Viallet A. Noncirrhotic presinusoidal portal hypertension associated with chronic arsenical intoxication. Gastroenterology 1975; May;68(5 Pt 1):1270-7.
15. Iwakiri Y, Cadelina G, Sessa WC, Groszmann RJ. Mice with targeted deletion of eNOS develop hyperdynamic circulation associated with portal hypertension. Am J Physiol Gastrointest Liver Physiol 2002; 283: G1074-G1081
16. Kathayat R, Pandey GK, Malhotra V, Omanwar S, Sharma BK, Sarin SK. Rabbit model of non-cirrhotic portal fibrosis with repeated immunosensitization by rabbit splenic extract. J Gastroenterol Hepatol. 2002 Dec;17(12):1312-6.
17. Kaza RM, Sharma BK, Sarin SK, Malhotra V, Kumar S, Rana BS. Evaluation of three surgical techniques for developing an animal model of non-cirrhotic portal fibrosis. In: Animal Models of Portal hypertension, 1988 pg73-79.
18. Komeichi H, Katsuta Y, Aramaki T, Okumura H. A new experimental animal model of portal hypertension. Intrahepatic

portal obstruction by injecting DEAE-cross-linked dextran microspheres into the portal vein in the rabbit. Nippon Ika Daigaku Zasshi. 1991 Jun;58(3):273-84.
19. Kono K, Ohnishi K, Omata M, Saito M, Nakayama T, Hatano H, Nakajima Y, Sugita S, Okuda K. Experimental portal fibrosis produced by intraportal injection of killed nonpathogenic Escherichia coli in rabbits. Gastroenterology. 1988 Mar;94(3):787-96.
20. Kountouras J, Billing BH, Scheuer PJ. Prolonged bile duct obstruction: a new experimental model for cirrhosis in the rat. Br J Exp Pathol 1984;65:305–11.
21. Kunio Okuda Non-cirrhotic portal hypertension: Why is it so common in India? Journal of Gastroenterology and Hepatology. 2002 17, 1–5.
22. Lee FY, Groszmann RJ. Experimental models in the investigation of portal hypertension. Ascites Ren Dysfunct Liv Dis Pathog Diagn Treat 1999;1:365–78.
23. Li X, Benjamin IS, Alexander B. Reproducible production of thioacetamide-induced macronodular cirrhosis in the rat with no mortality. J Hepatol 2002;36:488–93.
24. Miyakawa H, Iida S, Leo MA, Greenstein RJ, Zimmon DS, Lieber CS. Pathogenesis of precirrhotic portal hypertension in alcohol-fed baboons. 1985. Gastroenterology 88: 143-150.
25. Myking AO, Halvorsen JF. Two-stage occlusion of the portal vein in the rat: Survival related to weight variation and the interval between partial and total occlusion. Eur Surg Res 1975;7: 366-374.
26. Narang AP. Arsenicosis in India. J Clinic Toxicol 1987; 25 (4): 287-295
27. Omanwar S, Rizvi MR, Kathayat R, Sharma BK, Pandey GK, Alam MA, Pandey GK, Malhotra V, Sarin SK.A rabbit model of non-cirrhotic portal hypertension by repeated injections of E.coli through indwelling cannulation of the gastrosplenic vein. Hepatobiliary Pancreat Dis Int. 2004; 3(3):417-22.
28. Petermann H, Vogl S, Schulze E, Dargel R. Chronic liver injury alters basal and stimulated nitric oxide production and 3H-thymidine incorporation in cultured sinusoidal endothelial cells from rats. J Hepatol 1999;31:284–92.
29. Proctor E, Chatamra K. High yield micronodular cirrhosis in the rat. Gastroenterology 1982;83:1183–90.
30. Reynell PC. Portal hypertension in the rat. Br J Exp 1952; Pathol 33: 19-24.
31. Sakhuja P , Wanless I, Rizvi MR, Gondal R, Sarin SK. Liver histology in a rabbit model of E. coli induced non-cirrhotic portal hypertension. Modern Pathology 2006; 19 (suppl 3): 136
32. Santra A, Das Gupta J, De BK, Roy B, Guha Mazumder DN. Hepatic manifestations in chronic arsenic toxicity. Ind J Gastroenterol 1999; 18:152–155.
33. Sugita S, Ohnishi K, Saito M, Okuda K. Splanchinc hemodynamics in portal hypertensive dogs with portal fibrosis. Am. J. Physiol. Gastrointest. Liver Physiol 1987; 252: G748–54.
34. Villeneuve JP, Huet PM, Joly JG, Marleau D, Cote J, Legare A, Lafortune M, Lavoie P, Viallet A. Idiopathic portal hypertension. Am J Med 1976 Oct;61(4):459-64.
35. Vorobioff J, Bredfeldt JE, Groszmann RJ. Hyperdynamic circulation in portal-hypertensive rat model: a primary factor for maintenance of chronic portal hypertension. Am J Physiol 1983; 244: G52-G57
36. W. Laleman, I. Vander Elst, M. Zeegers, R. Servaes, L. Libbrecht, T. Roskams, J. Fevery and F. Nevens. A stable model of cirrhotic portal hypertension in the rat: thioacetamide revisited European Journal of Clinical Investigation 2006; 36, 242-249
37. Wanless IR (1987) On the pathogenesis of noncirrhotic portal hypertension. In: Boyer JL, Bianchi L (eds). Liver cirrhosis: Proceedings of the VII international congress of liver diseases (Falk Symoposium No. 44) MTP Press, London, pp 293-311
38. Yamana H, Yatsuka K, Kakegawa T. Experimental production of portal hypertension in dogs by a whole liver compression. Gastroenterol Jpn 1983; 18(2):119-27.

ROACH'S TYPE II VARIANT OF STURGE – WEBER SYNDROME: A CASE REPORT

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ABSTRACT

Sturge- weber syndrome is a neurocutaneous disorder caused by persistence of transitory primordial arteriovenous connection of the foetal intracranial vasculature. It manifests with vascular malformations involving the brain, eye and skin with resulting neurological and orbital manifestations. Port wine stain, glaucoma and seizures are some of the commonly seen symptoms, depending on the presence of these features sturge weber syndrome has been classified by Roach into three types. We report a case of a 26 year old female with facial portwine stain and minimal neurologic manifestations, which according to Roach's classification falls in type II category. This report also underlines the need for detailed laboratory and neurologic work up of all patients with facial portwine stain present along the distribution of trigeminal nerve, as the neurologic manifestations in sturge–weber syndrome may vary in severity from seizures and mental retardation to minimal radiographic changes. It also emphasizes the need for identification of such rare variants of this syndrome.

ملخص: متلازمة ستيرج ويبر هو اضطراب عصبي جلدي ناجم عن استمرار اتصال الشرايين والأوردة الأولية المؤقتة داخل جمجمة الجنين، و يظهر في شكل تشوهات وعائية في المخ والعين والجلد و يؤدي الي أعراض عصبية وأعراض في محجر العين. من أعراضه الشائعة تلون الجلد باللون الاحمر القاني, ارتفاع ضغط العين وتشنجات. حسب الاعراض تم تصنيف متلازمة ستيرج ويبر من قبل روتش إلى ثلاثة أنواع. سجلنا حالة لأنثى تبلغ من العمر 26 عاما تشكو من تلون بجلد الوجه واعراض عصبية بسيطة والتي تصنف حسب روتش في الفئة الثانية. هذا التقرير يؤكد أيضا الحاجة إلى مزيد من التقصي السريري و المخبري لجميع المرضى الذين يعانون من تلون الوجه على طول مسار العصب الثلاثي التوائم ، وخصوصا ان الاعراض العصبية في متلازمة ستيرج ويبر قد تختلف في شدتها من التشنجات و التخلف العقلي الي التغيرات البسيطة في الفحص الشعاعي. التقرير يؤكد أيضا على الحاجة إلى تحديد المتغيرات النادرة لمثل هذه المتلازمة.

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INTRODUCTION

Sturge-Weber Syndrome also called as encephalotrigeminal angiomatosis is an uncommon condition that is characterized by hamartomatous vascular proliferation involving the tissues of the brain and face. It occurs due to persistence of vascular plexus around the cephalic portion of the neural tube. This plexus develops during the sixth week of intrauterine life and usually regresses by the ninth week. The exact cause is unknown but a "2-hit hypothesis" which involves sporadic mutations as well as familial occurrences has been suggested as etiological basis[1]. Most cases are sporadic but occasionally cases within families have also been reported. Males and females seem to be equally affected. It has been reported in individuals of White, Hispanic, African and Asian heritage.

Clinically, patients typically presents with constellation of signs and symptoms such as congenital facial Angiomas (Port Wine Stain/PWS)[2,3], glaucoma, and variable neurologic manifestations including seizures, mental retardation, hemianopia, hemiparesis and learning difficulties[4-6]. Patients may also have emotional problems, such as depression, low self-esteem, shame, emotional outbursts and isolation. The facial angioma is usually unilateral but may be bilateral. It typically involves at least the upper face, superior eyelid, or periorbital region. The facial angioma conforms to sensory distribution of the trigeminal nerve, Angiomas may also involve gingiva, nasopharynx, palate, lips and tongue[7,8]. Port wine stain may also be found on the trunk or extremities of some individuals with Sturge Weber Syndrome.

Seizures and other neurologic complications are the result of leptomeningeal angiomas. The severity of the neurological manifestations depends on the location and amount of area involved by leptomeningeal angioma.

Glaucoma is also commonly seen in Sturge Weber Syndrome and is present in 60% of individuals. It can be present at birth or occur anytime throughout the lifespan. It can be unilateral or bilateral, untreated, glaucoma can cause blindness and can be extremely painful.

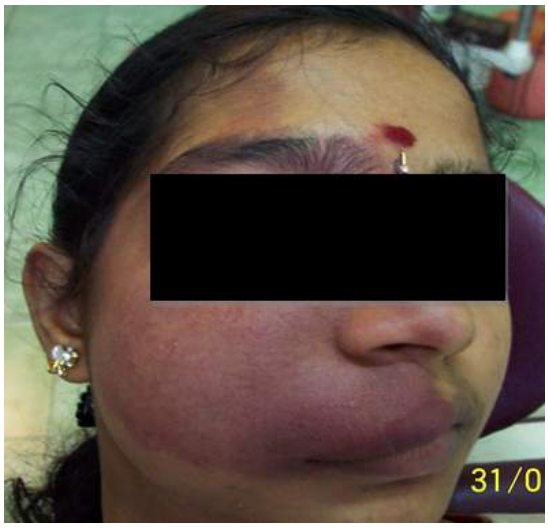

Figure 1: Characteristic unilateral involvement of face with ophthalmic and maxillary nerves affected

Depending on the presence of facial angiomas, leptomeningeal angiomas and glaucoma, Roach has classified Sturge Weber Syndrome as follows[9]

Type I - Both facial and leptomeningeal angiomas; may have glaucoma

Type II - Facial angioma alone (no CNS involvement); may have glaucoma

Type III - Isolated LA; usually no glaucoma

CASE HISTORY

A 26 year lady reported to the outpatient department with complaint of facial nevi involving the upper face on right side, she also complained of bleeding from the

gums. On detailed history patient reported nevi to be congenital, initially with pink colour and later progressing to purplish hue. There was no history of seizure or mental retardation but during examination the patient was dull and was answering with difficulty. On examination, the nevi was extending superiorly from the periorbital region to the angle of the mouth inferiorly, upto the midline (Fig 1).

Table 1 Clinical Manifestations of Sturge-Weber Syndrome

Risk of SWS with facial PWS	8%
SWS without facial nevus	13%
Bilateral cerebral involvement	15%
Seizures	72-93%
Hemiparesis	25-56%
Hemianopia	44%
Headache	44-62%
Developmental delay and mental retardation	50-75%
Glaucoma	30-71%
Choroidal Haemangioma	40%

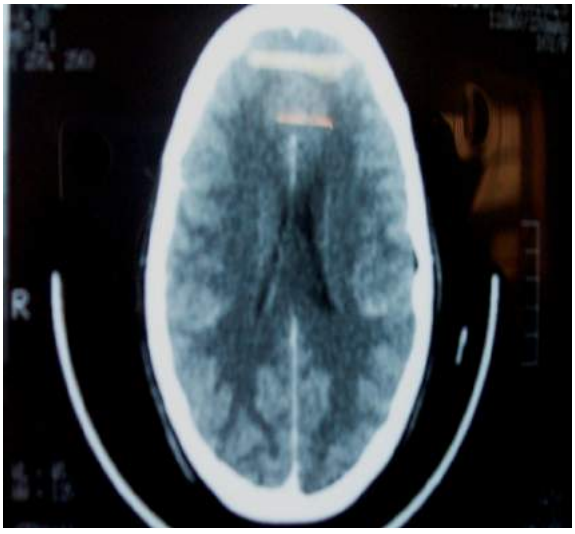

Figure 2: CT scan revealing mild cortical atrophy and focal calvarial thickening.

The CT scan revealed minor changes like gyriform enhancement in parietal lobe with mild cortical atrophy and focal calvarial thickening (Fig 2). Eye examination revealed no glaucoma and there was no history of pain or imperfect vision Intraorally the gingival hyperplasia was noticed in both upper and lower arch on right side characteristically extending till midline (Fig 3 and 4).

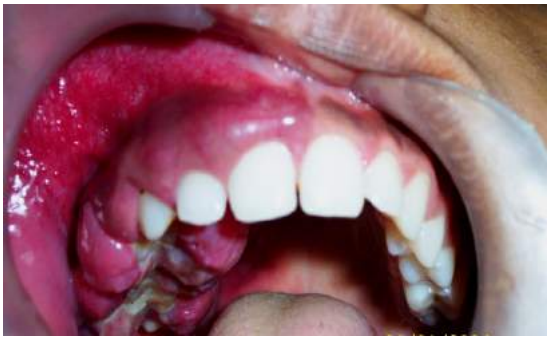

Figure 3: Hyperplastic maxillary gingiva extending till midline

Intra oral examination revealed gingival hyperplasia of both the arches extending up to the midline. Plaque and calculus was seen in the region of gingival enlargement, but this was because the patient could not brush that region due to bleeding. Gingival hyperplasia was more pronounced on the maxillary arch and covered almost the whole crown, buccal mucosa on the right side was also erythematous. The MRI findings revealed enhanced soft tissue mass lesion in the right oropharynx (Fig 5).

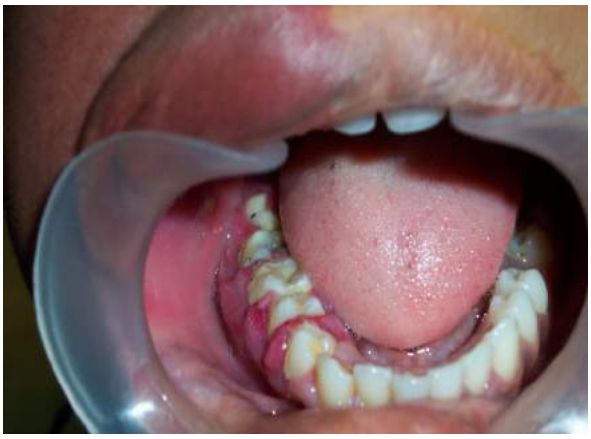

Figure 4: Gingival enlargement in lower arch is less compared to upper arch.

DISCUSSION

The Sturge-Weber syndrome (SWS) is a neurocutaneous disorder with angiomas involving the leptomeninges and skin of the face, typically in the ophthalmic and maxillary distributions of the trigeminal nerve. SWS is caused by residual embryonal blood vessels and their secondary effects on surrounding brain tissue. A vascular plexus develops around the cephalic portion of the neural tube, and normally regresses around the ninth week of gestation. Failure of this normal regression results in residual vascular tissue, which forms the angiomata of the leptomeninges, face, and ipsilateral eye. In a study by Tallman et al it was reported that 310 patients with PWS; 85% had unilateral and 15% had bilateral involvement, and 68% had involvement of more than 1 dermatome. Only patients with PWS involving the distributions of the V1 and V2 branches of the trigeminal nerve had CNS or eye involvement. Overall, in those with trigeminal involvement, only 8% had CNS and eye involvement[10]. Port wine stain is also associated with soft-tissue hypertrophy: The Sturge-Weber Foundation survey indicated that body asymmetry was seen in 164 of 171 patients, with soft-tissue hypertrophy in 38 of 164 patients and scoliosis in 11 patients. Basal cell carcinoma has been reported to occur within a PWS[11]. Intraorally, hypervascular changes may be seen on the ipsilateral mucosa and gingiva ranging from slight vascular hyperplasia to more massive hemangiomatous proliferation resembling a pyogenic granuloma.

Neurologic dysfunction results from secondary effects on surrounding brain tissue, which include hypoxia, ischemia, venous occlusion, thrombosis, infarction, or vasomotor phenomenon. A "vascular steal phenomenon"[12] may develop around the angioma, resulting in cortical ischemia and progressing to calcification, gliosis, and atrophy, which in turn increase the chance of seizures and neurologic deterioration[13]. The incidence of epilepsy in patients with SWS is 75-90%; seizures may be intractable. Seizures result from cortical irritability caused by cerebral angioma, through mechanisms of hypoxia, ischemia, and gliosis. Fibronectin is a molecule important in regulating angiogenesis, maintenance of the blood-brain barrier, blood vessel structure and function, as well as brain tissue responses to seizures. Comi et al reported that, in patients with SWS, decreased expression of fibronectin was noted in the leptomeningeal blood vessels[14].

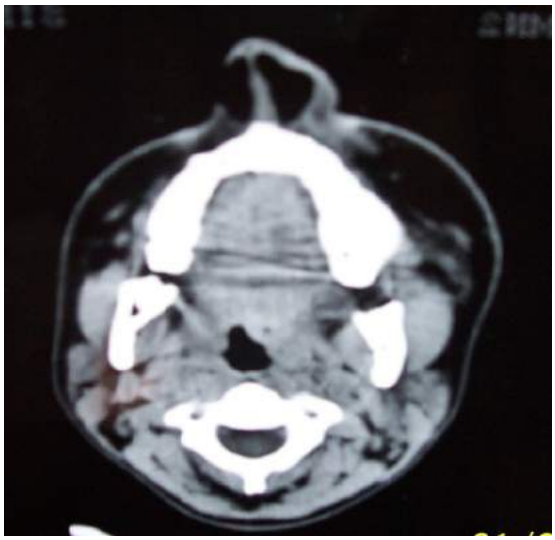

Figure 5: MRI revealing hyperplasia of right side

The main ocular manifestations (ie, buphthalmos, glaucoma) occur secondary to increased intra ocular pressure (IOP) with mechanical obstruction of the angle of the eye, elevated episcleral venous pressure, or increased secretion of aqueous fluid. Untreated, glaucoma can cause blindness. It can be extremely painful and may be a "silent" cause of behavior outbursts or self-injurious behavior in non-verbal individuals with Sturge Weber Syndrome. The incidences of the major

clinical manifestations of SWS are listed in Table 1[15].

In our case the patient complained only of the port wine stain and gingival hypertrophy with no history of seizure or ocular manifestations. The gingival hyperplasia reported in SWS has sometimes been attributed to the medications used for seizure control, but in our case the patient was not taking any medications and the hyperplasia was seen characteristically only upto the midline. The CT scan of brain did not show any obvious changes or calcifications but minor changes such as gyriform enhancement and some amount of cortical atrophy of the right half can be appreciated. This minimal involvement of the brain correlates well with the lack of neurologic manifestations seen in patient. This type of presentation of SWS is very rare and only reported by Bioxeda et al in 1993[16].

CONCLUSION

This is a rare case of SWS, which has minimal CNS involvement but no neurologic manifestations and hence this falls in Type II SWS according to Roach. Hence we suggest that any case having facial nevus along the course of trigeminal nerve should be suspected for SWS because the neurologic involvement in a given case may vary from minimal radiographic changes to overt clinical manifestations.

REFRENCES

1. Vishal Madan, Vijay Diwan, Sriram Ramaswamy, Ashish Sharma. Behavioral Manifestations of Struge Weber Syndrome: A case report. Prim Care Companion J of Clinical Psychiatry 2006;8:198-200
2. Bodensteiner JB, Roach ES. Sturge-Weber Syndrome: Introduction and Overview. In: Bodensteiner JB, Roach ES, eds. Sturge-Weber Syndrome. Sturge Weber Foundation. Mt Freedom, New Jersey. 1999.
3. Aicardi J. Diseases of the Nervous System in Childhood. 2nd ed. *London: Mac Keith Press*. 1998.
4. Thomas-Sohl KA, Vaslow DF, Mari BL. Struge Weber Syndrome: a review. Pediatr Neurol 2004; 30:303-310
5. Comi AM. Pathophysiology of Struge Weber Syndrome. J Child Neurol 2003;18: 509-516
6. Lisotto C, Mainardi F,Maggioni F,et al. Headache In Sturge Weber Syndrome: a case report and review of the literature. Cephalgia 2004;24:1001-1004
7. Haslam: RHA. Neurocutaneous Syndromes. In Behrman RE, Kliegman RM, Jenson HB (eds). Nelson Text book of Pediatrics. 17th edn. WB. Saunders Company, Philadelphia 2004 : 2015-19.
8. Berg Bo. Neurocutaneous Syndromes. In : Maria BL (ed) Current Management in Child Neurology. Hamilton BC Decker 1999.278-80
9. Roach ES. Neurocutaneous syndromes. *Pediatr Clin North Am*. Aug 1992;39(4):591-620.
10. Tallman B, Tan OT, Morelli JG. Location of port-wine stains and the likelihood of ophthalmic and/or central nervous systemcomplications. *Pediatrics*. Mar 199 1;87(3):323-7.
11. Sagi E, Aram H, Peled IJ. Basal cell carcinoma developing in a nevus flammeus. *Cutis*. Mar 1984;33(3):311-2, 318.
12. Aylett SE, Neville BG, Cross JH. Sturge-Weber syndrome: cerebral haemodynamics during seizure activity. *Dev Med Child Neurol*. Jul 1999;41(7):480-5
13. Okudaira Y, Arai H, Sato K. Hemodynamic compromise as a factor in clinical progression of Sturge- Weber syndrome. *Childs Nerv Syst*. Apr 1997;13(4):214-9
14. Comi AM, Weisz CJ, Highet BH. Sturge-Weber syndrome: altered blood vessel fibronectin expression and morphology. *J Child Neurol*. Jul 2005;20(7):572-7.
15. Thomas-Sohl KA, Vaslow DF, Maria BL. Sturge-Weber syndrome: a

review. *Pediatr Neurol*. May 2004; 30(5): 303-10

16. Bioxeda P,de Mesa RF, Arrazola JM. [Facial angioma and the sturge – Weber syndrome Likelihood a study of 121 Cases] Med clin (Barc) 1993 May 29, 101 (1); 1 – 4.

TUBERCULOSIS TIMEBOMB A GLOBAL EMERGENCY: NEED FOR ALTERNATIVE VACCINES

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Tuberculosis (TB) also known as white plague is a major infectious disease and a global emergency. It is one of the oldest recorded human afflictions and still continues to cause widespread morbidity and mortality in children and adults worldwide, despite the extensive use of a live attenuated vaccine and several antibiotics. One third of the world's population is already infected and about 3 million people die and 8 million people develop the active disease each year[1-2]. In the last decade there is a sharp rise in the cases of TB mainly due to emergence of multi-drug resistant (MTD), extensively drug-resistant (XDR) and totally drug-resistant (TDR) strains of Mycobacterium *tuberculosis*, which are virtually untreatable[3-7].

In the beginning of the last quarter of the 20th century, there was a glimmer of hope that TB could be brought under control; however, this was dashed with the emergence of HIV/AIDS TB co-infection[8]. HIV compromises the immune system, which needs to be competent for control of latent *M. tuberculosis* infection, and hence increases risk of active TB manifold, from 10% risk over a lifetime to 10% risk within of TB is becoming worse day by day. Use of BCG is effective in preventing TB in efficacies. The only approved and currently available vaccine against TB i.e. BCG has young children that too with varied the year of co-infection[9]. Despite the fact that highest number of people on the earth has been vaccinated with BCG still scenario been given 4 billion times over the last 100 years since its development; we don't even understand the precise immune mechanisms that protect BCG vaccinated infants and lacks protection in adults probably due to absence of generating long lasting memory cells. Thus, an effective vaccine for the prevention of pulmonary TB in adolescents and adults, many of whom are latently infected with M. tuberculosis in countries in which TB is endemic, is urgently needed to control the TB time bomb.

Immunity to Mtb is a two-edged sword: it protects the human host against disseminating infection, but also facilitates transmission of TB to contacts. Therefore, TB vaccines not only need to induce optimal immunity to Mtb, but also a balanced response that favors protective and avoids pathogenic mechanisms[10]. But the most successful vaccines today target pathogens against which humoral immunity suffices to achieve protection and often sterile eradication but TB vaccines need to drive primarily the cellular arm of the immune system.

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+Table 1: Next Generation vaccine candidates against Tuberculosis

Type of Vaccine	Product	Description	Indication	Sponsors
Recombinant Protein	r30	30KDa mtb Ag85B protein purified from rM. Smegmatis	B and PI	UCLA, NIH, NIAD
	R32KDA (Recombinant 85A)	Purified recombinant Ag85A protein from BCG	B, PI and IT	LEPRA Society, Blue Peter Research Centre, and BMMRC
	Latency fusion protein	recombinant fusion protein composed of antigens 85A- 85B-Rv3407, Rv3407-Rv1733c-Rv2626c, Rv0867c-Rv-1884-Rv2389c	B	Aeras
Recombinant Live	rBCG(mtbB)30	rBCG with limited replication overexpressing the 30kDa Mtb Ag85B	P	UCLA, NIH, NIAD
	HG856-BCG	rBCG overexpressing chimeric ESAT-6/Ag85A DNA fusion protein	B and PI	Shanghai Public Clinical Health Centre
	BCG zmp1	BCG zmp 1 deletion mutant	P	University of Zurich, TBVI
	rBCG38	rBCG Tice strain overexpressing the38KDa protein	P and B	Universidad Nacional Autonoma de Mexico
	Disruption of the SapM locus	Recombinant M. bovis BCG in which the SapM locus has been disrupted	P	FWO-Ghent University-VIB
	rBCG85C	rBCG overexpressing antigen 85C of M tb	P	University of Delhi; DBT, Govt. of India
	Streptomyces live vector	Recombinant Streptomyces expressing multiple T and B epitopes of Mtb.	P, B, PI and IT	Finlay Institute; Institute of Pharmacy and Food Cuba
	rBCG T+B rM. Smegmatis T+B	rBCG and rM. Smegmatis expressing multiple T and B epitopes of Mtb	P, B and PI	Finlay Institute; Universiti Sains Malaysia
Viral Vectored	rhPIV2-Ag85B	Replication deficient human parainfluenza type-2 virus expressing Ag85B	P and B	NIBI Japan; Japan BCG Laboratory
	Recombinant LCMV	r-LCMV expressing Ag85A, Ag85B or Ag85B-ESAT-6	P, B, PI and IT	University of Geneva, TBVI
DNA	HG856A	Chimeric DNA vaccines-ESAT-6/Ag85A; Ag85A/Ag85B	B and IT	Shanghai H&G Biotech
	DNAacr	DNA vaccine expressing alpha crystalline, a key latency associated antigen of Mtb	B	University of Delhi; DBT, Govt. of India
	HVJ-Envelope/HSP65 DNA+IL-12 DNA	Combination of DNA vaccines expressing Mtb HSP-65 & IL-12	B, PI and IT	Osaka University
	pUMVC6/7 DNA	DNA vaccine plasmid vector pUMVC6 or pUMVC7 expressing Rv 3872, Rv 3873, Rv3874, Rv3875 or Rv3619c	P	Kuwait University
	HG85A/B	Chimeric DNA vaccines-Ag85A/B	B and IT	Shanghai H&G Biotech

Key: P= Prime, B= Boost, PI= Post Immunization and IT= Immunotherapy

So the new vaccines candidates are needed which are better than BCG and must protect not only toddlers but also adults; be effective when administered pre-exposure and post-exposure with M. tuberculosis; and ultimately the next-generation candidates should be capable of eradicating or preventing infection with M. tuberculosis, while current vaccine candidates are aimed at preventing active TB disease by controlling latent M. tuberculosis infection[5]. Currently extensive efforts are being put into the development of a better vaccine. Some of the live vaccine alternatives are quite promising for prevention of primary disease. The development of new TB vaccines should follows two basic

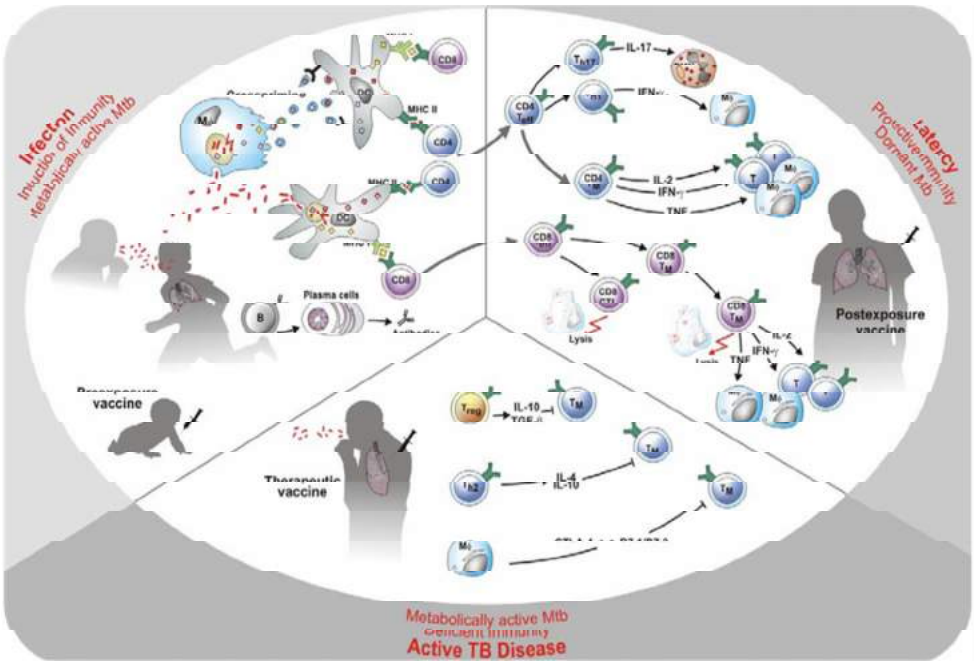

Figure*: *The three stages of tuberculosiss Disease. Stage *1: Infection of Mycobacterium tuberculosis (Mtb) frequently occurs at a young age. Metabolically active Mtb are inhaled and subsequently T-cells are stimulated which carry the major burden of acquired immunity. These include major histocompatability complex class II (MHC II)-restricted CD4 T-cells and MHC I-restricted CD8 T-cells. B cells are also activated but their protective role in TB remains elusive. Pre-exposure vaccines are given at this early stage. Novel pre-exposure vaccine candidates are given very soon after birth and thus generally before infection with Mtb. They either substitute for Bacille Calmette Gue´ rin (BCG) or boost immunity induced by BCG.* ***Stage 2:*** *Acquired immunity comprising CD4 and CD8 T-cells contains Mtb in a dormant stage within solid granulomas. T-cells produce type I cytokines and cytolytic effector molecules. They become memory T-cells which concomitantly produce multiple cytokines. Individuals remain latently infected without clinical signs of active tuberculosis (TB). Post-exposure vaccines are given to adolescents or adults who are latently infected but healthy.* ***Stage 3:*** *Mechanisms leading to deficient immunity and disease reactivation are numerous and include production of suppressive cytokines such as interleukin (IL)-10 and transforming growth factor-beta (TGFb) by T helper 2 (Th2) cells and regulatory T(reg) cells as well as T-cell exhaustion mediated by inhibitory receptor-coreceptor interactions on antigen presenting cells (APCs) and T-cells. Mtb becomes metabolically active and granulomas become caseous. Mtb can be spread to other organs and to other individuals. Therapeutic vaccines are given to TB patients in adjunct to chemotherapy. (adopted from Plos pathogen Kaufman S. H. E)*

avenues; the first aims at replacing BCG either by genetically attenuated *Mtb* or by improved recombinant (r)BCG. And in both the cases the vaccine should be: more immunogenic, capable of inducing long lasting protection; safer for human use and should also induce protection against highly virulent clinical isolates such as MDR, XDR, *TDR and Mtb* Beijing strains.

The promising alternatives are recombinant BCG expressing listeriolysin from Listeria monocytogenes, over-expression of antigen 85B in BCG or recombinant BCG expressing cytokines like IL-18 and IFN-g for more profound

Tuberculosis in different phases of clinical trails

Type of Vaccine	Candidate	Description	Clinical trial status
Fusion protein in adjuvant for pre-exposure booster vaccination	Hybrid 1+IC31	Fusion of Ag85B and ESAT-6 in adjuvant IC31	Phase I completed
	Aeras-404:Hyvac4+IC31	Fusion of Ag85B and TB10.4 in adjuvant IC31	Phase I ongoing
	M72AS01 or AS02	Fusion of Rv1196 and Rv0125 in Adjuvant AS01 or AS02	Phase II ongoing
	Hybrid 1+CAF01	Fusion of Ag85B and ESAT-6 in adjuvant CAF01	Phase I ongoing
	Hybrid 56+IC31	Fusion of Ag85B, ESAT-6 and Rv2660c in adjuvant IC31	Phase I ongoing
Recombinant BCG for pre-exposure prime vaccination	rBCG30	rBCG-expressing Ag85B	Phase I completed
	VPM 1002	rBCG-expressing listeriolysin and urease deletion	Phase II ongoing
	Aeras-422	rBCG-expressing listeriolysin	Phase I terminated
Viral-vectors for pre-exposure booster vaccination	AdAg85A	Replication deficient adenovirus 5 expressing Ag85A	Phase I
	Crucell Ad35/Aeras-402	Replication deficient adenovirus 35 expressing Ag85A, Ag85B, TB10.4	Phase II ongoing
	Oxford MVA85A/Aeras-485	Modified vaccinia Ankara expressing Ag85A	Phase II ongoing
Whole bacterial cell vaccine for therapeutic vaccination	M. vacca	Inactivated M. vacca	Phase Ii completed
	RUTI	Detoxified M. tuberculosis in liposomes	Phase II ongoing

Th1 cell polarization[10,11] and deletion of antiapoptotic genes to facilitate cross-priming, introduction of genes encoding dormancy antigens such as the DosR-regulated gene products for postexposure vaccination of latently infected individuals[12], subunit vaccines of fused MTB proteins with novel adjuvants, heterologous vectors such as modified vaccinia Ankara or adenovirus expressing MTB proteins; attenuating MTB by removing virulence genes such as secA. One more way to improve BCG is either by introducing immunodominant *Mtb*-specific antigens that are absent from BCG, such as RD1 locus-encoded antigens (ESAT6, CFP10)[13-17]; or by over-expressing antigens that BCG already expresses by itself (cognates of Ag85 complex), but probably not sufficiently high throughout all phases of infection. Another way to improve BCG is by introducing genetic modifications for superior targeting of essential immune pathways, for example, by enhancing or facilitating cross-priming; and to inhibit its ability to neutralize phagosomal maturation. The second major avenue to develop better TB vaccines relies on the development of subunit vaccines which are non-live, or in the case of viral vectors, non-replicating vaccines, which can be delivered safely into the human host regardless of immune-competence. Researchers are now able to exploit cutting edge technologies in designing the most potent vaccine combination by using the prime BCG vaccine with super BCG (a rBCG vaccine that expresses listeriolysin) followed by booster doses with a super subunit vaccine[18]. This logical approach of boost vaccination by introducing a second vaccine different from BCG at a later time point to use a heterologous prime–boost strategy for prevention of TB is also of high importance.

A booster dose may be used for two purposes, to strengthen the immunity of the BCG to prevent primary disease and to strengthen the immunity in individuals with latent infection with M. tuberculosis[19]. These vaccines would contain antigens secreted by metabolically active Mtb as well as dormancy antigens. However the first attempt might be to combine current vaccine candidates to

achieve sterile eradication of the pathogen, i.e., prime with the best BCG replacement vaccine followed by a selection of subunit boosters. Further the tremendous progress in standardizing animal models of MTB infection has allowed complete comparison of genetically manipulated mycobacteria and new TB vaccines across the research centres around the world[20-23].

In the near future with little bit of focus, we may be ready to reap the fruits of the efforts of decades of research in developing one or two vaccines with proven protective efficacy and safety but this by no means signals the end of scientific efforts. In fact, an emerging bottleneck may not be the number of pre-clinical TB vaccine candidates that TB researchers can produce, but rather the number of vaccines that can be Table 2: Most Advanced vaccine candidates against tested clinically in efficacy trials, given the limited clinical trial capacity worldwide, i.e., a shortage that exists not only in Africa but also in Asia. Finally, the identification of TB surrogate end-point biomarkers or "correlates of protection" may drastically reduce the need for the current long-term large-scale clinical trials, and thus will speed up TB vaccine discovery and clinical testing. But this all needs a special focus on the TB research funding and fortunately the European Commission, the National Institutes of Health, and private foundations like the Bill and Melinda Gates Foundation, have instigated several mechanisms to support TB-oriented research and clinical trials [24-25]. Hopefully, the sudden political interest in vaccine development will provide a unique opportunity for the TB research community to come up with a better vaccine candidate against TB for human use in the near future.

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REFERENCES

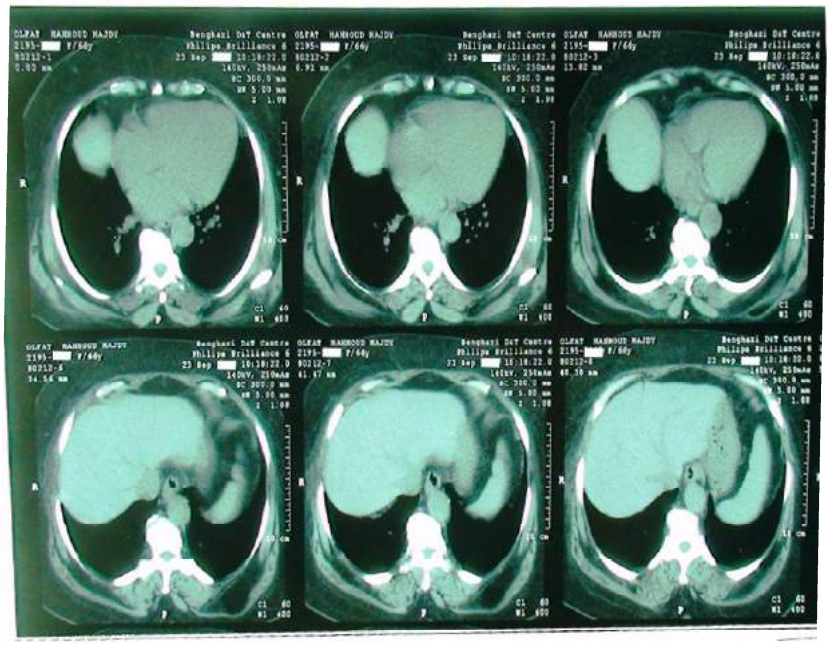
1. World Health Organization. Multidrug and extensively drug –resistant TB (M/XDR-TB): Global Report on Surveillance and Response, Geneva, Switzerland, 2010.
2. Stop TB Partnership. The Global Plan to Stop TB 2006–2015. WHO Press, Geneva, Switzerland 2006.
3. Announcement of the national tuberculosis prevention and control plan (2001–2010). State Council of the People's Republic of China, General Office: Beijing, China,. Document No. 75, 2001.
4. Ali Akbar Velayati, Parissa Farnia, Mohammad Reza Masjedi Recurrence after treatment success in pulmonary multidrug-resistant tuberculosis: predication by continual PCR positivity Int J Clin Exp Med 2012; 5(3):271-272.
5. Gandhi NR, Nunn P, Dheda K, Multidrug resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. Lancet 2010; 375: 1830–1843.
6. Velayati AA, Masjedi MR, Farnia P, Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. Chest 2009;136:420-425.
7. Velayati AA, Farnia P, Merza MA, Zhavnerko GK, New insight into extremely drug-resistant tuberculosis: using atomic force microscopy. Eur Respir J 2010; 36:1490-1493.
8. Ottenhoff TH Overcoming the global crisis: ''yes, we can'', but also for TB? Eur J Immunol 2009; 39: 2014–2020.
9. Kaufmann SH, Hussey G, Lambert PH New vaccines for tuberculosis. Lancet 2010; 375: 2110–2119.

10. Cooper AM Cell-mediated immune responses in tuberculosis. Annu Rev Immunol 2009; 27: 393–422.
11. Sutherland JS, Adetifa IM, Hill PC, Pattern and diversity of cytokine production differentiates between Mycobacterium tuberculosis infection and disease. Eur J Immunol 2009; 39: 723–729.
12. Kursar M, Koch M, Mittrucker HW, Cutting Edge: Regulatory T cells prevent efficient clearance of Mycobacterium tuberculosis. J Immunol 2007; 178: 2661–2665.
13. Pym AS, Brodin P, Majlessi L, Recombinant BCG exporting ESAT-6 confers enhanced protection against tuberculosis. Nat Med 2003;9: 533–539.
14. Ottenhoff TH, Doherty TM, van Dissel JT, First in humans: a new molecularly defined vaccine shows excellent safety and strong induction of long-lived Mycobacterium tuberculosis-specific Th1-cell like responses. Hum Vaccin 2010; 6: 1007–1015.
15. Shen HB, Wang C, Yang EZ , Novel recombinant BCG coexpressing Ag85B, ESAT-6 and mouse TNF-alpha induces significantly enhanced cellular immune and antibody responses in C57BL/6 mice. Microbiol Immunol 2010 ; 54: 435–441.
16. Ottenhoff TH, Doherty TM, van Dissel JT, First in humans: a new molecularly defined vaccine shows excellent safety and strong induction of long-lived Mycobacterium tuberculosis-specific Th1-cell like responses. Hum Vaccin 2010; 6: 1007–1015.
17. Shi CH, Wang XW, Zhang H. Immune responses and protective efficacy of the gene vaccine expressing Ag85B and ESAT6 fusion protein from Mycobacterium tuberculosis. DNA Cell Biol 2008; 27: 199–207.
18. Wu J, Ma H, Qu Q Incorporation of immunostimulatory motifs in the transcribed region of a plasmid DNA vaccine enhances Th1 immune responses and therapeutic effect against Mycobacterium tuberculosis in mice. Vaccine 2011; 29: 7624–7630
19. Tchilian EZ, Ronan EO, de Lara C, Simultaneous immunization against tuberculosis. PLoS ONE 2011; 6: e27477.
20. Skeiky, Y.A. Differential immune responses and protective efficacy induced by components of a tuberculosis polyprotein vaccine, Mtb72F, delivered as naked DNA or recombinant protein. J. Immunol. 2004; 172:7618–7628.
21. Olsen, A.W Protective effect of a tuberculosis subunit vaccine based on a fusion of antigen 85B and ESAT-6 in the aerosol guinea pig model. Infect. Immun 2004; 72:6148–6150.
22. Kaufmann, S.H., Baumann, S., and Nasser Eddine. A Exploiting immunology and molecular genetics for rational vaccine design against tuberculosis. Int. J. Tuberc. Lung Dis 2006;10:1068–1079, 2006
23. Ottenhoff T. H. M and Kaufman S. H. E Vaccines against tuberculosis; where are we and where do we need to go? PLoS Pathog 8(5): e1002607. doi:10.1371/journal/ppat.1002607, 2012.
24. Coakley C, Bhroin E, Buonadonna P. MEPs urge EU to fight tuberculosis worldwide. European Parliament February 3 2011.
25. Kupferschmidt K Infectious disease. Taking a new shot at a TB vaccine. Science 2011; 334: 1488–1490. doi:10.1371/journal.pone.0027477.

Medical Quiz

[1*]Wahengbam PS Al-Waheed

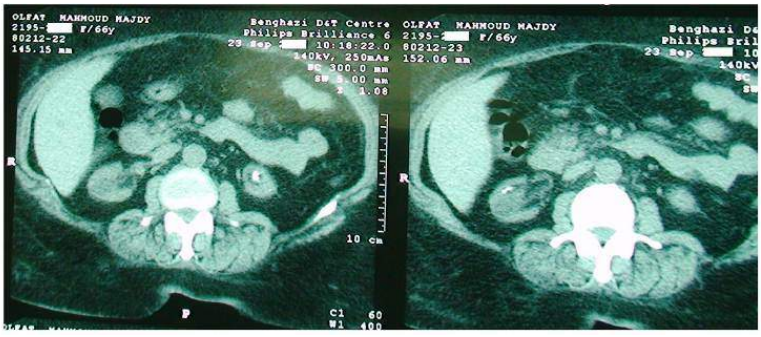
Case Summary: Olfat Mahmoud Magdy is 66 years old female resident from Benghazi, Libya was a known case of Diabetes Mellitus with End Stage Renal Disease(ESRD) on Dependant Haemodialysis. The whole Episodes were noticed after her last child birth at the age of 41 years with the detection of Diabetes and later landed into Renal Failure. She was some of the survival patients in such a prolong period of maintenance Haemodialysis.



The sequence of her disease is with a fluctuating renal profile parameters and repeated anemia and infection of hepatitis B and hepatitis C during the course of disease and later sero-conversion takes placed. She is non-reactive now when last detected six months ago. She is carried with Maintenance Haemodialysis three times a week and has an uneventful life.

She had repeated hospitalization due to rising renal profile of Serum Creatinine, Serum Potassium and ECG changes with associated symptoms of breathlessness and chest pain. Quite often she was required to admit with this problem in Emergency and managed with Emergency Haemodialysis.

On the line of further management she was re-investigated including blood, color echo cardiography, Immunoserolgy and MRI, the parameters are suitable for renal transplant, however due to non-availability of donor, Maintenance Haemodialysis is continuing.



The final clinical Impression is LVH (Left Ventricular Hypertrophy) with DC (Dilated Cardiomyopathy) with CRD (Chronic Renal diseases) & ESRD (End Stage Renal Disease) with Diabetes and Hypertension.

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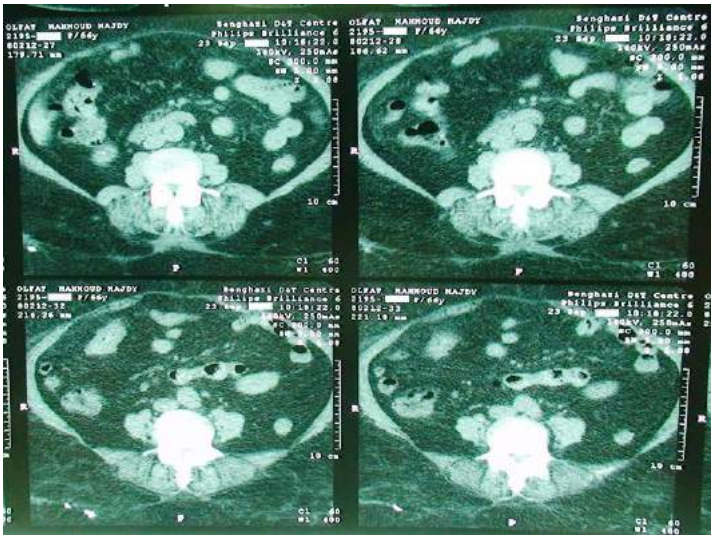
Some interacting questions (Select the one of the best answer)

1. ***What will be the percentage of magnitude of glomerular tubular balance?***
   a) Less than 10%.
   b) Loss upto 100%.
   c) More than loss of 50%.
   d) No loss.
2. ***What will be the indication and modalities treatment?***
   a) CAVH (continuous arterio-venous haemofiltration).
   b) CAVHD (continuous arterio-venous haemodialysis).
   c) CRRT (continuous renal replacement therapies).
   d) CVVHD (continuous veno-venous haemodialysis).



3. ***What are the outcomes of long term prognosis?***
   a) Renal failure associated with multi organ failure.
   b) Renal failure occurring less than 50% of renal impairments.
   c) Renal failure recovers up to 2%.
   d) Renal failures approximate 50% over 5 years.
4. ***What can be the explanation for LVH (Left Ventricular Hypertrophy) and DC (Dilated Cardiomyopathy) in CRD (Chronic Renal diseases) & ESRD(End Stage Renal Disease)?***
   a) Due to renal fluid overload
   b) Due to low Cardiac Ejection fraction
   c) Due to Obesity and Diabetes
   d) Due to prolong hypertension and ECFV (extracellular fluid volume) expansion.

Answer: 1(c), 2(b), 3(d) & 4(d)

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Jezan, Saudi Arabia

17th March 2013
3rd Annual Bridges Saudi Arabia
Jeddah, Saudi Arabia

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King Saud bin Abdulaziz
University for Health Sciences,
Riyadh, Saudi Arabia

15th April 2013
"2nd Evidence-Based Surgery
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16th April 2013
The 9th International Conference on
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Science, Culture and Clinical
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23rd April 2013
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Riyadh, Saudi Arabia

27th April 2013
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Jeddah, Saudi Arabia

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3 – 5 June, 2013
Hospital Health Middle East
Dubai, UAE

14th September 2013
12th Asian Oceanian Congress
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Riyadh, Saudi Arabia

16th December 2013
7th ASCAAD conference
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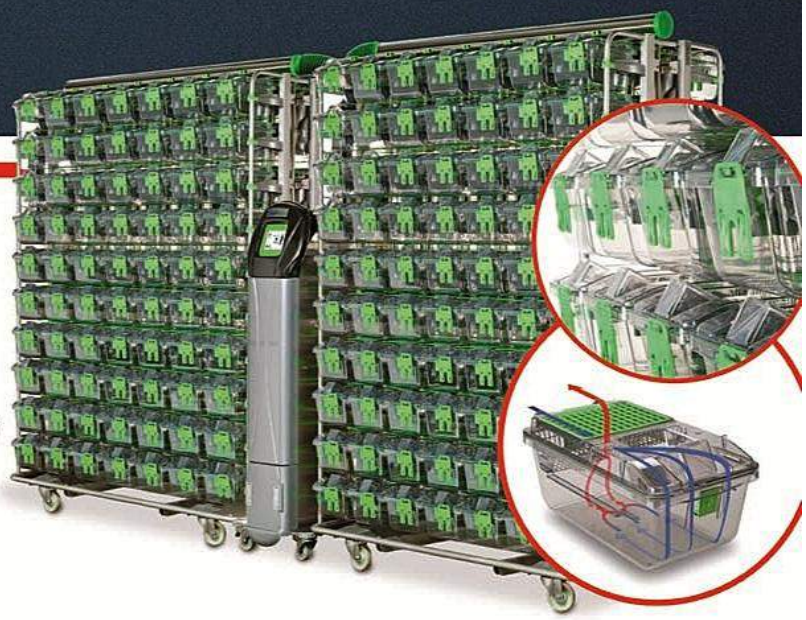

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