

ISSN 1015-0870



January 2017  
Vol. 35, No. 1

# Journal of Bangladesh College of Physicians and Surgeons

Official Journal of  
The Bangladesh College of Physicians and Surgeons

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# Journal of Bangladesh College of Physicians and Surgeons

Vol. 35, No. 1, January 2017

Official Journal of the Bangladesh College of Physicians and Surgeons  
BCPS Bhaban, 67 Shaheed Tajuddin Ahmed Sarani  
Mohakhali, Dhaka-1212, Bangladesh

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## PRINTED AT

Asian Colour Printing  
130 DIT Extension Road  
Fakirerpool, Dhaka-1000

## ANNUAL SUBSCRIPTION

Tk. 400/- for local and US\$ 40 for  
overseas subscribers

The Journal of Bangladesh College of Physicians and Surgeons is a peer reviewed Journal. It is published four times a year, (January, April, July and October). It accepts original articles, review articles, and case reports. Complimentary copies of the journal are sent to libraries of all medical and other relevant academic institutions in the country and selected institutions abroad.

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# Journal of Bangladesh College of Physicians and Surgeons (JBCPS)

## INFORMATION FOR AUTHORS

### MANUSCRIPT PREPARATION AND SUBMISSION

#### Guide to Authors

The Journal of Bangladesh College of Physician and Surgeons, provides rapid publication (quarterly publication) of articles in all areas of the subject. The Journal welcomes the submission of manuscripts that meet the general criteria of significance and scientific excellence.

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**Electronic submission** of manuscripts is strongly encouraged, provided that the text, tables, and figures are included in a single Microsoft Word file (preferably in Arial font).

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A manuscript number will be mailed to the corresponding author within two working days.

The **cover letter** should include the corresponding author's full address and telephone/fax numbers and should be in an e-mail message sent to the editor, with the file, whose name should begin with the first author's surname, as an attachment.

The Journal of Bangladesh College of Physicians and Surgeons will only accept manuscripts submitted as e-mail attachments or triplicate Hard copy with a soft copy

#### Article Types

Five types of manuscripts may be submitted:

**Editorials:** It will be preferably written invited only and usually covers a single topic of contemporary interest.

**Original Articles:** These should describe new and carefully confirmed findings, and experimental procedures should be given in sufficient detail for others to verify the work. The length of a full paper should be the minimum required to describe and interpret the work clearly.

**Short Communications:** A Short Communication is suitable for recording the results of complete small investigations or giving details of new models or hypotheses, innovative methods, techniques, images in clinical practice, letter to editors, short reports or apparatus. The style of main sections need not conform to that of original article. Short communications are 2 to 4 printed pages (about 6 to 12 manuscript pages) in length.

**Reviews:** Submissions of reviews and perspectives covering topics of current interest are welcome and encouraged. Reviews should be concise and no longer than 4 to 6 printed pages (about 12 to 18 manuscript pages). It should be focused and must be up to date. Reviews are also peer-reviewed.

**Case Reports:** This should cover uncommon and/or interesting cases with appropriate confirmation process.

#### Review Process:

All manuscripts are initially screened by editor and sent to selective reviewer. Decisions will be made as

rapidly as possible, and the journal strives to return reviewers' comments to authors within 3 weeks. The editorial board will re-review manuscripts that are accepted pending revision. The JBCPS editorial board will try to publish the manuscript as early as possible fulfilling all the rigorous standard journal needs.

#### **I. A. Preparing a Manuscript for Submission to JBCPS**

Editors and reviewers spend many hours reading manuscripts, and therefore appreciate receiving manuscripts that are easy to read and edit. Much of the information in this journal's Instructions to Authors is designed to accomplish that goal in ways that meet each journal's particular editorial needs. The following information provides guidance in preparing manuscripts for this journal.

#### **Conditions for submission of manuscript:**

- All manuscripts are subject to peer-review.
- Manuscripts are received with the explicit understanding that they are not under simultaneous consideration by any other publication.
- Submission of a manuscript for publication implies the transfer of the copyright from the author to the publisher upon acceptance. Accepted manuscripts become the permanent property of the Journal of Bangladesh College of Physicians and Surgeons and may not be reproduced by any means in whole or in part without the written consent of the publisher.
- It is the author's responsibility to obtain permission to reproduce illustrations, tables etc. from other publications.

#### **Ethical aspects:**

- Ethical aspect of the study will be very carefully considered at the time of assessment of the manuscript.
- Any manuscript that includes table, illustration or photograph that have been published earlier should accompany a letter of permission for re-publication from the author(s) of the publication and editor/publisher of the Journal where it was published earlier.
- Permission of the patients and/or their families to reproduce photographs of the patients where identity is not disguised should be sent with the manuscript. Otherwise the identity will be blackened out.

#### **Preparation of manuscript:**

**Criteria:** Information provided in the manuscript are important and likely to be of interest to an international readership.

#### **Preparation:**

1. Manuscript should be written in English and typed on one side of A4 (290 x 210cm) size white paper.
2. Margin should be 5 cm for the header and 2.5 cm for the remainder.
3. Style should be that of modified Vancouver.
4. Each of the following section should begin on separate page :
  - o Title page
  - o Summary/abstract
  - o Text
  - o Acknowledgement
  - o References
  - o Tables and legends.

Pages should be numbered consecutively at the upper right hand corner of each page beginning with the title page

#### **I. A. 1. a. General Principles**

- The text of observational and experimental articles is usually (but not necessarily) divided into the following sections: Introduction, Methods, Results, and Discussion. This so-called "IMRAD" structure is a direct reflection of the process of scientific discovery.
- Long articles may need subheadings within some sections (especially Results and Discussion) to clarify their content. Other types of articles, such as case reports, reviews, and editorials, probably need to be formatted differently.
- Electronic formats have created opportunities for adding details or whole sections, layering information, crosslinking or extracting portions of articles, and the like only in the electronic version.
- Authors need to work closely with editors in developing or using such new publication formats and should submit supplementary electronic material for peer review.
- Double-spacing all portions of the manuscript—including the title page, abstract, text, acknowledgments, references, individual tables, and

legends—and generous margins make it possible for editors and reviewers to edit the text line by line and add comments and queries directly on the paper copy.

- If manuscripts are submitted electronically, the files should be double-spaced to facilitate printing for reviewing and editing.
- Authors should number on right upper all of the pages of the manuscript consecutively, beginning with the title page, to facilitate the editorial process.

#### **I. A. 1. b. Reporting Guidelines for Specific Study**

##### **Designs**

Research reports frequently omit important information. Reporting guidelines have been developed for a number of study designs that JBCPS journals ask authors to follow. Authors should consult the Information for Authors of this journal. The general requirements listed in the next section relate to reporting essential elements for all study designs. Authors are encouraged also to consult reporting guidelines relevant to their specific research design. A good source of reporting guidelines is the EQUATOR Network (<http://www.equator-network.org/home/>) or CONSORT network (<http://www.consort-statement.org>).

##### **I. A. 2. Title Page**

The title page should have the following information:

1. Article title. Concise titles are easier to read than long, convoluted ones. Titles that are too short may, however, lack important information, such as study design (which is particularly important in identifying type of trials). Authors should include all information in the title that will make electronic retrieval of the article both sensitive and specific.
2. Authors' names and institutional affiliations.
3. The name of the department(s) and institution(s) to which the work should be attributed.
4. Disclaimers, if any.
5. Contact information for corresponding authors. The name, mailing address, telephone and fax numbers, and e-mail address of the author responsible for correspondence about the manuscript.
6. The name and address of the author to whom requests for reprints should be addressed or a Statement that reprints are not available from the authors.

7. Source(s) of support in the form of grants, equipment, drugs, or all of these.
8. A short running head or footline, of no more than 40 characters(including letters and spaces). Running heads are published and also used within the editorial office for filing and locating manuscripts.
9. The number of figures and tables. It is difficult for editorial staff and reviewers to determine whether the figures and tables that should have accompanied a manuscript were actually included unless the numbers of figures and tables are noted on the title page.

##### **I. A. 3. Conflict-of-Interest Notification Page**

To prevent potential conflicts of interest from being overlooked or misplaced, this information needs to be part of the manuscript. The ICMJE has developed a uniform disclosure form for use by ICMJE member journals ([http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf)) and JBCPS has accepted that.

##### **I. A. 4. Abstract**

- Structured abstracts are essential for original research and systematic reviews. structured abstract means introduction, methods, results and conclusion in abstract
- Should be limited to 250 words
- The abstract should provide the introduction of the study and blinded state and should state the study's purpose, basic procedures (selection of study subjects or laboratory animals, observational and analytical methods), main findings (giving specific effect sizes and their statistical significance, if possible), principal conclusions. It should emphasize new and important aspects of the study or observations. Articles on clinical trials should contain abstracts that include the items that the CONSORT group has identified as essential (<http://www.consort-statement.org>).
- Because abstracts are the only substantive portion of the article indexed in many electronic databases, and the only portion many readers read, authors need to be careful that they accurately reflect the content of the article

### **I. A. 5. Introduction**

- Provide a context or background for the study (that is, the nature of the problem and its significance). It should be very specific, identify the specific knowledge in the aspect, reasoning and what the study aim to answer.
- State the specific purpose or research objective of, or hypothesis tested by, the study or observation; the research objective is often more sharply focused when stated as a question.
- Both the main and secondary objectives should be clear.
- Provide only directly pertinent primary references, and do not include data or conclusions from the work being reported.

### **I. A. 6. Methods**

The Methods section should be written in such way that another researcher can replicate the study.

#### **I. A. 6. a. Selection and Description of Participants**

- Describe your selection of the observational or experimental participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria and a description of the source population. Because the relevance of such variables as age and sex to the object of research is not always clear, authors should explain their use when they are included in a study report—for example, authors should explain why only participants of certain ages were included or why women were excluded. The guiding principle should be clarity about how and why a study was done in a particular way. When authors use such variables as race or ethnicity, they should define how they measured these variables and justify their relevance.

#### **I. A. 6. b. Technical Information**

- Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow others to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well-known; describe new or substantially modified methods, give the reasons for using them, and evaluate their limitations. Identify precisely all drugs

and chemicals used, including generic name(s), dose(s), and route(s) of administration.

- Authors submitting review article should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

#### **I. A. 6. c. Statistics**

- Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals).
- Avoid relying solely on statistical hypothesis testing, such as *P* values, which fail to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated).
- Define statistical terms, abbreviations, and most symbols.
- Specify the computer software used.

### **I. A. 7. Results**

- Present results in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Please keep the result the sequence of specific objective selected earlier.
- Do not repeat all the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Extra or supplementary materials and technical detail can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.
- When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them.
- Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables.

- Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.” Where scientifically appropriate, analyses of the data by such variables as age and sex should be included.

#### **I. A. 8. Discussion**

- Emphasize the new and important aspects of the study and the conclusions that follow from them in the context of the totality of the best available evidence.
- Do not repeat in detail data or other information given in the Introduction or the Results section.
- For experimental studies, it is useful to begin the discussion by briefly summarizing the main findings, then explore possible mechanisms or explanations for these findings, compare and contrast the results with other relevant studies, state the limitations of the study, and explore the implications of the findings for future research and for clinical practice.
- Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data. In particular, avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses when warranted, but label them clearly as such.

#### **I. A. 9. References**

##### **I. A. 9. a. General Considerations Related to References**

- Although references to review articles can be an efficient way to guide readers to a body of literature, review articles do not always reflect original work accurately. Readers should therefore be provided with direct references to original research sources whenever possible.
- On the other hand, extensive lists of references to original work of a topic can use excessive space on the printed page. Small numbers of references to key original papers often serve as well as more exhaustive lists, particularly since references can now be added to the electronic version of published papers, and

since electronic literature searching allows readers to retrieve published literature efficiently.

- Avoid using abstracts as references. References to papers accepted but not yet published should be designated as “in press” or “forthcoming”; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication.
- Information from manuscripts submitted but not accepted should be cited in the text as “unpublished observations” with written permission from the source.
- Avoid citing a “personal communication” unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text. For scientific articles, obtain written permission and confirmation of accuracy from the source of a personal communication. Some but not all journals check the accuracy of all reference citations; thus, citation errors sometimes appear in the published version of articles. To minimize such errors, references should be verified using either an electronic bibliographic source, such as PubMed or print copies from original sources.
- Authors are responsible for checking that none of the references cite retracted articles except in the context of referring to the retraction. For articles published in journals indexed in MEDLINE, the ICMJE considers PubMed the authoritative source for information about retractions.

##### **I. A. 9. b. Reference Style and Format**

- References should be numbered consecutively in the order in which they are first mentioned in the text.
- Identify references in text, tables, and legends by Arabic numerals in superscript.
- References cited only in tables or figure legends should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure.

#### **I. A. 10. Tables**

- Tables capture information concisely and display it efficiently.

- Use tables /fig that are relevant to study
- Try to limit the number of tables/figure
- Type or print each table with double-spacing on a separate sheet of paper. Number tables consecutively in the order of their first citation in the text and supply a brief title for each.
- Do not use internal horizontal or vertical lines. Give each column a short or an abbreviated heading. Authors should place explanatory matter in footnotes, not in the heading. Explain all nonstandard abbreviations in footnotes, and use the following symbols, in sequence:  
\*, †, ‡, §, ‖, \*\*, ††, ‡‡, §§, \_\_, ¶¶, etc.
- Identify statistical measures of variations, such as standard deviation and standard error of the mean.
- Be sure that each table is cited in the text. If you use data from another published or unpublished source, obtain permission and acknowledge that source fully.

#### **I. A. 11. Illustrations (Figures)**

- Figures should be either professionally drawn and photographed, or submitted as photographic-quality digital prints. In addition to requiring a version of the figures suitable for printing,  
(for example, JPEG/ GIF)
- Authors should review the images of such files on a computer screen before submitting them to be sure they meet their own quality standards. For x-ray films, scans, and other diagnostic images, as well as pictures of pathology specimens or photomicrographs, send sharp, glossy, black-and-white or color photographic prints, usually 127 \_ 173 mm (5 \_ 7 inches)
- Letters, numbers, and symbols on figures should therefore be clear and consistent throughout, and large enough to remain legible when the figure is reduced for publication.
- Photographs of potentially identifiable people must be accompanied by written permission to use the photograph. Figures should be numbered consecutively according to the order in which they have been cited in the text.
- If a figure has been published previously, acknowledge the original source and submit written permission from the copyright holder to reproduce the figure. Permission is required irrespective of

authorship or publisher except for documents in the public domain.

- For illustrations in color, JBCPS accept coloured illustration but when it seems essential. This Journal publish illustrations in color only if the author pays the additional cost. Authors should consult the journal about requirements for figures submitted in electronic formats.

#### **I. A. 12. Legends for Illustrations (Figures)**

- Type or print out legends for illustrations using double spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations.
- When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs.

#### **I. A. 13. Units of Measurement**

- Measurements of length, height, weight, and volume should be reported in metric units (meter, kilogram, or liter) or their decimal multiples.
- Authors should report laboratory information in both local and International System of Units (SI).
- Drug concentrations may be reported in either SI or mass units, but the alternative should be provided in parentheses where appropriate.

#### **I. A. 14. Abbreviations and Symbols**

- Use only standard abbreviations; use of nonstandard abbreviations can be confusing to readers.
- Avoid abbreviations in the title of the manuscript.
- The spelled-out abbreviation followed by the abbreviation in parenthesis should be used on first mention unless the abbreviation is a standard unit of measurement.

#### **I. B. Sending the Manuscript to the Journal**

- If a paper version of the manuscript is submitted, send the required number of copies of the manuscript and figures; they are all needed for peer review and editing, and the editorial office staff cannot be expected to make the required copies.
- Manuscripts must be accompanied by a cover letter, conflicts of interest form, authorship and declaration, proforma of which is available in JBCPS web site.

**Editing and peer review:** All submitted manuscripts are subject to scrutiny by the Editor in-chief or any member of the Editorial Board. Manuscripts containing materials without sufficient scientific value and of a priority issue, or not fulfilling the requirement for publication may be rejected or it may be sent back to the author(s) for resubmission with necessary modifications to suit one of the submission categories. Manuscripts fulfilling the requirements and found suitable for consideration are sent for peer review. Submissions, found suitable for publication by the reviewer, may need revision/modifications before being finally accepted. Editorial Board finally decides upon the publishability of the reviewed and revised/modified submission. Proof of accepted manuscript may be sent to the authors, and should be corrected and returned to the editorial office within one week. No addition to the manuscript at this stage will be accepted. All accepted manuscripts are edited according to the Journal's style.

### Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

### Check Lists

Final checklists before you submit your revised article for the possible publication in the Journal of Bangladesh College of Physicians and Surgeons:

1. Forwarding/Cover letter and declaration form
2. Authorship and conflicts of interest form
3. Manuscript
  - o Sample of the above documents is available in the following links: <http://www.bcpsbd.org> (registration required for download)
  - o If you have submitted mention document (1, 2, 3 ) above, when you first submitted your article then you don't need to re-submit but if there is change in the authorship or related then you have to re-submit it.
- General outline for article presentation and format
  - Δ Double spacing
  - Δ Font size should be 12 in arial
  - Δ Margins 5 cm from above and 2.5 cm from rest sides.

- Δ Title page contains all the desired information (vide supra)
- Δ Running title provided (not more than 40 characters)
- Δ Headings in title case (not ALL CAPITALS, not underlined)
- Δ References cited in superscript in the text without brackets after with/without comma (,) or full stop (.)
- Δ References according to the journal's instructions – abide by the rules of Vancouver system. Use this link to get into the detail of Vancouver system.

- **Language and grammar**

- Δ Uniformity in the language
- Δ Abbreviations spelt out in full for the first time
- Δ Numerals from 1 to 10 spelt out
- Δ Numerals at the beginning of the sentence spelt out

- **Tables and figures**

- Δ No repetition of data in tables/graphs and in text
- Δ Actual numbers from which graphs drawn, provided
- Δ Figures necessary and of good quality (colour)
- Δ Table and figure numbers in Arabic letters (not Roman)
- Δ Labels pasted on back of the photographs (no names written)
- Δ Figure legends provided (not more than 40 words)
- Δ Patients' privacy maintained (if not, written permission enclosed)
- Δ Credit note for borrowed figures/tables provided
- Δ Each table/figure in separate page

If you have any specific queries please use at [www.bcps.com](http://www.bcps.com)

### Manuscript Format for Research Article

- **Title**

- Δ Complete title of your article
- Δ Complete author information
- Δ Mention conflict of interest if any

- **Abstract**
  - Δ Do not use subheadings in the abstract
  - Δ Give full title of the manuscript in the Abstract page
  - Δ Not more than 200 words for case reports and 250 words for original articles
  - Δ Structured abstract (Including introduction, methods, results and discussion, conclusion) provided for an original article and (Introduction, results and discussion , conclusion) for case reports.
  - Δ Key words provided – arrange them in alphabetical order (three – five )
- **Introduction**
  - Δ Word limit 150 -200 words
  - Δ Pertinent information only
- **Material and Methods**
  - Δ Study Design
  - Δ Duration and place of study
  - Δ Ethical approval
  - Δ Patient consent
  - Δ Statistical analysis and software used.
- **Result**
  - Δ Clearly present the data
  - Δ Avoid data redundancy
  - Δ Use table information at the end of the sentence before full stop between the small bracket
- **Discussion**
  - Δ Avoid unnecessary explanation of someone else work unless it is very relevant to the study
  - Δ Provide and discuss with the literatures to support the study
  - Δ Mention about limitation of your study
- **Conclusion**
  - Δ Give your conclusion
  - Δ Any recommendation
- **Acknowledgement**
  - Δ Acknowledge any person or institute who have helped for the study
- **Reference**
  - Δ Abide by the Vancouver style
  - Δ Use reference at the end of the sentence after the full stop with superscript
- **Legends**
  - Δ Table
  - Δ Figures

*Journal of Bangladesh College of Physicians and Surgeons* ISSN: 1015-0870

Indexed on HINARI, EMSCO, DOAJ, Index Copernicus, Ulrichs Web, Google Scholar, CrossRef, ProQuest, Scientific Common.

BanglaJOL is supported by IN

# JOURNAL OF BANGLADESH COLLEGE OF PHYSICIANS AND SURGEONS

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January 2017

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# Treatment of Hypertension in Adults Above the Age of 60

Treating hypertension is a day to day duty of any physician. But when it comes to treat hypertension in elderly patients, especially above the age of 60, achieving the target BP becomes difficult. Because of multiple co-morbidities and use of concomitant different kind of medications, very often, a single anti-hypertensive agent often fails to achieve the goal. Joint National Committee (JNC) publishes the guideline for hypertension management for several years and the latest one in JNC 8. In that also, the difficulty of treating hypertension in elderly patients have been mentioned.

In this editorial, we intend to focus on the latest updates as well as the modified target BP for elderly patients. — The American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) have published an evidence-based clinical practice guideline on the appropriate systolic blood pressure target for adults 60 years old and older with hypertension very recently<sup>1</sup>.

Hypertension, an elevation of systemic arterial blood pressure, is one of the most common chronic diseases in the United States. About 65 percent of adults in the U.S. over the age of 60 have hypertension, and the disease affects about 29 percent of all adults in the nation. We have no such national data in our country. ACP and AAFP recommend that physicians initiate treatment in adults aged 60 years old and older with persistent systolic blood pressure at or above 150 millimeters of mercury (mm Hg) to achieve a target systolic blood pressure of less than 150 mm Hg to reduce the risk of mortality, stroke, and cardiac events. Most benefits of targeting of less than 150 mm Hg apply to individuals regardless of whether or not they have diabetes. Appropriate management of hypertension reduces the risk for cardiovascular disease, renal disease, cerebrovascular disease, and death. However,

determining the most appropriate BP targets, particularly for adults aged 60 years or older, has been controversial. Debate about the goal for systolic BP (SBP) among adults treated for hypertension has intensified, especially in light of recent recommendations. In addition, when selecting BP targets for adults aged 60 years or older, clinicians need to consider comorbid conditions that could affect treatment choice. Treatments for hypertension include lifestyle modifications, such as weight loss, dietary modification, and increased physical activity, and antihypertensive medications, which commonly include thiazide-type diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), calcium-channel blockers, and  $\beta$ -blockers.

JNC 8 also suggested in patients 60 years or over, start treatment in blood pressures >150 mm Hg systolic or >90 mm Hg diastolic and treat to under those thresholds<sup>2</sup>.

The ACP/AA FP guideline notes that some patients may have falsely elevated readings in clinical settings (“white coat hypertension”). Therefore, it is important for physicians to ensure that they are accurately measuring blood pressure before initiating or changing treatment for hypertension. The most accurate measurements come from multiple blood pressure measurements made over time. These may include multiple measurements in clinical settings or ambulatory or home-monitoring.

### **The guideline emphasize on two recommendations:**

ACP and AAFP recommend that physicians consider initiating or intensifying drug therapy in adults aged 60 years old and older with a history of stroke or transient ischemic attack to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk of recurrent stroke.

ACP and AAFP recommend that physicians consider initiating or intensifying pharmacological treatment in some adults aged 60 years old and older at high cardiovascular risk, based on individualized assessment, to achieve a target systolic blood pressure of less than 140 mm Hg to reduce the risk of stroke or cardiac events.

Increased cardiovascular risk includes all people with known vascular disease and among others, is defined as most patients with diabetes, individuals with chronic kidney disease with estimated glomerular filtration rate (eGFR) <45 mL/min/per 1.73 m<sup>2</sup>, metabolic syndrome (abdominal obesity, hypertension, diabetes, and dyslipidemia), and older age.

Whatever the guidelines describe every patient has separate merit in elderly as because of their co morbid

conditions. A physician should weigh the risk versus benefit in all case management of treating hypertensive patients.

*(J Bangladesh Coll Phys Surg 2017; 35: 1-2)*

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2. JNC 8 Guidelines for the Management of Hypertension in Adults. *Am Fam Physician*. 2014 Oct 1;90(7):503-504

## Effect of Low Dose Oral Contraceptive Pill on Coagulation Status in Women with Normal and Low Body Mass Index

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### Summary:

**Background:** Oral contraceptive pill (OCP) is widely used by millions of women of various socioeconomic conditions. Use of low dose oestrogen and newer progesterone in OCP now associated with less thromboembolic and cardiovascular risk. The safety aspects of these pills had not been investigated in details in malnourished women of developing countries. In the present study the effects of the pill on coagulation status have been studied.

**Objective:** To explore the effect of the most widely used low dose OCP (Shukhi) on coagulation status of Bangladeshi women with normal and low BMI (Body Mass Index).

**Materials and Methods:** The study population group (n=29) comprised of women with normal BMI and the underweight group (n=11, BMI<18.5). Both groups use low dose OCP (30µg ethinyl estradiol and 150µg levonorgestrel) for 6-60 months.

The coagulation status were assessed as follows: Plasma Fibrinogen, Prothrombin time and Platelet aggregation and Anticoagulation status eg: Antithrombin III (ATIII).

**Result:** Coagulation status showed no significant difference in platelet aggregation between the groups. Plasma fibrinogen

median value (450mg/dl) just exceeded the upper limit of reference range (normal range: 200-400mg/dl) in normal BMI. In contrast, the corresponding value in the low BMI (318mg/dl) group was almost at the middle of the reference range. A significantly prolonged prothrombin time (13.80 seconds) was found in the low BMI group (p=0.058); values were still within the reference range (10-14 seconds). No significant correlation existed between plasma fibrinogen, prothrombin time and platelet aggregation in normal BMI or low BMI groups. Antithrombin III activity in normal BMI group was 108% and in low BMI group it was 105%. A tendency of positive correlation existed between antithrombin III activity and BMI in low BMI pill users (r=0.591, p=0.072).

**Conclusion:** The study suggested that a) Reported risk of procoagulant or thromboembolic changes in pill users is lower in low BMI & normal BMI and b) Low BMI users showed significantly longer prothrombin time due to the effect of malnutrition itself or due to the effect of pills in this nutritional background.

**Keywords:** Low dose OCP, Coagulation status, Normal and low BMI women.

(J Bangladesh Coll Phys Surg 2017; 35: 3-8)

### Introduction:

OCP (combined) are very important component of family planning program. It is one of the effective methods of

contraception and is well accepted by women of various socioeconomic conditions. Millions of women use these drugs. So questions regarding the safety of these agents are important.

A number of side effects were encountered by the users. These included nausea, vomiting, dizziness, metabolic disorders such as hypertension, diabetes and thromboembolic manifestations in the form of pulmonary embolism, leg vein thrombosis, coronary thrombosis and thus the estrogen component of the OCP was initially implicated in the pill-induced thromboembolic side effects<sup>1,2</sup>. But later it was shown that the gestagen component too played a vital role in enhancing cardiovascular side effects<sup>3,4</sup>. The introduction of low dose OCP with 30µg estrogens was a step in the right direction but further reduction resulted in breakthrough bleeding<sup>5</sup>.

The Dunlop committee for the safety of drugs in UK issued a declaration linking the estrogenic component

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**Received:** 6 May 2015

**Accepted:** 21 Sept. 2016

of the pill with the risk of venous thrombosis. Consequently the doses of estrogen in the pill were reduced again and again until affecting contraceptive efficacy. As a result, the risks which were attributed to high estrogen content such as venous thrombosis, hypertension, diabetes etc were reduced. This was confirmed by the Royal College of general practitioners and the Walnut Creek Contraceptive drug study<sup>6</sup>.

However, such low doses was possible primarily because highly effective and more specific progestogen such as levonorgestrel, desogestrel, gestadene, norgestimate etc were developed and introduced. The development of Levonorgestrel and third generation progestogens were potentially responsible for reducing severe cardiovascular side effects<sup>7</sup>.

Several retrospective and prospective studies have suggested the existence of an increased risk of cardiovascular diseases, in particular venous thromboembolism, pulmonary embolism, myocardial infarction (MI) and hemorrhagic stroke in users of OCP a risk possibly related to the dose of estrogen<sup>8,9,10</sup>. It has been suggested that adhesiveness of blood platelets to a glass surface was greater in women than in man in the presence of a histone like substance derived from human brain, the adhesiveness of platelets were increased in woman because of OCP therapy<sup>11</sup>.

A comparison of Japanese and American women using OCP, concluded that the effect on the fibrinolytic system were considerably better among the Japanese women than among the Americans, indicating a decreased risk of cerebral thrombosis in Japanese women<sup>12</sup>.

Antithrombin III (AT III) activity fell significantly during OCP use and the estrogen component was blamed for the fall<sup>13,14</sup>. Low serum ATIII activity was observed in patients with pulmonary embolism, MI and venous thrombosis. The use of low estrogen pill resulted in a significant reduction in the number of thromboembolic episodes and the reduction was found to be limited in venous thromboembolism<sup>15</sup>.

Effect of OCP on Caucasian woman was studied and observed acceleration of the procoagulants in extrinsic and intrinsic clotting systems and reduction of the plasma AT III levels, indicating some imbalance of the hemostatic mechanism towards hypercoagulability. These changes increased with the duration of therapy and took some months to resolve when OCP were

withdrawn. OCP should be avoided by woman with established cardiovascular disease or with cardiovascular risk factors, irrespective of age<sup>16</sup>. They further suggested that OCP appear to unsuitable method of contraception even for healthy and nonsmoker women over 40 years of age.

A large number of Bangladeshi women of various socioeconomic status are using low dose OCP. There are different types of combined low dose OCP used by the Bangladeshi women eg: Shukhi<sup>(R)</sup>, Femicon<sup>(R)</sup>, Nordette-28<sup>(R)</sup> and Marvelon<sup>(R)</sup>. All these OCPs contain 30µg of ethinyl estradiol, but their progestogen component varies.

Shukhi is mostly used by the women of low socioeconomic status, because the family planning program of the government of Bangladesh has made it available to them free of cost. Studies shows that newer combined low dose OCPs cause less upset in metabolic and coagulation parameters as it contains 30µg of ethinyl estradiol (EE)<sup>17,18</sup>. But these need to be confirmed in Bangladeshi population with low BMI as it is well known that diet and life style can affect pill induced changes in hepatic protein synthesis. Safety of OCP has not been studied in low BMI undernourished Bangladeshi women. Due to protein deficiencies in these low BMI groups there may be different biological response in these women resulting in different risk profile.

#### **Materials and Method:**

The study was conducted at the Department of Cell and Molecular Biology, Research Division, Bangladesh Institute of Research and Rehabilitation in Diabetes, endocrine and Metabolic disorders (BIRDEM) during the period of Jan 2001 to Dec 2001. The patients were collected from family planning centre, Dhaka Medical college Hospital (DMCH). A total number of 40 women were included in this study having age range between 25-45 years. 29 were with normal BMI (>18.5) and 11 were with low BMI (<18.5) consuming Shukhi for six months to five years. Patients who were normotensive with no coexisting medical disorders were included. Patients who were hypertensive, diabetic, smoker, alcoholic and obese (BMI >30) were excluded.

Subjects: After taking consent of the patient blood samples were collected and plasma/serum were stored at -70C for biochemical analysis. The coagulation factors were assessed as follows: Coagulation status–

(P Fibrinogen, Prothrombin time and Platelet aggregation) and anticoagulation status –Antithrombin III (ATIII).

Laboratory methods: Plasma fibrinogen was estimated by clotting method; Prothrombin time by using Simplastin Excel; Platelet aggregation by optical aggregometry and Antithrombin III was estimated by amidolytic method using a synthetic chromogenic substrate.

All statistical analysis were done by using SPSS. Results were expressed as median (range). The statistical comparison between the groups were done by Mann-Whitney test. Difference between BMI and other parameters were analysed by Pearson's correlation coefficient test. P value <0.05 was taken as level of significance.

#### Different groups discussed are as follows:

1. Clinical features (Age, BMI, Duration of pill use) of Normal BMI and low BMI study subjects.
2. Coagulation status (eg: Platelet aggregation, Plasma fibrinogen and Prothrombin time) of Normal BMI and low BMI study subjects.
3. Coagulation status among the Normal BMI and low BMI study subjects with the same duration of OCP use (<24 months).
4. Antithrombin III activity of Normal BMI and low BMI study subjects.
5. Pearson correlation coefficient between BMI and coagulation status (Platelet aggregation, Fibrinogen, Prothrombin time) and Antithrombin III.
6. Pearson correlation coefficient between plasma fibrinogen and Antithrombin III in Normal and Low BMI Group.

#### Results:

1. Clinical features of different groups of the study subjects shown in Table I. No significant difference was observed in clinical features of different groups.

2. Coagulation status-Platelet aggregation, Plasma fibrinogen, Prothrombin time of study subjects. There was no statistically significant difference in platelet aggregation ( $p=0.387$ ) and plasma fibrinogen level ( $p=0.332$ ) between the Normal BMI and Low BMI groups studied.

3. There is significant difference in prothrombin time between the two groups ( $p=0.019$ ), and significantly prolonged prothrombin time was noted among the Low BMI pill users (Table-III)

4. Antithrombin III activity of the study subjects. There was no statistically significant difference found in plasma antithrombin III activity between Normal and Low BMI groups ( $p=0.421$ ), showed in table-IV. The AT III activity has found to go up towards the upper limit in both groups of pill users (normal value 88-111%).

5. Pearson correlation coefficient between BMI and coagulation status and ATIII. A significantly positive correlation was found among AT III and Low BMI ( $r=0.591, p=0.072$ ) No significant correlation was found among others with BMI

6. A positive correlation was found between fibrinogen and antithrombin III in normal BMI, which is not maintained in Low BMI

**Table-I**

#### *Clinical features of different groups of study subjects*

Groups	Normal BMI (n=29)	Low BMI (n=11)
Age (years)	28.00 (25-45)	26.00 (25-32)
BMI (kg/m <sup>2</sup> )	23.06 (19.40-30.08)	18.44 (15.04-18.50)
Duration (months)	24.00 (7-60)	12.00 (6-24)

Results are expressed as median (range)

Normal BMI=Subjects with normal BMI

Low BMI=Subjects with low BMI

n=Number of subjects

BMI=Body Mass Index

Duration= Duration of OCP use

**Table-II***Coagulation status of Normal BMI and low BMI study subjects.*

Groups	Normal BMI (n=29)	Low BMI (n=11)	U/p value
Platelet aggregation(%)	20(6.25-71.25)	20(6.25-47.50)	131/0.387
Plasma fibrinogen(mg/dl)	450(165-700)	318(142-788)	127.50/0.332
Prothrombin time(Second)	12.60(10.50-16)	13.80(12.00-16.30)	97.00/0.058

**Table-III***Coagulation status among the Normal BMI and low BMI study subjects with the same duration of OCP use (<24 months).*

Groups	Normal BMI (n=20) use OCP<24 months	Low BMI (n=11) use OCP<24 months	U/p value
Platelet aggregation(%)	21.88(6.25-71.25)	20(6.25-47.50)	88.50/0.373
Plasma fibrinogen(mg/dl)	452(165-700)	318(142-788)	83.50/0.274
Prothrombin time(second)	12.20(11.10-16.00)	13.80(12.00-16.30)	53.50/0.019

**Table-IV***Antithrombin III activity of Normal BMI and low BMI study subjects.*

Groups	Normal BMI (n=29)	Low BMI(n=11)	U/p value
Antithrombin III (%)	108(66-210)	105(76-134)	120.00/0.421

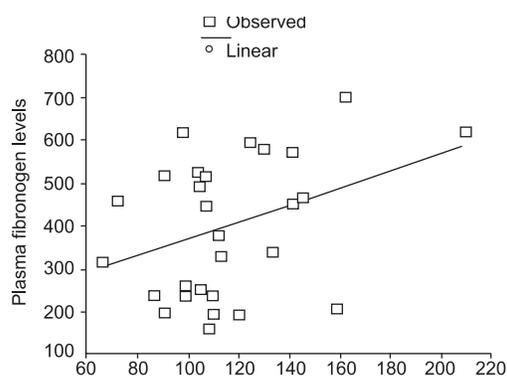
**Table-V***Pearson correlation coefficient between BMI and coagulation status and Antithrombin III.*

Group	Normal BMI		Low BMI	
	r	P	r	P
Pl.agg		.098.614		-.500.117
Fibrinogen	-.033	.867	-.483	.132
PT	.036	.855	.189	.577
AT III	-.033	.865	.591	.072

Pl.agg= Platelet aggregation, PT= Prothrombin time, ATIII=Antithrombin III.

**Table-VI***Pearson correlation coefficient between plasma fibrinogen and Antithrombin III in Normal and Low BMI Group.*

Groups	Normal BMI (n=11)		Low BMI (n=11)	
	r	P	r	P
Fibrinogen/AT III	.355	.059	-.189	.602



Plasma anti-thrombin III of the subjects having normal BMI

**Fig-1:** Person correlation coefficient between plasma fibrinogen and plasma antithrombin III of normal BMI OCP users.

#### Discussion:

Subtle but complex changes occur in coagulation mechanism in women on OCP. Oral contraceptives have been shown to induce more rapid platelet aggregation and adhesion and also to reduce the activity of the fibrinolytic system, which normally breaks down the blood clot. Thus, when clot forms, they may be less likely to dissolve and more likely to reach a size sufficient to block vessels and create a thromboembolic problem. The increased risk of venous thrombosis and pulmonary embolism is probably attributable in some women to the estrogen content of their oral contraceptives. A positive correlation was found by Inman et al in United Kingdom between the risk of thromboembolic disease and the dosage of estrogen contained in OCP, when combined OCP containing high doses (75-100 µg or more) of estrogen, were available at that time were used<sup>19</sup>. The availability of new generation monophasic and multiphasic formulations of OCP containing both low dose of estrogen and new progestogen has virtually changed the previous idea of thrombogenic effect of OCP<sup>20,21</sup>.

The general belief is that OCP intake leads to a high index of suspicion of thromboembolic episodes of pill users. There is limited data available regarding thrombogenic potential of OCP among Bangladeshi users. In this study, the effects of OCP on certain parameters were measured. To see the coagulation status platelet aggregation, plasma fibrinogen, prothrombin

time and antithrombin III activity were measured. There was no significant change in platelet aggregation, plasma fibrinogen and antithrombin III activity in the two groups of OCP users. The prothrombin time in low BMI users was slightly prolonged by 1.6 second in contrast to normal BMI (Table III), which was statistically significant. There may be deficiency in ionized calcium in low BMI OCP users as the study sample are from poor socioeconomic status. The plasma fibrinogen in normal BMI subject has gone up above the upper range as compared to low BMI subject (450mg/dl Vs 318 mg/dl in Normal BMI Vs Low BMI) but the difference is not significant ( $p=0.332$ ). In this study ATIII activity in both groups were gone at the upper limit eg: in normal BMI it is 108% and in low BMI 105% (normal range : 88-111%). It is well known that OCP increases the plasma fibrinogen level. Plasma fibrinogen and AT III activity in Normal BMI subjects has gone above the upper range (450mg/dl and 108% in Plasma fibrinogen and ATIII). A positive correlation found between plasma fibrinogen and AT III in the normal BMI OCP users ( $r=0.355, p=0.059$ ). We can say from the above relationship between plasma fibrinogen and AT III that the rise of plasma fibrinogen is due to pill use and rise in ATIII is a secondary response to plasma fibrinogen to counterbalance the coagulation activity. It may be assumed that after a certain level of BMI increment the plasma fibrinogen will be so high at which the ATIII will not be able to counterbalance with prolong use of OCP. There was no correlation exists between the plasma fibrinogen and AT III of Low BMI OCP users. There is no significant difference in platelet aggregation in normal BMI and low BMI groups. David et al revealed in their study that the platelet count, platelet aggregation ratio were not significantly altered and antithrombin III activity was not reduced among the users of low dose oral contraceptives<sup>20</sup>.

Since prolonged prothrombin time was found within low BMI OCP users and a positive correlation existed between AT III and low BMI subjects. Reasons for such findings may be nutritional or OCP in this nutritional background. So a large extensive and in depth further study with prothrombin time, AT III, serum calcium, total plasma protein and serum albumin are also required to clarify this issue in nutritionally deprived low BMI OCP users.

Finally, the less number of low BMI subject is a limitation of this study. Initially it was thought that number of low

BMI women of child bearing age using OCP will be widely prevalent. During data collection it was found that low BMI women in this age group are not so common as compare to normal BMI. Cause may be gaining of weight and less linear height in this nutritional group. Reasons for gaining of weight of these women might be child bearing ,increasing age or OCP itself. On the otherhand, average height of Bangladeshi women are low in comparison to nutritionally privileged women possibly this is how the normal range of BMI is maintained in women with low socioeconomic background and also the BMI parameter in developing country is different from that of developed country.

### Conclusion:

From the statistical analysis of the results obtained in present study and their comparison data suggested the following:

Low dose OCP do not seem to affect the coagulation status of Low BMI Subjects. The reported risks of procoagulant or thrombogenic changes in pill users seem to be dependent on obesity, in the lower weight playing a protective role. Precautions, however, is necessary for possible bleeding disorders in low BMI users who shows significantly longer prothrombin time due to the effect of malnutrition itself or due to the effect of pills in this nutritional background. Further studies are also required to clarify this issue of prothrombin time. AT III levels are not probably affected in underweight OCP users. It probably changes proportionately with serum fibrinogen in Normal BMI Subjects. But this relationship can not be maintained in Low BMI Subjects.

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## Comparative Study of Nutritional Status of Children (02-24 Months) with Acute Bronchiolitis and Pneumonia

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### Summary:

**Background:** Acute Bronchiolitis and pneumonia pose significant morbidity and mortality of under five children. This outcome is further influenced by poor nutritional status of the affected child because of depressed immunity.

**Objective:** We sought to evaluate nutritional status of children suffering from acute bronchiolitis and pneumonia in Bangladesh.

**Methods:** This cross sectional study was conducted in the Department of Pediatrics of Dhaka Medical College Hospital and Dhaka Shishu Hospital from July, 2010 to June, 2011. A total of 50 patients of pneumonia aged 2-24 months and 50 patients of acute bronchiolitis of same age were enrolled in this study according to case definitions. After enrolment, the patients were thoroughly assessed with particular emphasis on the anthropometric measurements. Weight, length, MUAC and OFC were measured and recorded in a pretested semi structured questionnaire. For each group Z score of weight for age, weight for length, length for age, OFC and MUAC were calculated. Z score +2 to -1 was defined as normal, -1 to -2 z score as mild poor, -2 to -3 z score as moderate poor and <-3 z score was defined as severe poor status. Results were

compared between pneumonia group and bronchiolitis group by using calculated Z value. A calculated Z value more than 1.96 was regarded significant (calculated z value > 1.96 is equivalent to p value < 0.05).

**Results:** Children with pneumonia more often had severe underweight (weight for age <-3 SD) (50% vs. 30%, p=0.04), microcephaly (OFC <-3SD) (30% vs. 12%, p=0.03), and low MUAC (<115 mm) (40% vs. 10%, p=0.03) compared to those with bronchiolitis. Although, there was an increased trend of severe wasting (weight for length <-3 SD) and severe stunting (length for age <-3 SD) in children with pneumonia compared to those with bronchiolitis, the difference was not significant.

**Conclusion:** There thus, the overall nutritional status in children having pneumonia was poor compared to those with bronchiolitis. However, multicenter case control study with larger sample is imperative to consolidate our observation.

**Key Words:** Acute Bronchiolitis, pneumonia, Nutritional Status.

(J Bangladesh Coll Phys Surg 2017; 35: 9-14)

### Introduction:

Acute respiratory tract infection (ARI) accounts for nearly one third of all under five deaths in Bangladesh<sup>1</sup>. Among them, pneumonia is the single largest contributor and accounts for almost 28-34% of all under five deaths globally<sup>2,3</sup>. Acute bronchiolitis, another common respiratory problem, is responsible for hospital admission

of 2-3% of all babies younger than one year of age<sup>1,4</sup>. Poor nutritional status leaves children susceptible to ARI and secondary infection because of impaired cellular immunity<sup>5</sup>. A recent systematic review revealed that death from pneumonia is as high as 15 folds with the co-morbidity of severe malnutrition compared to those without severe malnutrition<sup>6</sup>. Impact of severe malnutrition in children with bronchiolitis is also enormous<sup>7</sup>. However, in Bangladesh the studies evaluating the nutritional status of children suffering from pneumonia as well as bronchiolitis are limited. This study was designed to see the nutritional status of children suffering from pneumonia and bronchiolitis and to compare the results between the two groups. This understanding would encourage the improvement of nutritional status of children as a preventive measure against these two common respiratory problems.

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Received: 22 August 2015

Accepted: 9 Sept. 2016

### Materials and Methods:

Study design, place and period: This observational cross sectional study was carried in Dhaka Medical

College Hospital and Dhaka Shishu Hospital during July 2010 to June 2011.

**Study population:** The study was carried out among the 02-24 months old infants who were admitted in the selected hospitals with acute bronchiolitis and pneumonia.

**Case definitions:**

**(A) Bronchiolitis:** child below 2 years of age with fast breathing, wheeze, coryza and radiological evidence of bronchiolitis e.g hyperinflation of chest. (National ABC guideline, 2005, Asthma association, Bangladesh)

**(B) Pneumonia:** child below 2 years of age with cough, fast breathing, lower chest wall indrawing, fever, coarse crackles on auscultation and radiological evidence of pneumonia like consolidation or perihilar infiltrate (Pocket Book Of Hospital Care For Children: guideline for the management of common illness with limited resources: WHO 2005:71).

In both of the pneumonia and bronchiolitis groups' features of hypoxia like nasal flaring, grunting, head nodding were noted.

**Selection of cases:**

**Inclusion criteria:** Any child from two months to two years of age with meeting the case definition of pneumonia or bronchiolitis irrespective of sex and nutritional status were enrolled in the study.

**Exclusion criteria:** Patients having congenital heart diseases or other congenital anomalies, suffering from chronic illness like TB, thalassemia, malabsorption syndrome were excluded from the study.

**Sample size and sampling:** The samples are selected purposively based on the inclusion and exclusion criteria from Dhaka Medical College Hospital and Dhaka Shishu Hospital during July 2010 to June 2011. A total of 100 cases were selected initially in the pneumonia group. 45 of them were excluded because of having no radiological evidence of pneumonia and five were excluded because of having associated congenital heart diseases. 85 cases were selected in bronchiolitis group but 35 of them were excluded because of having no radiological evidence. Finally 50 patients were enrolled in each group.

**Data collection:** After enrolment, thorough clinical assessment was done using a pretested semi structured questionnaire. As a part of anthropometric measures weight, length, Occipito Frontal Circumference (OFC) and Mid Upper Arm Circumference (MUAC) were noted. Naked weight was measured using an electronic scale

that stands a maximum weight 15 Kg with 100gm precision. The measurement of length was done in infantometer from the top of the head to the heels with the child lying on a wood slab with a fixed piece on one side and a movable one on the other side (top of the head on the fixed part). MUAC and OFC were measured by a measuring tape with a precision of 1 mm. MUAC was measured among children of more than 6 months of age. We measured weight in Kilogram, Length and OFC in Centimeter and MUAC in Millimeter.

**Classification of nutritional status:** To assess the nutritional status z scores of weight for age, weight for length, length for age, MUAC and OFC were calculated. Normal range was defined as +2 to -1 z scores, mild poor status as -1 to -2 z scores, moderate poor status as -2 to -3 z scores and severe poor status as <-3 z score<sup>8,9</sup>.

**Statistical analysis:** Calculated Z values were determined for each group for comparison between pneumonia and bronchiolitis cases. Z values > 1.96 were considered as significant (Z values > 1.96 equivalent to p < 0.05).

**Ethical consideration:** The ethics and research committee of Dhaka Medical College Hospital approved the study and was carried out.

**Results:**

In this study, among the data of 100 cases (50 in pneumonia and 50 in bronchiolitis group) male outnumbered female (58% in pneumonia and 68% in bronchiolitis groups). Children of 2-6 months age group were predominant (Table I). Fever, cough, respiratory distress and chest indrawing were present in 100% patients of pneumonia group. On the other hand, respiratory distress and wheeze were present in 100% patients of bronchiolitis group. Features of hypoxia like flaring of ala nasae, head nodding, grunting and cyanosis were more frequent among the children of pneumonia group than their bronchiolitis counterparts (Table II). Among the pneumonia cases, perihilar infiltrate on the chest x ray was the predominant finding (42%) followed by lobar consolidation (36%) and bilateral patchy opacity (22%). On the other hand hyperinflation (46%) was predominant among the bronchiolitis cases followed by both hyperlucency and hyperinflation (22%) (Table III). Children with microcephaly (OFC < -3SD), severe underweight (weight for age < -3 SD), and MUAC < 115 were significantly more in pneumonia cases than their bronchiolitis counterparts (Table IV). Number of mild to severely wasted and stunted children were also more in pneumonia group than their bronchiolitis counterparts, though the differences were not statistically significant (Table IV).

**Table-I***Age and sex distribution of pneumonia and bronchiolitis patients*

Characteristics	Pneumonia n=50	Bronchiolitis n=50
Age (in months)		
2-6	25 (50%)	31(62%)
6-12	14 (28%)	14 (28%)
12-24	11 (22%)	5 (10%)
Sex		
Male	29 (58%)	34 (68%)
Female	21 (42%)	16 (32%)

**Table-II***Clinical features of pneumonia and bronchiolitis patients.*

Clinical features	Pneumonia=50 (%)	Bronchiolitis=50 (%)
Fever	50 (100)	32 (64)
Cough	50 (100)	42 (84)
Respiratory distress	50 (100)	50 (100)
Chest indrawing	50 (100)	35 (70)
Wheeze	10(20)	50 (100)
Flaring of ala nasae	20 (40)	12 (24)
Head nodding	13 (26)	03 (06)
Grunting	08 (16)	05 (10)
Cyanosis	06 (12)	02 (04)

**Table-III***Radiological features of pneumonia and bronchiolitis patients*

Group of patients	Radiological features	No. of patients (%)
Pneumonia	Perihilar infiltrate	21 (42%)
	Bilateral patchy opacity	11 (22%)
	Lobar consolidation	18 (36%)
Bronchiolitis	Hyperinflation	23 (46%)
	Hyperlucency	9 (18%)
	Both hyperlucency and hyperinflation	11(22%)
	Hyperinflation and streaky density	6 (12%)

**Table-IV***Comparison of anthropometric measures of Pneumonia and Bronchiolitis patients*

Anthropometry	Standard Deviation	Pneumonia n (%)	Bronchiolitis n (%)	Calculated Z value	p
Occipito Frontal Circumference	+2 to -1	06(12%)	06(12%)	0	1.00
	-1 to -2	15 (30%)	23 (46%)	1.67	0.09
	-2 to -3	14 (28%)	15 (30%)	0.22	0.08
	<-3	15 (30%)	06 (12%)	2.26	0.03
Weight/Age(under nutrition)	+2 to -1	06(12%)	09(18%)	0.843	0.4
	-1 to -2	09(18%)	12 (24%)	0.73	0.4
	-2 to -3	10(20%)	14(28%)	0.94	0.3
	<-3	25(50%)	15 (30%)	2.08	0.04
Weight/Length (wasting)	+2 to -1	08 (16%)	16(32%)	1.9	0.06
	-1 to -2	12 (24%)	16(32%)	0.89	0.4
	-2 to -3	15 (30%)	10 (20%)	1.25	0.2
	<-3	15 (30%)	08 (16%)	1.68	0.09
Mid upper arm circumference	≥ 115	15 (60%)	17 (89.8%)	4.14	0.03
	<115	10 (40%)	02 (10.2%)	4.14	0.03
Length/Age(stunting)	+2 to -1	08(16%)	12 (24%)	1.005	0.3
	-1 to -2	20 (40%)	24 (48%)	0.8	0.4
	-2 to -3	12 (24%)	06 (12%)	1.5	0.1
	<-3	10 (20%)	08 (16%)	0.52	0.6

**Discussion:**

The most important observation of this study is the frequent association of microcephaly (OFC<-3SD), severe underweight (weight for age <-3 SD), and MUAC <115 with children having pneumonia compared to the children with bronchiolitis. Although, children with pneumonia proportionately more likely to be wasted and stunted compared to those with bronchiolitis, the difference was not significant and this might be due to small sample.

Common age group of pneumonia and bronchiolitis cases were 2-6 month of age. Several studies showed same findings that the younger age group is more vulnerable to lower respiratory tract infection<sup>10,11</sup>. There is a male predominance in both pneumonia (58%) and bronchiolitis (68%) groups. ARI as a whole affects males more frequently than females throughout the world<sup>12,13</sup>. This may be due to genetic factors or cultural practice of seeking medical care frequently for males than females, considering males more precious<sup>14,15</sup>.

It is known that poor nutrition is one of the causes of microcephaly<sup>16</sup>. In this study under nutrition and wasting is more prevalent in pneumonia group and consistently microcephaly is also significantly more in pneumonia group in comparison to bronchiolitis group (p<0.05).

In a study conducted in Bangladesh to investigate the host risk factors in the outcome of severe pneumonia, the findings were consistent. Similar type of another study conducted on ARI in Bangladesh also had consistent observation<sup>17</sup>. On the other hand, one study on nutritional status of bronchiolitis patient showed that only 7.5% had severe under nutrition, 72% had good nutritional status<sup>18</sup>. And these are almost consistent with the observation of our study population with bronchiolitis.

A number of previous studies were conducted to evaluate the nutritional status of children with pneumonia and bronchiolitis. Most of those studies assessed only one or two components of nutritional

anthropometry. But our study is unique in the context of assessing most of the components of nutritional anthropometry (such as weight for age, weight for length, length for age, OFC and MUAC) of children having pneumonia and bronchiolitis patients of same demographic characteristics. Thus, on the basis of all the evaluated parameters our main observation was that the children with pneumonia more often had poor nutritional status compared to the children having bronchiolitis. The observation is understandable but very important. Children with poor nutritional status are immune-compromised due to depressed cell mediated and humoral immune responses and often more susceptible to severe bacterial infection<sup>19</sup>. Bacterial infection in children more likely to be associated with pneumonia compared to bronchiolitis<sup>20</sup>. Moreover, children with poor nutritional status more likely to be associated with bacterial pneumonia<sup>21,22</sup>. This explains our observation of association of pneumonia with poor nutritional status compared to bronchiolitis.

There were limitations in the study. The study was performed over small sample of children and selected the samples purposively. The selection bias could not be ruled out. But the study included all the children meeting the case definition and inclusion and exclusion criteria. As it was a cross sectional study, the findings did not determine the temporal relationship between the nutritional status and pneumonia and bronchiolitis.

#### Conclusion:

In conclusion, the results of our data suggest that children with low MUAC, severe under nutrition and microcephaly were more prone to have pneumonia compared to bronchiolitis. Overall nutritional status was poor in pneumonia cases in comparison to bronchiolitis cases.

#### Recommendation:

Multicenter case control study with large sample size may be conducted to determine more precise relationship between the nutritional status and pneumonia and bronchiolitis.

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# Impact of Seminal Plasma Zinc and Serum Zinc Level on Semen Parameter of Fertile and Infertile Males

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## Summary:

**Background:** Despite Zinc (Zn) deficiency being prevalent in humans, less emphasis has been given on the understanding of its impact on male reproduction. Spermatogenesis has a strict requirement for zinc. The relationship of seminal plasma zinc level and semen parameter until now is controversial.

**Objective :** The study was done to find out the impact of seminal plasma zinc and serum zinc level on semen parameter of fertile and infertile males.

**Subjects and methods:** The study was done in Center for Assisted Reproduction, a tertiary Infertility center in Dhaka and in the Biochemistry Department of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Sixteen fertile males were taken as control and sixty nine infertile males were taken as cases. Semen analysis was done according to WHO criteria (.2004). Serum zinc and seminal plasma zinc levels were measured in the Biochemistry Department of BSMMU by Graphite Furnace Atomic Absorption Spectrophotometer.

**Result:** Seminal parameters between fertile and infertile men showed significantly high sperm count, sperm motility, rapid linear motility, and morphology in fertile group. In fertile men, serum zinc level was lower than the infertile

group, whereas the seminal plasma zinc level was higher in the fertile than the infertile group which was not statistically significant. In fertile men except for serum zinc, all parameters showed positive relationship; and in infertile men, except sperm morphology, all other parameters showed negative relationship. Seminal plasma zinc shows positive correlation with all semen parameters in fertile group and negative correlation in infertile group except for sperm morphology. There is negative correlation of serum zinc and seminal zinc-in both groups. Regarding other parameters, semen zinc shows positive correlation with all parameter except sperm morphology in fertile men and negative correlation with all parameter except sperm count in infertile men.

**Conclusion:** Seminal zinc levels in fertile men are higher than those in the infertile patients although the serum zinc level is lower. Zinc levels in seminal plasma has a direct relationship with semen parameters. Zinc deficiency may be an important risk factor for low semen parameters and idiopathic male infertility.

**Key words:** Seminal plasma zinc, Semen parameter, Male infertility.

(J Bangladesh Coll Phys Surg 2017; 35: 15-19)

## Introduction:

Zinc is essential for reproduction in human. World Health Organization (WHO) estimates that one-third of world population is deficient in zinc. The geographical regions

most affected are believed to be in descending order of severity, South Asia (in particular, Bangladesh and India), Africa and the Western Pacific<sup>1</sup>. Although there is high prevalence of zinc deficiency in humans, the consequences of zinc deficiency on male reproduction is not well-understood. The Zinc concentration of semen is 87 times than that in the blood and has been reported to protect sperm from bacteria and chromosomes damage<sup>2</sup>. Male fertility is influenced by zinc and plays an important role in normal testicular development, spermatogenesis, and sperm motility<sup>3,4</sup>. The concentration of zinc in human seminal plasma is higher than in other tissues. There are conflicting reports on the role of human seminal plasma zinc on sperm quality. Some authors reported significantly different seminal zinc levels between fertile and subfertile groups, indicating low seminal zinc levels in the subfertile populations,<sup>5,6</sup> while some others have shown that there is no difference between the two groups<sup>7,8</sup>. Low zinc

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levels have a negative effect on serum testosterone concentration and seminal volume<sup>9</sup>. Infertile males have lower levels of seminal plasma zinc, which is associated with reduced levels of zinc in the blood<sup>9</sup>. Zinc in seminal plasma stabilizes the cell membrane and nuclear chromatin of spermatozoa<sup>10, 11</sup>. It may also have an antibacterial function<sup>12</sup> and protect the testes against the degenerative changes<sup>13</sup>. It may play a regulatory role in the process of capacitation and acrosome reaction<sup>14</sup>. Despite the high prevalence of marginal Zn deficiency in humans, less emphasis has been placed on the understanding of its impact on male reproduction. Poor zinc nutrition may be an important risk factor for low quality of sperm and idiopathic male infertility<sup>15</sup>. The study was done to find the impact of seminal plasma zinc and serum zinc levels on semen parameters in fertile and infertile males.

#### Materials and methods:

The study was done in Center for Assisted Reproduction, a Tertiary infertility center in Dhaka, and in the Biochemistry Department of Bangabandhu Sheikh Mujib Medical University, Dhaka. Sixteen fertile males whose wives were pregnant at the time of the assessment were taken as control and sixty nine infertile males whose wives were facing difficulty in conceiving due to poor semen parameters, were taken as cases. Semen analysis was done according to as per World Health Organization guidelines (2004). Serum zinc and seminal plasma zinc levels were measured in the Biochemistry Department of BSMMU by Graphite Furnace Atomic Absorption Spectrophotometer.

#### Results:

In Table I semen parameters and zinc levels of the fertile and infertile males showed mean semen volume to be  $2.46 \pm 1.27$  ml and  $2.47 \pm 1.07$  ml respectively which was statistically not significant. Comparison of other seminal parameters between fertile and infertile group showed significantly positive parameters in fertile group. Total sperm count, total sperm motility, rapid linear motility of sperm and sperm morphology were  $85.00 \pm 32.04$  and  $47.87 \pm 46.45$  million/ml ( $P < 0.01$ );  $81.88 \pm 7.50$  and  $52.39 \pm 23.68\%$  ( $P < 0.001$ );  $69.06 \pm 8.98$  and  $31.45 \pm 20.55\%$  ( $P < 0.001$ ); and  $52.50 \pm 4.47$  and  $25.00 \pm 11.97\%$  ( $P < 0.001$ ) respectively among the fertile (control) and infertile (case) group. Comparison of serum zinc and semen zinc between control and case showed no significant difference in serum zinc  $68.39 \pm 14.37$  and  $75.83 \pm 17.41$  ig/dl ( $P = 0.116$ ); and semen plasma zinc  $6,175.44 \pm 2,569.52$  and  $5,851.46 \pm 2,076.11$  ig/dl ( $P = 0.593$ ) respectively.

Table II shows correlation coefficient (r) of seminal plasma zinc concentration with semen parameters. In fertile group, all parameters showed positive relationship; and in infertile, except sperm morphology, all other parameters showed negative relationship. In fertile group, only semen motility showed statistically significant relationship ( $r = +0.504$ ,  $P < 0.05$ ); but none in infertile group.

Table III shows correlation coefficient (r) of serum zinc concentration with semen parameters. In control, except semen morphology and semen zinc, all parameters

Table-I

*Semen parameters and Zinc levels in fertile and infertile males*

Parameters ( $\mu\text{g/dl}$ ) Mean $\pm$ SD	Control (n=16) Mean $\pm$ SD	Case (n=69)	P value
Semen volume (ml)	$2.46 \pm 1.27$	$2.47 \pm 1.07$	0.978 <sup>ns</sup>
Total sperm count (million/ml)	$85.00 \pm 32.04$	$47.87 \pm 46.45$	0.003 <sup>**</sup>
Sperm motility (%)	$81.88 \pm 7.50$	$52.39 \pm 23.68$	0.0001 <sup>***</sup>
Rapid linearity (%)	$69.06 \pm 8.98$	$31.45 \pm 20.55$	0.0001 <sup>***</sup>
Morphology (%)	$52.50 \pm 4.47$	$25.00 \pm 11.97$	0.0001 <sup>***</sup>
Serum zinc (ig/dl)	$68.39 \pm 14.37$	$75.83 \pm 17.41$	0.116 <sup>ns</sup>
Seminal P zinc ( $\mu\text{g/dl}$ )	$6175.44 \pm 2569.52$	$5851.46 \pm 2076.11$	0.593 <sup>ns</sup>

Unpaired Student's 't' test, ns = Not significant, \*\* = Significant ( $P < 0.01$ ), \*\*\* = Significant ( $P < 0.001$ )

**Table-II***Correlation coefficient (r) of seminal plasma zinc concentration with semen parameters*

Parameters	infertile (n=69)			
	r value	P value	r value	P value
Volume (ml)	+0.384	0.142 <sup>ns</sup>	0.164	0.179 <sup>ns</sup>
Total sperm count (million/ml)	+0.080	0.768 <sup>ns</sup>	0.222	0.067 <sup>ns</sup>
Motility (%)	+0.504	0.047*	0.076	0.536 <sup>ns</sup>
Rapid linearity (%)	+0.426	0.100 <sup>ns</sup>	0.048	0.698 <sup>ns</sup>
Morphology (%)	+0.298	0.262 <sup>ns</sup>	+0.156	0.202 <sup>ns</sup>

Pearson correlation coefficient test, ns = Not significant, \* = Significant (P&lt;0.05)

**Table-III***Correlation coefficient (r) of serum zinc concentration with semen parameters*

Parameters	Case (n=69)			
	r value	P value	r value	P value
Volume (ml)	+0.130	0.631 <sup>ns</sup>	0.086	0.481 <sup>ns</sup>
Total sperm count (million/ml)	+0.079	0.770 <sup>ns</sup>	+0.086	0.481 <sup>ns</sup>
Motility (%)	+0.337	0.201 <sup>ns</sup>	0.002	0.988 <sup>ns</sup>
Rapid linearity (%)	+0.508	0.045*	0.065	0.595 <sup>ns</sup>
Morphology (%)	0.368	0.161 <sup>ns</sup>	0.220	0.069 <sup>ns</sup>
Semen zinc (ig/dl)	0.019	0.945 <sup>ns</sup>	0.112	0.360 <sup>ns</sup>

Pearson correlation coefficient test, ns = Not significant, \* = Significant (P&lt;0.05)

showed positive relationship; and in case, except semen total sperm count, all other parameters showed negative relationship. In control, only semen rapid linearity showed statistically significant relationship ( $r = +0.508$ ,  $P < 0.05$ ); none of the parameters showed significant relationship in case group.

**Discussion:**

About 6 decades ago, zinc was recognized as an essential micronutrient for human health by Dr. Ananda Prasad, a nutrition chemist at Wayne State University in Detroit, Michigan<sup>16</sup>. The human body contains approximately 2 g zinc in total. Daily requirement of zinc is 10 mg Zn per day for adult women and 12 mg Zn per day for adult men. World Health Organization estimates that zinc deficiency affects one-third of the world's population (about two billion people) with the prevalence rates ranging from 4 to 73% in various regions<sup>17</sup>. In 1990

lower levels of zinc were noticed in infertile patient by Kvist et al<sup>18</sup> which was similar in our study.

Some studies indicated that there is no significant difference between Zinc content in fertile and infertile men<sup>19-22</sup>. Although in our study serum zinc and seminal zinc was low between fertile and infertile group also did not show any significant difference, serum zinc  $68.39 \pm 14.37$  and  $75.83 \pm 17.41$  ig/dl ( $P = 0.116$ ); and semen zinc  $6,175.44 \pm 2,569.52$  and  $5,851.46 \pm 2,076.11$  ig/dl ( $P = 0.593$ ), but some studies found a significant difference between them<sup>23-26</sup>. In our study, fertile subjects had higher levels of zinc in their seminal plasma than infertile group which was in concurrence with the study of Colagar<sup>15</sup>.

Comparison of other seminal parameters between fertile and infertile group showed significantly positive parameters in fertile group with statistically significant

increase in total sperm count, total sperm motility, rapid linear motility of sperm and sperm morphology among the fertile(control) and infertile(case) group. Similar findings have reported in previous studies by different authors. High concentration of zinc to be associated with enhanced sperm parameters, including sperm count, motility<sup>23-25,27</sup>, and normal morphology<sup>25, 28</sup>, Zhao et al<sup>26</sup> observed a positive relationship between poor production of sperm and poor sperm motility with a lower content of Zn in the seminal plasma of infertile subjects which is in concurrence with our study. In a study done in 1983 Stanwell found a significant positive relationship between sperm density and seminal plasma zinc concentration in the fertile, but not in the infertile men<sup>29</sup>. Wong *et al.*<sup>19</sup> reported increased proportion of spermatozoa with progressive motility after oral zinc supplementation. Steven *et al.*<sup>30</sup> in his study observed a negative correlation between seminal zinc content and sperm head defect. In the present study it was observed that there is positive but not significant correlations between zinc content of seminal plasma and motility, total count and sperm concentration. In contrast to our study Wong *et al.*<sup>4</sup>, demonstrated that zinc content in fertile men were not different from those of infertile men. Abou-Shakra *et al.*<sup>31</sup>, reported that zinc content in men grouped by sperm concentration was not different from each other.

#### Conclusion:

Zinc may contribute to fertility through its significant effects on various semen parameters. It seems that the estimation of seminal plasma zinc may help in investigation and treatment of infertile males. Seminal zinc may contribute to fertility through its effect on various semen parameters. Seminal zinc level in fertile men is higher than the infertile patients although the serum zinc level is lower. Zinc levels in seminal plasma has a direct relationship with semen parameters. Zinc deficiency may be an important risk factor for low quality of sperm and idiopathic male infertility.

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# Acute Kidney Injury in Sick Neonate: Incidence and Outcome

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## Summary:

**Introduction:** Acute kidney injury (AKI) is an important clinical problem in sick neonate. In most patients, AKI accompanies with a predisposing factor such as sepsis, asphyxia and surgery. The aims of this study were to determine the incidence, associated contributing factors and short term outcome of AKI in hospitalized newborn infants.

**Materials and Methods:** This prospective cohort study was done in Dhaka Shishu Hospital from March 2011 to September 2011. This study included 300 sick neonates admitted during the study period. AKI was defined when serum creatinine level >1.5 mg/dl and BUN was >20 mg/dl on two separate occasions at 24 hours apart. Oliguria was defined as urine output <1ml/kg/ hr. Medical records of those patients were reviewed and data were analyzed using SPSS software.

**Results:** Fourteen babies (4.66%) out of 300 sick neonates had AKI, of whom 64.2% were male and 35.7% female. The

term and preterm neonates were 71% and 29% respectively. While a normal birth weight was observed in 57% cases, 35% had low birth weight and 7.14% had very low birth weight. Sepsis was the most common (71%) association of AKI, followed by perinatal asphyxia (52%). All patients had more than one predisposing factors. Frequency of oliguric kidney injury was 57% and non-oliguric was 43%. Mortality among the hospitalized neonate with AKI was 21%.

**Conclusion:** This study showed that in a tertiary care hospital AKI is not uncommon (4.66%) in neonatal care unit. It is associated with some preventable conditions such as sepsis, perinatal asphyxia and shock. Outcome is poor in sick neonates with AKI (21% mortality) in comparison to sick neonates without AKI (10.3%).

**Key words:** Acute Kidney Injury, Sick neonate.

(J Bangladesh Coll Phys Surg 2017; 35: 20-23)

## Introduction:

Acute kidney injury (AKI) is a common problem among sick newborns.<sup>1,2</sup> The sick newborns are those who are admitted in a hospital for any morbidities like perinatal asphyxia (PNA), septicemia, necrotizing enterocolitis (NEC), shock, heart failure, respiratory distress syndrome etc. Any critical illness in neonate leads to multiorgan dysfunction and the kidney is one of the organs frequently afflicted.<sup>3,4</sup> AKI previously called acute renal failure is characterized by a reversible

increase in the blood concentration of creatinine and nitrogenous waste products and by the inability of the kidney to regulate fluid and electrolyte homeostasis appropriately.<sup>5,6</sup> It is diagnosed on the basis of clinical history such as decreased urine production (Oliguria), and laboratory findings such as elevated blood urea nitrogen and creatinine. Although non-oliguric neonatal kidney injury is being detected with increasing frequency.<sup>1,7</sup>

Study done by Stapleton FB et al.<sup>1</sup>, Gharehbaghi MM<sup>8</sup>, Airede A et al.<sup>9</sup> and Andreoli SP<sup>10</sup> found that the incidence of acute kidney injury was 3% to 8% in sick neonate. A wide variety of predisposing factors such as asphyxia (40%), sepsis (22%), feeding problems (18%), heart failure, prematurity and urogenital anomalies are commonly reported causes of AKI in the developed countries.<sup>2,11</sup> Studies done in India showed that AKI was the common sequel of sepsis in neonatal care unit.<sup>3,12</sup>

Mortality among hospitalized neonate due to kidney injury was 20-50% and patient with sepsis had significantly higher rate.<sup>8,13</sup> In Bangladesh, neonatal mortality rate is still high which is more than two third

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**Received:** 10 Oct. 2015

**Accepted:** 17 Nov. 2015

of infant mortality rate<sup>14</sup> The major causes of death in hospitalized neonates are preterm low birth weight and related consequences, asphyxia, infection, trauma etc.<sup>15</sup> To the best of our knowledge, a few studies have been conducted on assessment of renal function in perinatal asphyxia and preterm neonates in Bangladesh.<sup>16</sup> But it seems to be essential for early detection of AKI for planning appropriate fluid and electrolyte therapy and thereby for improved outcome. This study was conducted to see the incidence, predisposing factors of acute kidney injury in sick neonate and their outcome.

### Materials and methods:

This prospective cohort study was conducted in Neonatology unit of Dhaka Shishu Hospital from March 2011 to august 2011. During the study period, admitted sick neonates were evaluated for presence of AKI. The sick neonates were those who were admitted for different morbidities like septicemia, perinatal asphyxia with hypoxic ischemic encephalopathy, shock, respiratory distress syndrome, necrotizing enterocolitis and undergone surgical procedure. Neonates of any congenital anomalies like skeletal, renal, urinary tract were excluded from this study. For each patient detailed history was taken and physical examination was done. First blood sample(2-3ml venous blood) was collected at admission and send to the Clinical Pathology and Biochemistry department in Dhaka Shishu Hospital for blood urea, serum creatinine and serum electrolytes values. For an abnormal value, repeat test was done after 24 hrs. Urine was collected by adhesive urine bag.

AKI was defined as serum creatinine concentration >1.5 mg/dl and blood urea nitrogen >20mg/dl on two separate tests 24 hours apart. Oliguria was defined as urine output less than 1ml/kg/h. Statistical analysis was performed using SPSS Version 17. Outcome was compared with the use of the Chi-square test. P value <0.05 was considered statistically significant.

### Result:

Three hundred sick neonates were evaluated during the study period. Among them, 66.7% were male and 33.3% were female, 60% were term, 40% were preterm and 46% were normal birth weight and 38% were low birth weight. The newborns were admitted for different

morbidities like sepsis (35.3%), perinatal asphyxia (34.6%)(Table-I).

Among 300 sick neonates 14(4.66%) babies developed AKI. Male to female ratio was 1.8:1. Most of the patients with AKI were term (n-10, 71%) and 4 (29%) cases were preterm (Table -2). Oliguric renal injury was found in 8 cases (57%) and non-oliguric was found in 6 cases. Sepsis was found to be the most common cause (71%) followed by perinatal asphyxia (52.8%) (Table II). There were more than one predisposing factors in all patients.

Mortality was significantly higher ( $p<0.05$ ) in neonates with AKI (21%) than in neonates without AKI (10%). (Table-V)

**Table-I**

*Disease pattern of the sick neonates (n=300)*

Diagnosis	Frequency	Percentage (%)
Sepsis	106	35.33
Perinatal asphyxia	104	34.67
Neonatal jaundice	71	23.67
Respiratory distress syndrome	14	4.67
Pneumonia	13	4.33
Shock	13	4.33
Heart diseases	12	4
Surgical causes	10	3.33

**Table-II**

*Demographic characteristics of neonates with AKI (n=14)*

	Frequency	Percentage (%)
Sex Male	9	64.2
Female	5	35.7
Gestational age		
Term	10	71.4
Preterm	4	28.5
Birth weight		
Normal(2500-4000gm)	8	57
LBW(<2500gm)	6	43

**Table-III**

*Predisposing factors for developing AKI in neonates (n=14)*

Diagnosis	Frequency	Percentage (%)
Sepsis	10	71.43
Perinatal asphyxia HIE-III	6	52.86
Surgical causes	3	21.43
Shock	3	21.43
Intrauterine growth retardation	2	14.2
SIADH	3	21.3

**Table-IV**

*Renal function and serum electrolytes values in repeat sample of AKI cases (n=14)*

Investigations	1 <sup>st</sup> sample	2 <sup>nd</sup> sample
	Mean+ _SD	Mean+ _SD
S. creatine (mg/dl)	2.8+ _1.25	2.7+ _1.15
BUN (mg/dl)	57+ _27	47+ _16.2
S. sodium (mmol/l)	134+ _8.7	132.0+ _6.5
S. Potassium (mmol/l)	5.6+ _1.3	5.3+ _1.2

**Table-V**

*Short-term outcome of the sick neonates*

Patients	Mortality (%)
Total sick neonates (300)	31(10.3%)
AKI(14)	3 (21.4%)

p value=<0.05

### Discussion:

In this study, it was found that good number of sick neonates developed AKI. Stapleton et al.<sup>1</sup>, Ghaebaghi MM et al.<sup>8</sup>, Airede A et al.<sup>9</sup> and Andreoli SP<sup>10</sup> found that the incidence of AKI was 3-8% in sick neonates. In several studies<sup>8,9,17</sup> it was found that predominantly male and term babies developed renal impairment. In our study, similar findings were found. The high frequency of AKI in boys may be due to the susceptibility of boys to some perinatal disorders such as sepsis and respiratory distress syndrome.<sup>17</sup>

A wide variety of predisposing factors or prenatal, natal or postnatal events may cause AKI. In this study sepsis (71%) was the most common cause of AKI. Study done in India by Mathur NB<sup>12</sup> found that 26% septic babies developed AKI. The exact pathophysiology of sepsis-induced AKI is not known, however, it is generally accepted that it has a multi-pronged injury pathway. It may be due to ischemia-reperfusion injury, direct inflammatory injury, coagulation and endothelial cell dysfunction, and apoptosis.<sup>3</sup>

Perinatal asphyxia was high in this study. It was 53% in a study done by Airede A et al.<sup>9</sup> and Mortazavi F et al.<sup>18</sup> found 29.8% babies with perinatal asphyxia developed AKI. As kidneys are very sensitive to oxygen deprivation, renal insufficiency may occur within 24 hours of a hypoxic ischemic episode, which if prolonged, may lead to irreversible cortical necrosis.<sup>18</sup>

Other factors responsible for developing AKI were shock (hypovolemia and sepsis) (21%), surgical procedure (21%) and SIADH

(21%). Gharehbaghi MM<sup>8</sup> found that 43.5% neonates developed AKI following surgical procedure.

Serum creatinine and BUN were determined as an indicator of renal function following an initial insult. These laboratory tests are relatively inexpensive and widely available. Obstruction of tubular lumen and back leak mechanism (by damage to the intracellular junctions) contributed to increase in urea and creatinine levels in sick neonates<sup>18,19</sup>. In this study hyperkalemia was the main electrolyte abnormality. Hyperkalemia is a common complication of AKI as the kidney tightly regulates potassium balance and excretes 90% of dietary potassium intake.<sup>20</sup> It was observed that the babies with AKI had higher incidence of hyponatremia. The capacity of sodium reabsorption is limited and if the load of sodium reaching the distal convoluted tubule (DCT) increases significantly, reabsorption does not occur proportionately and sodium load excretes in the urine. Other contributing factors to develop hyponatremia may be occurrence of SIADH secondary to perinatal asphyxia and partial resistance to aldosterone.<sup>21</sup> Here, 7.14% babies with AKI were hypernatremic which might be due to association of poor feeding, VLBW etc.

Mortality rate was also high in sick neonates with AKI in comparison to sick neonates without AKI (10.3%). In

this study, renal function of 11 babies (out of 14) returned to normal and discharged. Gharehbaghi MM et al.<sup>8</sup> and Mortazavi F et al.<sup>17</sup> also reported the mortality rate of 20%, and 20.6% respectively. Mathur NB et al.<sup>12</sup> reported 70% mortality in septic neonates with AKI. The major risk factors for mortality were sepsis, perinatal asphyxia, IUGR, dehydration, electrolyte abnormality and delayed hospitalization.

### Conclusion:

Renal function impairment is not uncommon in sick neonates. The predisposing factors for developing AKI are sepsis, perinatal asphyxia, IUGR, shock surgical procedures etc. Mortality of sick neonates with AKI is high in comparison to sick neonates without AKI.

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# Type 2 Diabetes Mellitus in Children and Adolescents: An update

UHBEGUM<sup>a</sup>, MA RAHMAN<sup>b</sup>

### Summary:

*Childhood type 2 Diabetes Mellitus (DM) has increasingly been reported worldwide. It is commonly associated with childhood obesity. It may be presented with classical manifestation of DM such as polyuria, polydipsia, weight loss or acute complications like Diabetic ketoacidosis (DKA), Hyperglycemic Hyperosmolar State (HHS) or features of insulin resistance syndrome. Many a cases it may remain asymptomatic and hence undiagnosed. So, overweight children and adolescents who met screening criteria such as family history of type 2 DM, signs of insulin resistance, and high risk ethnics should undergo screening. Emphasis should be given on early diagnosis and optimum management plan to avoid grave consequences of it in early part of life. Diagnosis of type 2 Diabetes Mellitus in children should be done on the basis of standard diagnostic criteria such as American Diabetic Association (ADA) criteria. Both non-pharmacological and drug management are important equally. Multidisciplinary*

### Introduction:

Type 2 diabetes mellitus (DM) happens when the body cannot effectively use the insulin it produces. Formerly, it was called non-insulin dependent or adult onset diabetes mellitus as because, for many years it was seen only in adults. In type 1 diabetes mellitus, the body does not produce insulin and it is usually diagnosed in children and young adults. Recently, type 2 diabetes mellitus has increasingly been reported in children and

*team approach including self-management plan is mandatory for obtaining optimal therapeutic goals of type 2 DM in children and adolescents. Lifestyle modification, dietary intervention, weight reduction, patient education, psychological support, and oral anti diabetic drugs and insulin therapy should be included in comprehensive diabetic management plan. Complications of type 2 DM should be minimized by all means with strict glycemic control and management of co-morbidity if any. Emphasis should also be given on prevention of type 2 DM by adopting a healthy lifestyle characterized by healthy eating behavior, regular physical activity and subsequent modest weight loss that can prevent the progression of impaired glucose tolerance to clinical diabetes mellitus.*

*Key words: American Diabetic Association (ADA), Diabetic Ketoacidosis (DKA), Hyperglycemic Hyperosmolar State (HHS), Overweight, Type 2 Diabetes Mellitus (DM).*

*(J Bangladesh Coll Phys Surg 2017; 35: 24-30)*

adolescents, so much so that in some parts of the world type 2 diabetes has become the main type of diabetes in children. The global rise of childhood obesity and physical inactivity is widely believed to play a crucial role<sup>1</sup>. Currently, more than 200 children and adolescents develop the disease every day worldwide<sup>2</sup>. But healthy eating and lifestyle habits are a strong defense against the disease.

### Risk factors and Pathophysiology of Type 2 DM:

Type 2 DM is a complex metabolic disorder of heterogeneous etiology with social, behavioral, and environmental risk factors unmasking the effects of genetic susceptibility<sup>3</sup>. There is a strong hereditary component of the disease. The major risk factors of type 2 DM in children are: obesity and inactivity, family history of type 2 DM, age of 12-16 years, maternal gestational diabetes or type 2 diabetes, not breast feeding during infancy and ethnicity. Other factors that appear to increase risk include poor fetal growth, low birth weight and high birth weight<sup>4</sup>. Impaired glucose

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**Received:** 1 May 2016

**Accepted:** 6 Dec. 2016

homeostasis is the key mechanism in type 2 DM and it depends on the balance between insulin secretion by the pancreatic  $\beta$ -cells and insulin action. The mean age range of onset of type 2 diabetes in youths coincides with the relative insulin resistance that occurs during pubertal development, resulting in hyper-insulinemia and play a major role in the development of type 2 DM in children and adolescents. The adverse effect of obesity on glucose metabolism is evident early in childhood. Obese children are hyper-insulinemic and have approximately 40% lower insulin-stimulated glucose metabolism compared with non-obese children<sup>5</sup>.

#### **Epidemiology of Type 2 DM in children and adolescents:**

Type 2 DM in youth appears to be emerging as a serious clinical issue. Its prevalence in the United States (USA) is approximately 12:100,000, while it is still rare in Europe<sup>6</sup> (approx. 2.5:100,000). In Bangladesh the exact prevalence of Type 2 DM is not known. But in a study among 2152 students volunteers in Bangladesh, Abu Sayeed et al<sup>7</sup>. observed that the prevalence of type 2 DM and impaired fasting glucose (IFG) appears to be 1.8% and 3.4% respectively. The majority of USA young people diagnosed with type 2 diabetes are found in specific ethnic subgroups such as African-American, Hispanic, Asian/Pacific Islanders and American Indians being highest in Pima Indians (22.3/1000 in 10-14 year old children). Furthermore, the great majority of the children are obese. Screening studies in obese adolescents have reported a prevalence of 0.4% up to 1% of type 2 diabetes in obese children<sup>8</sup> 12 years<sup>8</sup>.

#### **Clinical presentation of Type 2 DM:**

The presentation of type 2 DM in children and adolescents varies according to the disease stage. Early in the disease, before diabetes diagnostic criteria are met, insulin resistance predominates with compensatory high insulin secretion, resulting in normoglycemia and the patient likely to be asymptomatic<sup>9</sup>. At this stage, the disease may only be detected by abnormal blood glucose concentrations identified during screening. Obesity is the hallmark of type 2 diabetes in children and adolescents. Most children are obese or extremely obese at diagnosis and present with glycosuria without ketonuria, absent or mild polyuria and polydipsia, and little or no weight loss. In its severest form, the child presents with polyuria, polydipsia, and weight loss. Up to 33% in particular ethnic groups have ketonuria at

diagnosis and 5%-25% ketoacidosis at presentation<sup>10</sup>. Vary rarely, type 2 diabetes mellitus manifest with a hyperglycemic hyperosmolar state (HHS). Acanthosis nigricans and polycystic ovarian syndrome (PCOS), disorders associated with insulin resistance and obesity, are common in youth with type 2 DM<sup>11</sup>. Children with type 2 diabetes frequently have a positive family history, and 74%-100% first or second degree relative have type 2 DM. Some syndromes such as Klinefelter syndrome, Bardet Biedl Syndrome, Prader Willi Syndrome and Alström Syndrome are also associated with type 2 DM. They all are associated with mental retardation and frequently to extreme obesity<sup>12</sup>.

#### **Differential Diagnosis:**

Patients with type 2 DM may have clinical presentations indistinguishable from those of patients with other types of diabetes mellitus<sup>11</sup>. It is important to classify diabetes mellitus in children and adolescents correctly, so that appropriate therapy may be instituted. Typically, children with type 1 diabetes mellitus are not overweight and have recent weight loss, polydipsia, and polyuria. They have a short duration of symptoms and frequently have ketoacidosis at presentation<sup>11</sup>. Type 2 diabetic children and adolescents may represent a form of early-onset latent autoimmune diabetes mellitus similar to that described in adults (LADA). These patients with LADA share insulin resistance with that of type 2 diabetes mellitus patients but display a more severe defect in  $\beta$ -cell capacity<sup>12</sup>. Following the terminology 'latent autoimmune diabetes mellitus in adulthood, LADA', the non-insulin dependent diabetic children and adolescents with  $\beta$ -cell autoantibodies could be named 'latent autoimmune diabetes mellitus in youth' (LADY)<sup>13</sup>. Double diabetes mellitus or type 1.5 diabetes mellitus are other proposed names for this entity<sup>13</sup>. Maturity-onset of diabetes mellitus of the young (MODY) is another rare form of diabetes mellitus in children that includes several disorders caused by monogenic defects in  $\beta$ -cell function<sup>14</sup>. MODY 2 and MODY 3 (defect in glucokinase and HNF1 $\alpha$  respectively) are the most frequent types of MODY. Patients with MODY have a dominant genetic trait, usually are non-obese and have low fasting insulin levels. Recent studies suggest that the clinical presentation of MODY is broad, ranging from asymptomatic hyperglycemia to a severe acute presentation<sup>13</sup>.

**Diagnostic criteria for Type 2 Diabetes Mellitus:**

Diagnosis of type 2 Diabetes Mellitus in children and adolescents can be made on the basis of American Diabetic Association (ADA) revised diagnostic criteria (Table 1)<sup>15</sup> or any other diagnostic criteria. In the absence of unequivocal hyperglycemia, random, fasting or two-hour blood sample should be confirmed by repeat testing. Other tests may be necessary in difficult cases for diagnosis of type of DM, such as fasting insulin or C-peptide determination and occasionally,  $\beta$ -cell autoantibodies measurements. C-peptide levels are elevated in individuals with type 2 diabetes mellitus in contrast to patients with type 1 diabetes mellitus or MODY diabetes.

**Table-I***Diagnostic criteria for type 2 DM<sup>15</sup>*

- Symptoms of diabetes mellitus such as polydipsia, polyuria, and unexplained weight loss plus
- Random glucose concentration  $\geq 200$  mg/dL (11.1 mmol/L) in venous plasma,
- Fasting glucose  $\geq 126$  mg/dL (7.0 mmol/L) in venous or capillary plasma,
- Or two-hours glucose during oral glucose tolerance test (oGTT)  $\geq 200$  mg/dL (11.1 mmol/L) in venous plasma or capillary whole blood sample And
- Hemoglobin A1c (HbA1c)  $\geq 6.5\%$

**Screening for Type 2 Diabetes Mellitus:**

Most of the children and adolescents with type 2 diabetes remain asymptomatic at diagnosis. So screening for it is necessary<sup>16</sup>. It is found that unrecognized hyperglycemia contributes to both microvascular and macrovascular risk in later life<sup>17</sup>. However, at the present time, a general screening for type 2 DM in youth is unlikely to be cost effective and so a targeted screening is necessary. The ADA recommends a screening in overweight children and adolescents at onset of puberty in high risk patients (Table 2). Screening test should be performed every 2 years starting at the age of 10 years or at onset of puberty. It should be done by testing fasting glucose or oGTT<sup>18</sup>.

**Table-II***Criteria for screening tests for type 2 DM in children and adolescents<sup>18</sup>*

Overweight (BMI > 90 percentile) plus one of the following risk factors:

- Family history of type 2 DM in 1<sup>0</sup> or 2<sup>0</sup> relative;
- Race/ethnicity (Asian, American Indian, African-Americans, Hispanics);
- Signs of insulin resistance; or conditions associated with insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome (PCOS);
- Extreme obesity (BMI > 99.5 percentile).

**Complications of Type 2 Diabetes Mellitus:**

The chronic complications of type 2 DM in children and adolescents are macrovascular diseases like accelerated development of cardiovascular disease leading to stroke and myocardial infarction, and microvascular diseases like nephropathy, retinopathy and neuropathy leading to end-stage renal disease, loss of visual acuity, and limb amputations. Microvascular disease is the hallmark of hyperglycemia diagnosed at a younger age. As because the complications of DM are related to the duration of disease itself, risks of complications more common in children and adolescents as compared to adult diabetics<sup>19</sup>. All of these complications contribute to the excess morbidity and mortality in individuals with diabetes mellitus. Young people with type 2 DM appear to be at a much higher risk of developing early diabetes associated complications than those with type 1 diabetes mellitus<sup>20</sup>. This higher level of risk does not appear to be related to overall levels of glycemic control or duration of disease but to occurrence of hypertension and dyslipidemia.

**Management of Type 2 Diabetes Mellitus:**

The ideal goal of management (Table 3)<sup>21</sup> of type 2 diabetes in children and adolescents is normalization of blood glucose values, HbA1c and to decrease the risk of diabetes related acute and chronic complications. Successful control of the associated comorbidities, such as hypertension and dyslipidemia, is also important<sup>11</sup>. The American Academy of Pediatrics has, very recently,

published the management guidelines for children and adolescents with type 2 diabetes mellitus<sup>22</sup>.

**Table-III**

*Therapeutic goal of type 2 DM in children and adolescents<sup>21</sup>*

- Before breakfast sugar: 90–130 mg/dL (5.0–7.2 mmol/L);
- Before bed/ overnight sugar 90–150 mg/dL (5.0–8.3 mmol/L);
- Target HbA1C <7%;
- Target blood pressure consistently, <90th percentile for age, sex, and height;
- Target LDL cholesterol value, 100 mg/dL (2.6 mmol/L).

Insulin therapy should be initiated for children and adolescents with type 2DM who are ketotic or in diabetic ketoacidosis and in whom the distinction between type 1 and type 2DM is unclear; and, in usual cases: who have random venous blood or plasma sugar concentration  $\geq 250$  mg/dL; or whose HbA1c is  $>9\%$ . In all other instances, lifestyle modification program, including nutrition and physical activity, and Metformin should be started as first-line therapy at the time of diagnosis of type 2DM<sup>22</sup>. Despite of severe manifestation, initial management of obese children and adolescents with type 2 DM should consist of behavior modification strategies for lifestyle change such as decreasing high-caloric high-fat food choice and sedentary behavior, while increasing physical activity. Lifestyle changes should not be imposed and self-motivation is necessary<sup>23</sup>. Treatment options of type 2 DM include:

**Diet:** Balanced macronutrient diets at 900 to 1200 kcal per day are associated with both short and long-term (e<sup>2</sup> 1 year) improvements in weight status and body composition in children 6 to 12 years of age<sup>24</sup>. These calorie management are to be incorporated with lifestyle changes, including increased activity and medication. Restrictions of no less than 1200 kcal per day in adolescents 13 to 18 years old result in improved weight status and body composition<sup>25</sup>.

**Physical activity:** It is an integral part of weight management for prevention and treatment of type 2DM.

Children and adolescents are encouraged to engage in ‘moderate-to-vigorous’ exercise for at least 60 minutes daily and to limit non-academic ‘screen time’ to less than 2 hours a day. Screen time contributes to a sedentary lifestyle, especially when the child or adolescent eats while watching television or playing computer games<sup>26</sup>.

**Patients education:** All children with type 2 diabetes mellitus should receive comprehensive self-management education which include teaching self-monitoring of blood glucose, performed as needed and during periods of acute illness or when symptoms of hyper- or hypoglycemia occur<sup>27</sup>.

**Pharmacological treatment:** If treatment goal with nutrition education and exercise is not met, pharmacological therapy is indicated. Metformin and insulin are the only anti-diabetic agents currently recommended for use in children. Thiazolidinediones and incretins are occasionally used in adolescents younger than 18 years<sup>28</sup>. Metformin, a biguanide, is the most appropriate starting point for pharmacological treatment in children with type 2 diabetes mellitus if insulin therapy is not indicated. The effectiveness has been proven for adolescents in clinical trials. Metformin decreases hepatic glucose output and enhances primarily hepatic and also muscle insulin sensitivity without a direct effect on  $\beta$ -cell function. It has the advantage of weight reduction, decrease in lipids without the risk of hypoglycemia. Because of concerns about lactic acidosis metformin is contraindicated in patients with impaired renal function and should be discontinued with the administration of radiocontrast material or hypocaloric diet. Metformin should not be used in patients with known hypoxic conditions, severe infection, hepatic disease, or alcohol abuse. The most common side effects of metformin are gastrointestinal disturbances. The dose of metformin should be increased up to 2 gm in split doses, unless there are gastrointestinal side effects. Metformin has a good safety record, but should not be given if there is any doubt at all about the nature of diagnosis. Rosiglitazone, a thiazolidinedione has been studied in some randomized trial in adolescents compared to lifestyle intervention and metformin and found some effects. However, rosiglitazone has been withdrawn from the market due to its side effects and is not available any more<sup>13</sup>.

If monotherapy with metformin is not successful over a reasonable period of time (3-6 months), insulin treatment will often be the only feasible way of controlling hyperglycemia. There is no specific contraindication to insulin in children. Any type of insulin and analogs can be used. Insulin regimes should be adopted that are carefully tailored to lifestyle such as bedtime insulin alone, twice-a-day insulin or multidose insulin regimes<sup>13</sup>. Basal insulin is provided through either the use of long acting, relatively peak-free insulin by needle or via an insulin pump. Bolus insulin doses are given at meal-time, using one of the rapid-acting insulin analogs. The bolus dose is calculated by using a correction algorithm for the premeal blood sugar concentration as well as a "carb ratio," in which 1 unit of a rapid-acting insulin analog is given for "X" grams of carbohydrates ingested (For example, see Table 4)<sup>15</sup>.

**Table-IV**

*Calculation of Basal Bolus Insulin Regimen<sup>15</sup>*

- If an adolescent has a blood glucose of 250 mg/dL, is to consume a meal containing 60 gm of carbohydrates, with a carbohydrate ratio of 1:10 and an assigned correction dose of 1:25 > 125 the mealtime bolus dose of insulin would be as follows:  
 $60 \text{ gm}/10 = 6 \text{ units rapid-acting insulin for meal}$   
 plus  
 $(250-125)/25 = 125/25 = 5 \text{ units rapid-acting insulin for correction};$  Thus, total bolus insulin coverage at mealtime is: 11 Units (6 + 5)
- Note: Insulin sensitivity-25; Target blood glucose level-125mg/dl, 'carb ratio'-10.

**Monitoring of Diabetes Mellitus and treatment of complications:**

All children and adolescents with newly diagnosed type 2 DM, regardless of prescribed treatment plan, should perform finger-stick blood glucose monitoring before meals and at bedtime until reasonable metabolic control is achieved<sup>29</sup>. Once blood glucose concentrations are at target levels, the frequency of monitoring can be modified depending on the medication used, the regimen's intensity, and the patient's metabolic control. Monitoring of HbA1c concentrations every 3 months and intensification of treatment is required if treatment goals for blood sugar and HbA1c

concentrations are not being met. Patients on insulin should also be monitored periodically for asymptomatic hypoglycemia. To monitor retinopathy, dilated eye examinations should be performed regularly. Screening for microalbuminuria should be performed yearly<sup>26</sup>. Angiotensin converting enzyme (ACE) inhibitors are the agents of choice in children with microalbuminuria. Control of hypertension in children with type 2 diabetes mellitus is mandatory. If normotension is not achieved by ACE inhibitors, combination therapy with  $\alpha$ -blockers, calcium antagonists or low-dose diuretics may be needed. It is unclear whether foot examinations are important in children. Testing for and treating lipid abnormalities are necessary to avoid macrovascular complications<sup>30</sup>.

**Psychological impacts of Type 2 DM in children and adolescents:**

Adolescents with type 2 diabetes mellitus rate lower 'Quality of Life' scores than their peers with type 1 DM and the burden of neuropsychiatric disorders in young people with type 2 DM is high, with as many as one in five experiencing either psychiatric illness or neurodevelopmental/behavioral problems. It is found that psychosocial factors represent a significant barrier to optimum self-management in adolescents with type DM, often leading to a vicious circle of spiraling poor self-management and increasing psychosocial problems. Poor psychosocial health may also be physiologically related to poorer glycemic control. Therefore psychologists should be the core component of care of children and adolescents with type 2 diabetes mellitus<sup>13</sup>.

**Prevention of Type 2 Diabetes Mellitus:**

Prevention of Type 2 Diabetes Mellitus should start very early in life, even before birth. Primary prevention has proven to be difficult or impossible in most societies. A multidisciplinary team approach is needed to develop and secure preventive strategies. Good nutrition and modest exercise for pregnant women as well as monitoring of intrauterine growth of the fetus are mandatory. After birth, rapid weight gain should be avoided and the principles of good nutrition and physical activity are to be taught at all ages. Breastfeeding should be strongly recommended. Children's food choice can be influenced by early intervention and guidance<sup>18</sup>. Teacher training, modification of school meals and physical education are effective in reducing

risk factors for obesity which is the hallmark of type 2 DM in children. Recent intervention studies have convincingly demonstrated that adoption of a healthy lifestyle characterized by healthy eating behavior, regular physical activity and subsequent modest weight loss can prevent the progression of impaired glucose tolerance to clinical diabetes mellitus. The use of metformin is not effective to prevent type 2 DM in obese adolescents with impaired glucose tolerance<sup>31</sup>.

### Conclusion:

Type 2 diabetes mellitus is emerging as a new clinical problem within pediatric practice. Clinicians should be aware of the frequent mild or asymptomatic manifestation of type 2 diabetes mellitus in childhood. Therefore, a screening seems meaningful especially in high risk groups such as children and adolescents with obesity, relatives with type 2 diabetes mellitus, and clinical features of insulin resistance. Emphasis should be given on early diagnosis and comprehensive management plan to avoid grave consequences of it in early part of life. All efforts should be given on prevention of type 2 DM such as, healthy eating, physical activity, and modest weight reduction. Collaborative efforts from all corners of the modern society can efficiently combat against this emerging disease.

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# Colouterine Fistula

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### Summary:

*Colouterine fistula is a extremely rare condition .It may be congenital,iatrogenic or secondary to malignancy.Here we report a congenital type of colouterine fistula with successful primary repair without hysterectomy in a nulliparous*

### Introduction:

Colouterine fistula is an extremely rare condition because the uterus is a thick, muscular organ. It can be congenital or may be caused by foreign body, during surgery, following trauma or accidental or secondary to malignancy, diverticulitis & endometriosis. This condition can be deleterious for an infertile female because of introduction of infection via the colon. Treatment of colouterine fistula in parous women is hysterectomy followed by repair of rent in the colon. We present the case of a colouterine fistula in which repair of the uterus was done as primary procedure and colostomy done for sigmoid fistula. The uterus was conserved because the patient was a nulliparous woman.

### Case Report:

A 18 years old married girl resident of Kamarpara, Shadullapur, Gaibandha, educated upto class ten, admitted in surgery ward of Prime Medical College & Hospital, Rangpur on 14.7.2013, presented as 5 months pregnancy with bouts of per rectal bleeding for 3 days & lower abdominal pain for 4 days. On admission, patient was moderately anaemic, pulse, blood pressure normal, abdomen tense and tender, fundal height of uterus was

*woman. Usually treatment of a parous women is hysterectomy followed by repair of rent in the colon.*

**Key words:** Colouterine fistula, cause, diagnosis, treatment.

*(J Bangladesh Coll Phys Surg 2017; 35: 31-33)*

24 weeks size. USG findings was 22 weeks pregnancy, placenta posterior away from the os with active fetal movement & cardiac activity, no sign of intestinal obstruction. Conservative treatment and boold transfusion started in the surgery ward as there was severe per rectal bleeding. One day after admission abortion process was started & on the next day early morning on 16.7.2013 she complained that something coming out per rectum. The attending doctors of surgery unit found that the placenta was outside through rectum & the umbilical cord was hanging from anus (fig-1). The patient was then transferred to gynae ward & on per vaginal examination a very premature infected dead foetus with foul smelling was found protruding through cervix with breech presentation (fig-2). Oxytocin drip was started for spontaneous expulsion of the foetus but still waiting up to mid noon there was no progress. So planned for examination under anesthesia and breech extraction. Under spinal anesthesia just a pull for extraction of the foetus the head was separated from the neck & retained inside the uterus. Then decision was taken for laparotomy & hysterotomy to remove the retained aftercoming head of breech. Abdomen was opened by right lower paramedian incision. The abdominal cavity was contaminated with fecal matter. The uterus was enlarge about 24 weeks size & part of the sigmoid colon was found adherent to anterior upper segment of uterus. So, the case was diagnosed as colouterine fistula, possibly congenital, which is extremely rare condition. The attachment was very dense & clean cut well defined, no omental or any other surrounding adhesion was found(fig-3). Surgery team dissected and separated the sigmoid colon from the uterus. A big hole in the anterior uterine wall near fundus admits two finger through which the retained head was searched but not found. Ultimately the head was found

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**Received:** 23 March 2014

**Accepted:** 16 Sept. 2016

in rectum which was driven down through the large fistula to the capacious colon to rectum & was brought out per rectum by an assistant. The big hole of the uterus was then closed with vicryl 1 in two layers. Colostomy was done at the level of sigmoid fistula by Hartman's procedure. Peritoneal toileting was done & a drain tube was placed in pelvic cavity. Abdomen was closed in layers. Patient was put on broad spectrum antibiotics & nothing per oral for seven days. Total six units blood was transfused. The post-operative period was uneventful except the abdominal wound got infected & secondary suture was given on 3.8.2013. The patient was discharged after ten days & advised to come for follow up.



**Fig-1:** The umbilical cord was hanging per rectum & anus from where placenta was delivered first.



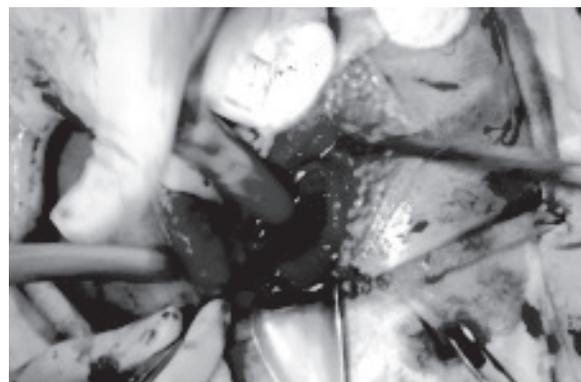
**Fig-2:** Aborted foetus delivered vaginally with breech presentation & the umbilical cord was hanging from anus.



**Fig-3:** Laparotomy shows fistula in between the uterus & sigmoid colon.



**Fig-4:** Separation & dissection of fistula was done.



**Fig-5:** This figure shows fistula at the uterine site after dissection from sigmoid colon.

#### **Discussion:**

Since long vaginal deliveries with obstetric & gynaecological interventions have been associated with vesicovaginal & rectovaginal fistulae<sup>1</sup>. Vesicouterine fistulae are relatively rare but world literature documents

only few case of colouterine fistula<sup>2</sup>. Usually these cases of colouterine fistulae were diagnosed by computerized tomography<sup>3</sup> or sonohysterography<sup>4</sup>. Just a conventional hysterosalpingography can also lead to the diagnosis<sup>5</sup>. Colouterine fistulae documented till now were secondary to malignancy<sup>6</sup>, diverticulitis<sup>6</sup> & endometriosis. All these cases were treated by hysterectomy & resection of sigmoid colon<sup>7</sup> or colostomy with subsequent repair<sup>8</sup>. We report this case of colouterine fistula with successful primary repair of uterus without hysterectomy.

Initial evaluation comprises a detailed history. Important information includes associated symptoms such as pain, fever or changes in bowel or bladder function. Although clinical manifestations of a colouterine fistula vary according to causative pathology, typical symptoms include malodorous fecal or purulent vaginal discharge for days or months because the colonic lumen & the uterus are linked via a fistula tract<sup>9, 10, 11</sup>. In our case we suspect the fistula is congenital type, though there was no history of per rectal bleeding during menstruation nor any symptoms of malodourous fecal or purulent vaginal discharge. It is probably due to, the non-pregnant uterus is small and the fistular attachment with colon is partially closed and non-communicating. But when the patient became pregnant the uterus enlarged and the muscle wall comparatively thinner. The placenta implanted at or near the site of fistula. Subsequently the fistula opened up and due to separation of placenta there was severe per rectal bleeding and lower abdominal pain, the symptoms which appeared first. Later on the whole placenta separated and through the fistula it passed to the sigmoid colon, rectum, anal canal and ultimately come out through anus (Fig:1). So, the colouterine fistula was diagnosed as a congenital type and primary repair of uterus was done successfully. From patient detailed history, she got married just six month back and it was her first conception. There was no history of MR or induced abortion or any injury or trauma which may favour the diagnosis of acquired variety of fistula.

In conclusion a uterocloic fistula is a very very rare condition. Computed tomography (CT) is routinely performed for diagnosis is patients with a suspected

colouterine fistula. However, confirming the diagnosis by using computed tomography (CT) might be difficult. Therefore other less-invasive modalities such as fistulography may be necessary & the utility of recently introduced modalities remains to be verified.

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# Aorto-esophageal Fistula Caused by Descending Aortic Pseudoaneurysm

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## Summary:

A 60 year old man presented in Square Hospitals LTD with hypovolaemic shock, and massive haematemesis. His BP was non-recordable with soft, non-tender abdomen and Hb was 8g/dl with normal prothrombin time and partial thromboplastin time and normal platelets. By endoscopy and CT scans aorto-esophageal fistula with aortic pseudoaneurysm

## Introduction:

Aorto-esophageal fistula (AOF) is a rare cause of gastrointestinal haemorrhage. Early diagnosis and surgical intervention are mandatory for survival. We report a case of an aorto-esophageal fistula due to a descending aortic pseudoaneurysm and review the causes, clinical manifestations, and diagnosis of this uncommon but often fatal case of upper gastrointestinal haemorrhage.

Computed tomography is the most valuable diagnostic method in the diagnosis of aorto-esophageal fistula. CT may detect the aneurysm, its relation to the oesophagus and surrounding structures. It can also differentiate between true and false aneurysms. Once AOF is identified, immediate surgery is mandatory.

## Case report:

The patient, a 60 year old man, presented with hypovolumic shock and massive haematemesis. The patient had repeated episodes of massive haematemesis & malaena without dysphagia, chest pain or loss of weight. The patient was detected HbsAg. positive incidentally. He was a smoker. On admission, his blood pressure was non-recordable and pulse rate was 125 beats/min, confirming haemorrhagic shock. Physical examination included a soft, non-tender abdomen with normal bowel sounds. Additional results were

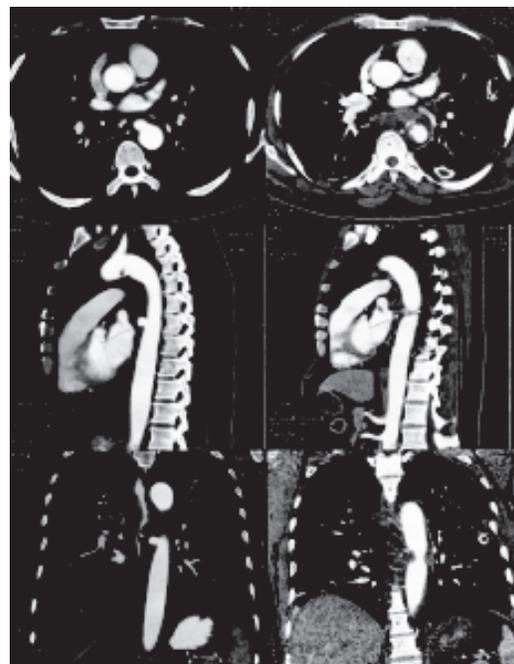
was identified and immediate surgery was done with complete occlusion of the pseudoaneurysm, which was confirmed by repeat CT scan.

**Key words:** Aorto-esophageal fistula, Aortic pseudo aneurysm.

(J Bangladesh Coll Phys Surg 2017; 35: 34-35)

haemoglobin 8 g/dl, creatinine 0.9 mg/dl, normal prothrombin and partial thromboplastin times and normal platelets. Chest X-ray was normal.

After receiving and 5 units of blood, the patient was stabilized and after that endoscopy was performed. Under endoscopy, a large globular mass compressing



**Fig.-1**

the mid oesophagus was seen at 30 cm from the incisor teeth. A visible blood vessel was seen at the base of the ulcer at the tip of the mass. The vessel started spurting of the blood during the endoscopic process. Haemostasis was achieved instantly by injecting 10 ml of 5% Ethanolamineoleate was injected in and around the bleeding vessels.

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**Received:** 2 March 2015

**Accepted:** 24 Nov. 2016

A subsequent contrast enhanced computed tomographic scan of the chest documented an outpouching at the antero-medial aspect of the mid part of descending aorta measuring approx. 2.5 cm x 1.3 cm in size suggesting oesophageal pseudoaneurysm ( Fig.1). The aneurysm is situated approx. 6 cm distal to the isthmus, compressing and indenting the adjacent oesophageal lumen. Oesophageal wall at this site was mildly thickened. This may suggest aorto-oesophageal fistula. Two small 9 mm right paraoesophageal lymph nodes are also detected.

Urgent surgery was planned to excise or occlude the pseudoaneurysm. Descending thoracic aorta was approached by left posterolateral thoracotomy through 4<sup>th</sup> intercostal space. Aneurysmal sac was identified and found badly adherent to the surrounding soft tissue. Decision was made to occlude the base of pseudoaneurysm and to avoid excessive difficult dissection. Control of aorta was taken both proximal and distal to the pseudoaneurysm. Purse string suture was given at the base of sac by 3-0 prolene. Blood pressure was lowered to 70 mm Hg and purse string suture tied. Two additional transfixation suture of 3-0 prolene through the aneurysmal sac were given and tied down. Haemostasis was achieved and chest was closed by keeping a drain tube.

A subsequent CT confirmed that the pseudoaneurysm was completely occluded (Fig. 2). The patient recovered well before discharge.

#### Discussion :

Development of a fistula between the aorta and oesophagus has an extremely poor prognosis. In 1991 Hollander and Quick (1) published a comprehensive review, including 500 cases of AEF gathered from the literature. The main aetiological factor involved aortic disease with 54.2% of cases being secondary to rupture of an aneurysm of the descending thoracic aorta into the esophagus. The next most frequent causes were foreign body (19.2%) and advanced oesophageal cancer (17.0%). Secondary AEF following operative treatment were rare (4.8%) with 50% occurring after aortic surgery and 50% after oesophageal surgery. Diagnosis of AEF is rarely made before massive haematemesis. However most cases are associated with characteristic CHIARI's triad of aorto oesophageal syndrome, including chest pain and sentinel haematemesis of red blood followed at a variable interval of time by rapidly fatal massive exsanguinating haematemesis. Characteristic triad features were present in 45% of patients included in the review series of Hallander' Quick (2), 80% of patients

describe by Carter et al<sup>2,3</sup>. In a few cases AEF can be suspected on the basis of isolated sepsis or septic embolism in a lower extremity. Our suggestive findings include dysphagia and or chest pain, H/O surgical treatment of thoracic aorta.

Except in patients who require immediate emergency surgery, various investigative modalities can be used to confirm diagnosis, plan treatment.

Barium oesophagus may show compression by the aneurysm of the oesophagus<sup>4</sup>.

Esophagoscopy can also show the presence of a variable amount of sub-mucosal haematoma indicating extravasation of blood into the oesophageal wall<sup>5</sup>. However even though some investigations advocate esophagoscopy as the diagnostic modality of choice for evaluation of AEF, others have advised against its use because several cases of fatal haemorrhage precipitated by flexible endoscopy have been reported<sup>6</sup>.

Although arteriogram rarely reveal the fistula site they can provide useful data for surgical planning.

#### Conclusion:

Pre operative contrast enhanced CT chest of the patient revealed the aorto-oesophageal fistula with pseudoaneurysm and post operative CT demonstrated complete occlusion of the tract (Fig1). So, CT scan is a valuable diagnostic method for both pre operative diagnosis and post operative follow-up in these patients.

#### Acknowledgement:

We remain indebted to Director, Square Hospitals Ltd. for his permission to publish this report.

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## Dissociative Disorders with Haemolacria: Series of Case Reports

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### Summary:

*Bloody tears (Haemolacria) are a rare symptom that can be caused by local or systemic pathology. It is one of the most alarming symptom in ophthalmology. Besides those, idiopathic cases have been reported. A case of hyperthyroidism where haemolacria was secondary to the condition has also been reported. Haemolacria are also reported as secondary to epistaxis. Psychogenic causes are described including Munchausen Syndrome by proxy. Here we describe a series of four cases of haemolacria along with bleeding from other sites, found as associated features of dissociative disorders. In this series, patients with age ranging from 14-17 years, three of them are female and one male have been included.*

### Introduction

Hemolacria is a rare clinical condition, literally meaning “bloody tears”. In the literature, it has been reported in cases with conjunctival capillary hemangioma, conjunctival telangiectasias, bacterial conjunctivitis, lacrimal sac tumors, lacrimal sac infections, nasal and paranasal sinus tumors<sup>1</sup>. There are cases of idiopathic haemolacria with no identified causes have been reported<sup>2</sup>. A case of bloody tears in a hyperthyroid female patient who displayed no evidence of localized ocular pathology has been reported<sup>4</sup>. Haemolacria has been described in Hereditary hemorrhagic telangiectasia<sup>5</sup>, Hensch-Schönlein purpura and

*Examination excluded local ocular and nasal pathology, coagulopathy and hyperthyroidism. In course of their illness, two of these cases met the DSM 5 criteria for both dissociative disorders and conversion disorders, rest of them have been diagnosed as mixed dissociative disorders. After appropriate intervention, three patients recovered completely and in one patient symptoms (also bleeding) recurred on re-exposure to the previous stress factors.*

*We report three cases of Dissociative disorders and one with both dissociative and conversion disorder where bloody tears were one of the feature. To the best of our knowledge this is the first official report of its kind in Bangladesh.*

*(J Bangladesh Coll Phys Surg 2017; 35: 36-42)*

retrograde epistaxis and in women during menstrual period. Cases of ‘bloody tears’ in a hysterical young female<sup>1</sup>, during episodes of cluster headache in a case of Gardner-Diamond syndrome<sup>6</sup> have been reported as well. Psychogenic purpura consists in the spontaneous appearance of recurrent bruising, is an unexplained reality which, in addition to cutaneous ecchymoses, may have bleeding from multiple sites, like, haemolacria along with haematuria, menometrorrhagia, GIT bleeding and epistaxis. There may be spontaneous psychogenic as well as self-inflicted iatrogenic bleeding. There is virtually no scientific information on the interaction between the nervous system and hemostasis or blood coagulation<sup>5</sup>. It is remarkable that blood coagulation and other hemostatic tests remain normal in all patients of psychogenic bleeding, including haemolacria. Other bleeding disorders with normal coagulation tests are an inherited failure of collagen biosynthesis or congenital or acquired vascular disorders, but no note of haemolacria as a sign in those disorders has been found<sup>12</sup>. Although in some literatures, haemolacria has been noted as a symptom of ‘Hysteria’ and other ‘Psychological’ illnesses<sup>1,2,5</sup>. This sign has not been categorically included in any particular psychiatric disorder.

### Case 1

A 16 years old male student of class X, from Sylhet City, admitted in Sylhet Women’s Medical college Hospital

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**Received:** 6 Oct. 2016

**Accepted:** 3 Nov. 2016

in the department of psychiatry on 1/6/2012 with the complaints of episodes of bloody tears from both eyes (haemolacria), bleeding from mouth, bleeding per urethra, chest pain and severe convulsion and inability to talk.

History revealed that the patient was alright about two years ago. Since then he had had multiple episodes of abnormalities characterized by unresponsiveness, convulsions, loss of power in the limbs, inability to hear and see and bleeding from the nose and eyes. According to the parents, first he developed difficulty in breathing and stiffness in both limbs followed by convulsion and paralysis of the lower limbs. Likely precipitating factor was the death of a cousin to whom he was very much attached. That was a single episode relieved after sometime with medical intervention. On another occasion, patient developed pricking sensation on the left side of his body followed by breathlessness, on receiving treatment from a nearby hospital he became symptom free after 24 hours. Since then episodes with different types of features have been continued off and on. About one and half months from the last episode, he started to bleed through mouth. Sometimes he cut his hands to bleed. His schooling hampered seriously and became irregular.

The patient had been evaluated by multiple doctors of different specialties. No physical abnormalities were detected. He was also seen by psychiatrist and clinical psychologist before admission in the hospital.

His father is a businessman, mother house wife; lives in an extended family with his parents, a brother and two sisters along with uncle, aunt and cousins. High expressed emotions within the family members noted from history. No consanguinity within the parents. The family is economically solvent. There is no history of psychiatric disorders among 1<sup>st</sup> degree relatives.

Patient's birth and early development was normal but in childhood, he used to show temper tantrums and increasingly became demanding, easily gets hurt. Patient complains of apparent lack of appreciation from his parents.

Relation with his siblings is mostly friendly, parents are over caring and classmates are cooperative. He lacks a sense of humor and unable to cope with the sarcastic remarks of his classmates and sometimes become irritated. He is polite, gets easily hurt, and very much sensitive; most of the time he remains depressed, and

always tries to find a negative meaning of any remark made by his parents and peers. His performance was mediocre in the school. He has no hobby, passes the leisure time by walking around the house or sitting idle.

Past medical and psychiatric history is nothing contributory. No history suggestive of seizure disorder, mood disorder, anxiety symptoms or PTSD or Malingering. Factitious Disorder also excluded as per DSM 5 criteria.

General and systemic physical examination revealed normal findings. His mental state was otherwise normal except that he was found distracted most of the time during interview.

He complained of poor memory and thinks that he has no disease excepting sometimes his lower limbs become stiff and he lives with sorrow and pain.

All of his lab investigations on different occasions at different hospitals revealed normal findings which include: CBC, Calcium level, USG whole abdomen, CXR, Endoscopy of upper GIT, BT, CT, CT scan of the brain, MRI of the brain, S. bilirubin, AST, ALT, S. alkaline phosphatase, S. protein, urea, S. creatinine, phosphate, LDH, TFT, Urinalysis, APTT, S.C3, C4, ANA, CRP, Anti DS DNA, RF.

Patient is diagnosed as Mixed Dissociative Disorder.

Low dose antidepressants and anxiolytics have been used during his stay in the hospital and counselling continued. Improvement was minor and patient's parents wanted discharge for social reason.

As desired by his family, patient was referred to the National Institute of Mental Health and Neurosciences (NIMHANS), Bangalore, India, for further evaluation and management, where he was treated as inpatient for three months. During his stay, the patient was started on individual therapy addressed intra-psycho conflicts, behavioral principles used to improve concentration and family therapy. Low dose antidepressant and anxiolytic used for a short period. Two other follow up visits every 6 months have been made.

Patient have been found stable without recurrences of features on a single follow up visit after 1 year in our hospital.

### **Case 2 (Fig.-1)**

A 17 years old unmarried girl from a township of Sylhet, admitted in the department of psychiatry of Sylhet



**Fig-1**

Women's Medical College on 30/8/2012 with the complaints of episodes of flowing of tear (haemolacria) from both eyes, abnormal abdominal movement followed by blood vomiting after food and paroxysms of abdominal pain for about 2½ years; episodes of convulsions and loss of consciousness and could not remember anything after recovery. These features, episodic in nature, lasted for about 4½ years.

Patient stated that she was reasonably well about four years ago. At the outset, she started episodes of dizziness, headache and vomiting which lasted for about one and half months. After few days when she was a student of class VII (2007), one evening she had seen a small boy climbing in a bamboo in a nearby bush, on other occasion she saw a stranger milking a cow in their premises. As stated by the informant (maternal aunt), since then she used to have transient abnormal experiences, like hearing song or sudden single voice while nobody was around her, or as if somebody was coming to kill her. After About 2 months of marriage of her elder sister in mid-2008, changes in her behavior was noted by relatives; like loss of appetite, vomiting after meal, sometimes became increasingly demanding and aggressive. Whenever she wanted something, if not met with, she started screaming, talked non understandable languages, fell on the ground followed by loss of consciousness for a brief period.

She was very much shy since childhood but after development of above features, she became more extroverted and demonstrative, used to spend more time on grooming. (e.g. changing hair style frequently, putting on colors, plucking brow and manicure). She spent most of her time by watching TV or with her cell phone. She tries to act like TV Models, videos herself along with other family members. Her father works abroad, mother is a house wife, no consanguinity present. She has two

sisters and no brother. She lived in a well to-do extended family along with her parents, grandparents, uncle, aunt and cousins and has very strong attachment with her mother. Born with low birth weight (?), achieved usual milestones, shy and reserved during childhood. Schooling was difficult as she has to walk alone about a kilometer to reach.

So when she was at class V, she left home to her maternal grandparents' house where school was nearer. Although her elder sister had been there since before, she missed her mother too much. When she was a student of class VIII, she started to see glimpses of things which nobody else can see.

She suffered from measles in her childhood. Infrequent migraine attacks on exposure to direct sunlight. No history of any other major medical illness is obtained.

Within her family, most of the time she remained happy and cheerful, passes leisure time watching TV. Her relationship was intense with her mother, aunt and maternal uncle. General examination revealed normal findings.

Among other examination, CBC, BT, CT, Endoscopy upper GIT, S. Electrolytes, S. Creatinine, ECG, CXR, and TSH, were within normal limits.

Patient was diagnosed as having mixed Dissociative Disorder and Migraine attacks. Factitious disorder, Malingering, Psychotic disorders and other differentials excluded.

Anxiolytics and low dose antidepressants used for short period. Interpersonal psychotherapy with explanation of her problems discussed targeting the patient and family.

Patient maintained irregular follow up at OPD up to 2 years without further sequel.

### **Case 3 (Fig.-2)**

A 14 years old girl of 8<sup>th</sup> grade, presented at psychiatric OPD of Sylhet Women's Medical College Hospital 19/05/2014, with the complaints of episodes of burning sensation all over the body followed by bizarre behavior and unconsciousness, episodic bleeding through mouth, eyes and ears; self-mutilating behavior-particularly chewing of lower lip, and stiffness in the limbs; for about 2 months. All the symptoms started after a familial stress.



**Fig.-2**

As per statement of the patient and informants, she was reasonably well 7-8 years ago. When she was 6 years old, she suffered episodic respiratory distress, which was continued despite treatment. For about last 2 years, she has been suffering these episodes with increasing frequency. Moreover, for each episode new features were developed including bizarre behavior, like, tearing apart her clothes, breaking of household things, extreme agitation, running away from the house, biting herself and people around her, followed by brief unconsciousness when sometimes blood coming up through her mouth and both eyes. Each episode lasted for about 40 minutes and after regaining consciousness, patient could not remember anything regarding her behavioral abnormalities. With time she started bleed through her ear and eyes periodically without any other symptom. It was noted that her elder sister, used to have fits even with mild stress, when the patient also got the same by seeing her sister unconscious.

Her father is a businessman, step mother is a house wife. She has 2 sisters and 1 brother. No history of consanguinity between parents, neither any psychiatric illness among her 1<sup>st</sup> or 2<sup>nd</sup> degree relatives was obtained. Her birth was domiciliary. Mother died of cancer when she was 9 months old. Since then she has been living with her maternal aunt and brought up in an extended family along with her Grandparents, 2 sisters, uncle and aunt and cousins.

Early development was normal with no abnormal traits. Schooling was uneventful. Age of menarche was at 11. Family environment is otherwise favorable except

overindulgence of superstitions. Social circumstances is also good. She had pneumonia in her childhood but no documents were obtained. Since her childhood she maintained a good relationship with her family members and other associates, always cheerful and fond of grooming beautifully. Leisure activity seems to be limited to watching TV. Currently she was asked by her father to shift from her grandparent's family to join her own family but she is unwilling to leave her aunt and live with her step mother.

General physical examination was revealed normal findings. Mental state exam was also normal, anxiety features are noted.

Routine laboratory examinations with BT, CT, were within normal limits.

**Diagnosis-** Mixed Dissociative Disorder

Patient has been treated with low dose antidepressants. Nature of her illness explained to the patient and family. She became symptom free within one month and remained so for about a year.

On re exposure to the foregoing family stressor, her symptoms recurred. She has been admitted on 31/05/2015 in the psychiatry department. Feigning or factitious disorder excluded by clinical assessment.

Patient received anxiolytics and inter personal psychotherapy therapy along with family therapy and discharged with improvement.

#### **Case-4**

A young 15 years old female student of class-IX from a semi urban area of Sylhet district was admitted 01/06/2014 in the psychiatry department of Sylhet Women's Medical College Hospital with the presenting complaints of episodic nose bleeding, bleeding through both ears and decreased sleep. All for about 8 months; episodes of fits for about 10 months; headache for 2 years.

History reveals that patient was in good health 2 year ago. When she was a student of class-VII, once she had an accident while travelling in tricycle (Rickshaw). Since then she had headaches off and on till now. She noticed unexplained change in her mind since then. When she was a student of class-VIII, her brother passed SSC examination and migrated to Sylhet city for higher study, she started to feel lonely as her brother was her

only playmate and friend within the house. Although her parents were willing to migrate to Sylhet city with all other members, she refused to leave her house mainly because her old friends. Gradually she became more demanding, easily gets angry and impulsive. The patient blamed her mother of not to be sympathetic enough to understand her. When she becomes sick her mother use to tell her of negative social impact of her illness which hurt her so much that sometimes she considered suicide. Due to strong religious conviction and considering her family status in the society, she refrained herself from committing so. Regarding fits she stated that whenever she gets hurt she used to cry which gets her a headache, when she read for a long time she gets headache, exposure to excessive heat also brings headache. Whenever she gets a headache irrespective of cause, she at first feels dizzy, then dimness and blurring of vision and loss of hearing, until she loses consciousness.

As her parent state, then she bleeds through nose and ears and recovers after a brief period. The patient's father is an established businessman, mother is a housewife. She has 3 sisters and 1 brother. No history of consanguinity between parents. Her family holds a middle class status. No history of mental illness in the family, but a cousin of her has been suffering from Bipolar Disorder. Her birth was domiciliary and early development was normal. Since childhood she was demanding and showed heightened reactivity to stress. Schooling and education was uneventful. Her age of menarche was at 11 years. She was born in an extended family but brought up in nuclear one.

Past medical and psychiatric history is normal. She used to maintain good and stable relationship with peer group as well as with her family members, especially with her brother and elder sister but somewhat reserved with her mother. She was always cheerful, with an up to the mark living standard. Her free time activities were limited to mobile gaming and occasionally reading books.

General physical examinations and neurological examinations are normal. ENT examination done previously was also normal. Routine laboratory tests including BT, CT, revealed normal findings.

Patient was diagnosed as Conversion Disorder and Migraine with anxiety features. Any other medical and ENT problems excluded after consulting respective specialties.

After discharge from the hospital the patient did not come back for scheduled follow up but her father responded over telephone. Patient remained symptom free for 1 year.

#### **Discussion:**

Bloody tears or haemolacria is an inexplicable and alarming condition to the physician, patient and guardian. Haemolacria literally means bloody tears, either frank blood and/or blood mixed discharge from one or both eyes. In the literature, this condition have been reported in the patients of different disciplines of medicine. Historically haemolacria could be traced back to the medieval 'stigmatists' of catholic faith, where bleeding from different wound sites (locations corresponding to the crucifixion wounds of Jesus Christ). Stigmata could take various forms including bloody tears<sup>9,10</sup>. In ophthalmology, sanguineous discharge is a relatively frequent finding in acute conjunctival hyperaemia and inflammation but occurrence of bleeding from eyes in isolated form is unusual and extremely rare. Many causes are outlined by different authors; like, conjunctivitis, capillary haemangioma, conjunctival telangiectasia, lacrimal sac tumours or trauma. Ahwalia et al reported case of haemolacria in a young female where episodes of blood tearing was only under stress, like house examinations. Presence of hysterical trait was confirmed by the consulting psychiatrist. We found mutiple stressors working in our cases at the outset of symptoms. M F Wiese reported a 56 years old woman presented with the history of bleeding from the right nostril. When she had tried to stop it by pinching her nose, she then experienced bleeding from her right eye and ear. Bleeding was ultimately found to be due to haemorrhagic telangiectasia inside nasal cavity<sup>7</sup>. Cases of haemolacria secondary to other ENT causes has also been found in literature which include nasal and paranasal tumours. Ozcan KM reported an 11 years old paediatric patient with the complaints of bilateral haemolacria along with recurrent epistaxis where examination revealed a right side deviated nasal septum and increased hyperemic vascularity in the nasal mucosa, other ENT examinations were normal<sup>3</sup>. A case of haemolacria and epistaxis secondary to hyperthyroidism has been reported by Jason et al where local pathology and coagulopathy have been excluded by examination. Symptoms resolved after appropriate treatment<sup>4</sup>. Ho et al reported a series

of four cases, one boy and three girls ranging 6-14 years where workup findings were normal. In all cases haemolacria resolved without any sequelae over a follow up period of 9-11 months; those cases were reported as idiopathic<sup>2</sup>. Oyenusi and Ananti reported two cases of bloody tears, first one, a boy, presented with cough and bloody tears, the bleeding stopped after routine treatment. The second case was a girl, presented with redness and yellowish mucoid discharge from both eyes with low grade fever for three days followed by bloody tears; this patient was finally diagnosed as orbital cellulitis and managed with antibiotics<sup>8</sup>. M Versetrat wrote in his paper regarding psychogenic bleeding. Psychogenic purpura (Auto-erythrocyte sensitisation) consists in the spontaneous appearance of recurrent bruising, which is still unexplained. Most often women with an underlying emotional disorder are affected. In addition to cutaneous ecchymoses and hematomas, there may be many other complaints encompassing multiple organ systems along with menorrhagia, metrorrhagia, haematuria, epistaxis and gastrointestinal bleeding and haemolacria. Spontaneous psychogenic cutaneous bruising is very difficult to distinguish from self-inflicted iatrogenic bleeding. The only therapeutic approach in patients with psychogenic bleeding is psychiatric, with particular attention to the sociocultural background of the patient and his family<sup>5, 12</sup>. In our report, four cases of haemolacria along with bleeding from multiple sites associated with psychiatric disorders are described. After meticulous history, direct observation, mental state examinations, examinations to exclude local pathology in collaboration with other departments and work-up for all relevant laboratory investigations, three patients were diagnosed as Mixed Dissociative Disorder and one case with conversion disorder. Dissociative disorders are characterized by a disruption and/or discontinuity in the normal integration of consciousness, memory, identity emotion, perception, body representation motor control, and behavior. Dissociative symptom can potentially disrupt every area of psychological functioning. Dissociative disorders have a high percentage of comorbidities like depression, PTSD, anxiety, self-mutilation, non-epileptic seizure and other psychiatric disorders.<sup>13</sup> Bozkurt et al found high comorbid depression and PTSD in adolescents diagnosed with Dissociative disorder.<sup>14</sup> In our case no. 1, conversion symptoms witnessed might be an associated

feature, but history revealed that in a previous occasion at least once the patient was diagnosed as conversion disorder. No associated physical illnesses were found in any of them. In case no. 4, concomitant migraine was present. All cases were given the diagnoses as per DSM 5 criteria. Dissociative Identity Disorder (300.14), Dissociative amnesia (300.12), Depersonalization/Derealization (300.6), along with found.

All of our cases possess hysterical trait, all are adolescents, and there is a female preponderance, which is a common occurrence in Dissociative Disorders. It was noted that, most of the time, severity and intensity of the condition either aggravated or precipitated by detachment (actual or perceived) from the attachment figures. In all of our reported cases, we witnessed the events during their hospital stay.

Limitations: All of our reported cases did not present to us at the beginning of their symptoms. Physicians of different disciplines were consulted for physical symptoms. Parents also sought for treatment from traditional and Spiritual healers. As it is not within the scope of this reporting, we did not provide the detailed psychiatric history and diagnostic issues which could be helpful for better understanding. We excluded malingering and factitious disorder through psychiatric assessment as it is known that those who feign dissociative symptoms remain undisturbed with their symptoms and they only report symptoms those are well known to other members of the society, yet definite absence of feigning could not be reliably determined, as no test or procedure is available to date. Could it be a self-injurious behaviour prior to hospital presentation, were not known.

Conclusion: Bloody tearing or haemolacria is an unusual complaint which concerns patients and guardians and many times may baffle physicians. In most of the cases reported so far, haemolacria accompanied bleeding from other body sites as well. This unusual condition has been described in patients with underlying pathology and more importantly sometimes without any known pathology. In the literature, haemolacria has been described as a 'rare' phenomenon, but we are in the opinion that this condition is not that uncommon, as similar cases are increasingly being reported than before. Many cases have been described as idiopathic from different countries. We suggest a multidisciplinary

approach including psychiatric consultation for evaluation of the haemolacria patients when there is no known pathology. Although it is not recorded as an associated feature of Dissociative Disorders in any literature so far, we found bleeding through eyes in our cases of Dissociative disorders and conversion disorder, where no physical pathology were present. However, it needs more case reports by psychiatrists. We reported physical symptom of bleeding through eyes in our cases of dissociative disorders and conversion disorder which cannot be explained by any standard criteria practiced at present.

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# Posterior Reversible Encephalopathy Syndrome (PRES)

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## Summary::

*Posterior Reversible Encephalopathy Syndrome is a rare and acute neuro-radiological entity, characterized by several symptoms of different aetiologies. The main etiologies of PRES are HTN, Pre-eclampsia, Eclampsia, Immunosuppressive therapy etc, but there are many*

*unexplained causes too. Here we report a case of post-partum woman who developed PRES in post-operative period, who was complicated by the postdural puncture headache following spinal anesthesia- a rare and uncommon etiology.*

*(J Bangladesh Coll Phys Surg 2017; 35: 43-45)*

## Introduction:

Posterior Reversible Encephalopathy Syndrome (PRES) is a proposed cliniconeuroradiological entity, characterized by several symptoms of different etiology. It predominantly affects the posterior circulation territory and clinical hallmarks are headache, confusion, altered mental status, seizures, visual disturbance and rarely other neurological signs<sup>1</sup>. PRES is seen, not only in relation to pre-eclampsia, but in a variety of disease or condition<sup>3</sup>. Postdural puncture headache is a well described complication of spinal anesthesia in caesarian delivery. Although PRES has not been associated with postdural puncture headache after spinal anesthesia in post partum women<sup>4</sup>.

This is a case report of post partum women of an uneventful pregnancy who developed PRES after spinal anaesthesia which was complicated by the postdural puncture headache.

## Case Report:

A 20 years old primipara underwent caesarean delivery under spinal anesthesia at her 40<sup>th</sup> week of gestation because of failure to progress. Her medical history and laboratory examination were unremarkable and pregnancy was uneventful throughout the antenatal period.

After an initial I/V preload of Lactate Ringer's solution (1000 ml), Spinal block was performed, using a midline approach. On the first attempt, clear cerebrospinal fluid was obtained. The patient delivered a healthy baby. The mother's vital signs were normal in per-operative and post operative period.

The patient was well until two days of post surgery. On the third day she developed severe postdural headache over bi frontal area, particularly in erect posture, which was relieved by recumbent position. The diagnosis of post dural puncture headache was made. The headache improved after two days of supportive therapy which includes aggressive intravenous hydration, bed rest without pillow and oral analgesics. On 5<sup>th</sup> postoperative day the patient developed a severe throbbing headache over the occipital area which was no longer postural. On the same day, she developed convulsion which was tonic-clonic in nature with aura. There were 2-3 episodes of convulsion at an interval of 1-2 minute within 25-30 minutes. During this seizure she was unconscious, B/P was 120/80mmHg, pulse 100/m, and urine albumin was nil. Her hematological and biochemical marker were within normal limit. She was nursed in ICU with Anticonvulsive (Mgso4) for 24 hrs, parenteral antibiotic and sedative. Routine hematological, biochemical test as well as chest X- ray, ECG were done and found normal. Diagnostic lumbar puncture revealed clear CSF fluid without any inflammatory cell. The patient's condition was stabilized after 48 hours of ICU nursing. Afterward CT scan and MRI of brain were performed and revealed edema of the bilateral Parieto occipital lobes with density changes and signal alteration respectively, impression was PRES.

During the period of post convulsion hospitalization, there was no episode of marked hypertension, urine albumin was nil and biochemical marker were absolutely normal. After diagnosis patient was treated by multidisciplinary approach by medical specialists and obstetricians. Treatment regimen was initial intravenous nalespin followed by Injection Mannitol, parenteral steroid and later on oral phenytoin were added.

Considering the stability and general condition of the patient gradually medications were withdrawn. She was

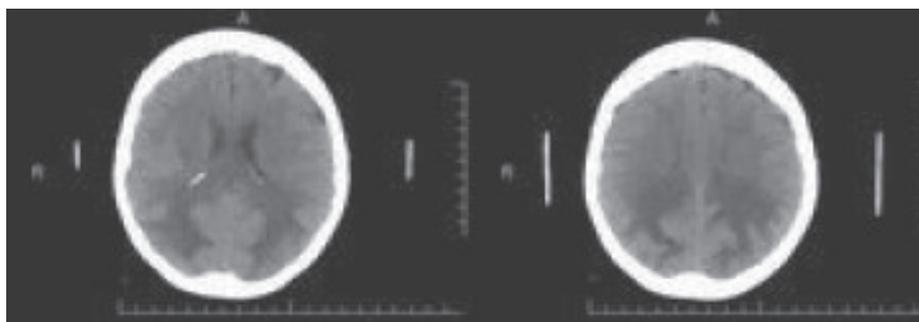
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b. Prof. (Col) Khaleda Khanam (Rtd.), Gynaecologist, Army Medical Corps.

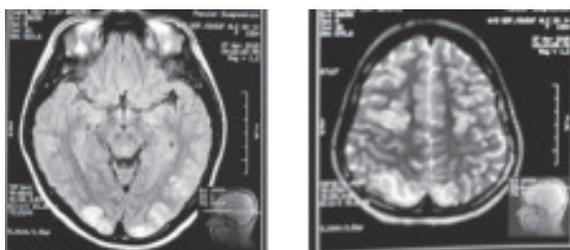
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**Received:** 18 May 2016

**Accepted:** 6 Nov. 2016



**Fig.-1:** CT Scan- Diffuse hypodensity in both parieto occipital region.



**Fig.-2:** MRI- Hyper intense signal in both parieto occipital region in T2 and flare image.

discharged from hospital at 12<sup>th</sup> post operative day with the advice for follow -up after 02 weeks. After 02 weeks MRI of brain was done which showed an almost complete resolution of the previous lesion.

### Discussion.

PRES was first introduced into clinical practice in 1996<sup>2</sup>. Pathogenesis of PRES is thought to be multi-factorial, yet two different theories are dominating and still being debated<sup>3</sup>. The hyper perfusion theory also called the “vasogenic theory” and the hypo perfusion/ ischaemic theory also called the “cytotoxic theory”<sup>3</sup>. However, the pathogenesis is attributed to a failure of cerebral auto regulation that is probably facilitated in posterior brain region due to sparse sympathetic innervations of the vertebrobasilar vascular system<sup>2</sup>.

Clinical symptoms, as well as neuroimaging finding in this patient are compatible with PRES. The patient presented with severe headache over the frontal followed by occipital area, decreased awareness and confusion followed by convulsion. These occurred 2 days after an episode of typical postdural puncture headache following spinal anesthesia for cesarean delivery. CT scan finding was bi lateral patchy hypodensities involving the cortex and subcortical white

matter in parieto-occipital lobe. The MR imaging revealed cytotoxic edema of the cerebrum involving bilateral parieto-occipital lobes; MR angiography was unremarkable. These finding indicate that the lesion of PRES of this patient was associated with ischemia-induced cytotoxic edema.

Although the exact mechanism for PRES remains unknown, the temporal association of encephalopathy with diffuse cerebral vasospasm after an episode of postdural puncture headache may have been causative in this patient<sup>4</sup>. Persistent leakage of CSF through the dural opening left by the lumbar puncture needle can result in sagging of the brain and traction on nerves and meningeal vessels. Presumably, the diminished volume of CSF in the cerebral ventricle may collapse the ventricle. This traction might cause mechanical stimulation on the arterial wall and in theory, could induce vasospasm. Clearly, more clinical data are needed to prove this putative mechanism of collapsed ventricle-induced vasospasm<sup>4</sup>. In the current patient, diffuse cerebral artery vasospasm possibly was due to the traction of this vessel by anatomic brain displacement, could It provides an explanation for the development of PRES after spinal anesthesia .Furthermore, lack of evidence for systemic vasculopathy argues against an immune-mediated vacuities in our patient. In addition due error in the CNS, blood pressure auto regulation, and lack of sympathetic innervations of vessels emanating from basilar and vertebral arteries , blood flow in the CNS will increase. this cause elevated capillary filtration pressure and damage the capillary wall, eventually leading to increase blood brain barrier permeability and the consequence of cerebral oedema. All these observations suggest that diffuse cerebral vasospasm after an episode of post dural puncture

headache following spinal anesthesia could have caused PRES in this patient.

PRES has been reported to be reversible; although, irreversible brain damage can sometimes occur due to late recognition or incorrect treatment<sup>2, 4</sup>. Importantly, institution of early treatment, leads to symptom resolution without neurologic deficit, as was seen in this patient. Therefore, aggressive treatment for cerebral vasospasm is essential.

Several clinical studies have also shown that intravascular magnesium sulfate safely relieved maternal cerebral vasospasm<sup>4</sup>. In this case, all syndromes subsided after treatment with magnesium sulphate, Mannitol, steroid, with sedative and other supportive treatment. The abnormal findings on neuro imaging had almost reversed after 15 days.

We describe the successful management of a postpartum woman with cerebral vasospasm-induced PRES associated with postdural puncture headache following spinal anesthesia as another condition underlying PRES. This management could be successful only with good intensive care support, proper monitoring and a team work combined with obstetrician and medical specialist.

### Conclusion:

The cause of PRES is certainly multifactorial. The syndrome should be promptly recognized since it is reversible. The key to diagnosis is certainly the image, but clinicians must raise suspicion when there is a case with atypical features.

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# Atypical Presentation of Pretibial Myxoedema in Graves' Disease

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(*J Bangladesh Coll Phys Surg 2017; 35: 46*)

A 26-year-old man presented with gradual swelling of both legs for the last 5 years (Figure 1). The skin over the legs are thickened, with irregular nodular swelling. He also complained of significant weight loss in past few months, together with frequent passage of loose

stool, sweating and palpitation. Patient was previously treated by Diethylcarbamazine as a case of Filariasis. His thyroid profile revealed TSH - 0.00 mIU/L, F-T4 - 30.27 pmol/L, F-T3 - 16.51 pmol/L, Anti-Thyroglobulin Ab - 1.66 IU/ml

The patient was diagnosed with Thyrotoxicosis due to Graves disease with Thyroid acropachy with Dermopathy. This atypical nodular dermatopathy is a rare presentation in Graves diseases.



Fig.-1:



Fig.-2:

stool, sweating and palpitation. Patient was previously treated by Diethylcarbamazine as a case of Filariasis.

On examination the patient was anxious with a staring look and mildly anaemic. There was clubbing (Figure: 2) in digits of hands and feet, tachycardia, irregular nodular non tender and firm goitre with no bruit or retrosternal extension, warm and moist palm, fine tremor.

There was bilateral non pitting oedema of the legs (Figure: 3) and overlying skin is thick, irregular, nodular. There is no organomegaly, ascites or lymphadenopathy. There was exophthalmus, but no diplopia, ophthalmoplegia, lid lag or lid retraction.



Fig.-3:

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## ***FROM THE DESK OF EDITOR in CHIEF***

*(J Bangladesh Coll Phys Surg 2017; 35: 47)*

Dear Fellows,

Seasons Greetings and Happy New Year.

I take the opportunity to thank all my Authors, Reviewers, Editors and Office Bearers for their fabulous support throughout 2016. You have made the last year a very successful year for JBCPS. We have been able to publish numerous wonderful articles that has been well appreciated here and

abroad. Now we look forward to take our beloved journal to a higher level in 2017.

Your all out support is my strength.

Thank you

**Prof. Khan Abul Kalam Azad**

Editor-in-Chief

Journal of BCPS