JMGV001N02

April-June 2014 Volume 1 Number 2

ISSN 2347-7946
eISSN 2347-7962

MGM Journal of MEDICAL SCIENCES

MGMJMS

Also available online at
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Bibliographic Listing:
WHOIMSEAR

The Official Publication of
Mahatma Gandhi Mission Institute of Health Sciences
(Deemed University u/s 3 of UGC Act 1956)
Kamothe, Navi Mumbai, Maharashtra, India

April-June 2014 Volume 1 Number 2 ISSN 2347-7946

MGM Journal of Medical Sciences

The Official Publication of
Mahatma Gandhi Mission Institute of Health Sciences
(Deemed University u/s 3 of UGC Act 1956)

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MGM Journal of Medical Sciences

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MGM Institute of Health Sciences (Deemed University) recognizes the urgent need for promoting medical education in the country, so that the quality of life for individuals and community could be improved by promoting health, preventing and curing diseases, advancing biomedical and clinical research and educational programs for tomorrow's physicians and scientists. The University is committed to creativity, innovation and excellence in every sphere of its working. The University will transform lives and serve the society by educating, creating knowledge and putting knowledge to work. In this endeavor the University has launched a quarterly peer-reviewed scientific journal 'MGM Journal of Medical Sciences' to encourage investigators to publish their research findings for wider dissemination with the aim of applying those for the benefit of the society.

The newly launched peer-reviewed quarterly journal would cover full spectrum of the specialties in biomedical and clinical research. Its first issue would be released in December 2013. The journal aims to publish articles arising out of original research, specialized topics, review articles, editorials, and description of new diagnostic and therapeutic techniques and technologies. In addition, the journal will include pictorial reviews, letters to the editors, book review, and notices of meetings and courses. In this endeavor, the journal hopes to provide a forum for the stimulation of new developments, clinical practices and research in the field of health and allied sciences. The salient feature of the journal would be to bring out from time to time special issues focusing on specific themes of national relevance including the outcome of scientific meetings, etc. A section would be devoted exclusively to young researchers and students in order to encourage them to publish their innovative ideas and research findings. **In fact, it will be a 'student friendly' journal.**

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eISSN 2347-7962

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MGMJMS

April-June 2014 Vol. 1 No. 2

MGM Journal of Medical Sciences

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Editorial

In our daily lives, we get sucked so willingly into nurturing an engrossingly busy schedule that over time it converts itself into a necessity for fulfilling our self-actualization needs. We are busy bees building our own beehives. It then takes a shock event to occur, for us to realize our frog in the well-situation. It is then that we eventually seek wisdom from the macro picture and realize the tininess of our micro beehive.

One such macro picture relevant to each of us in the healthcare service is that of India's disease burden. Be prepared to be shocked—not that I wish to scare you, but to ignite a fire within you to realize your micro responsibility toward our macro nation of 1.3 billion people. Let this responsibility always reside at the back of your mind, as you continue to serve your important roles in preventing and curing diseases, buzzing around your beehives.

- Seventeen percent of the world's population today are Indians. We have tripled in the last 65 years from 0.4 to 1.3 billion, and growing.
- We account for 21% of the world's disease burden, that is, every 5th 'diseased' person globally is an Indian.
- Rapid changes in our lifestyles and society have led to a rise in noncommunicable diseases responsible today for 53% of the total deaths, expected to be 59% by 2015. India is home to the greatest burden of maternal, newborn, and child deaths in the world.
- The female-to-male sex ratio in the 0 to 6-year-old age group declined steeply from 0.945 in 1991 to 0.914 in 2011.
- India is losing more than 6% of its Gross Domestic Product (GDP) annually due to premature deaths and preventable illnesses. A total of 70% of our people's expenses made toward healthcare are out of pocket, that is, their personal spending not covered under medical insurance.

The way to cure this Tsunami of India's disease burden challenge is engaging research, education, awareness of the macro challenge, embracing hygiene and discipline in our micro environments, effecting preventive measures as a part of our lifestyle habits, ensuring that we cure what is curable, completely, that is, not abandoning treatment midway or until the doctor says so.

The Research-Prevent-Cure cycle is one effective and healthy solution out of the doctor's First Aid Box!

Editors-in-Chief
Shibban K Kaul MS MCh FIACS
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MGM Journal of Medical Sciences

April-June 2014 Volume 1 Number 2

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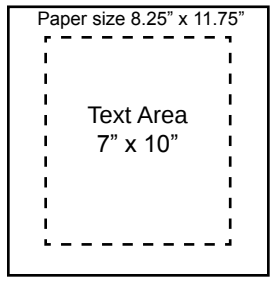

Technical Details

Paper size	8.25 x 11.75 inches
Print size	7 x 10 inches
Digital file format	EPS on CD (at 300 dpi resolution)

Printed on art paper using offset printing.

Schedule

Issues are published in the months of January, April, July and October.
Advertisement material along with purchase order and payment should reach us at least four weeks prior to the scheduled print date.

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10.5005/jp-journals-10036-1009

ORIGINAL ARTICLE

Fetal Liver CD34$^+$-Cells in Dynamic of Human Fetus Development

[1]AB Padma Priya, [2]O Kukharchuk

ABSTRACT

Fetal liver stem cells are not homogeneous but represented mostly by polyploidy hepatocytes and hepatoblasts and likewise early hematopoietic cells. Both cells lately used in regenerative medicine. However, fact remains unclear that, in which period of gestation preferably produces liver parenchyma stem cells and hematopoietic stem cells. In this case practically there is absence of phenotypic characteristics of liver cells in the dynamics of its development. Phenotype of cells reflects the status of its genome, therefore such information are necessary for further development of cell transplantation.

Aim: To create CD34$^+$ phenotypic map of fetal stem cells, isolated from abortive material (fetal liver) obtained by means of MTP in gestation periods from 6 to 20 weeks.

Methods: Flow cytometry phenotypic characteristics of hematopoietic fetal stem cells: CD34$^+$-cells.

Results: Results show that maximum total amount of fetal liver cells could be isolated in the gestation period 20 weeks, minimum – in the gestation period of 6 to 7 weeks. Maximum absolute quantity of CD34$^+$-cells observed in the period of gestation 20 weeks, minimum – in the period of gestation 6 to 7 weeks. Viability of the cells while using our method of isolation is high and varies from 91.5 to 95.5%. The highest percent of CD34$^+$-cells observed in the gestation period 11 weeks, and lowest – in the period of gestation 6 to 7 weeks.

Conclusion: Obtaining results allows making preliminary conclusion, that optimal period for isolation of fetal liver hematopoietic CD34$^+$-cells are 11 weeks and 18 to 20 weeks periods of gestation age.

Keywords: Fetal liver, Stem cells, Phenotype.

How to cite this article: Priya ABP, Kukharchuk O. Fetal Liver CD34$^+$-Cells in Dynamic of Human Fetus Development. MGM J Med Sci 2014;1(2):47-52.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Currently, regenerative medicine is rapid practical developing field in all leading countries of the world.[1,2] India is one among them. Significance in the level of Indian legislation concludes the process of recommended (guidelines) for the applications of stem cells in practical medicine. As stated in the recommended (guidelines), fetal stem cell related to the permitted field of research and prophylatic applications. Several studies indicate that expression of classical markers for stem cell classification, such as CD34, CD45, and CD133, may differ between the virtually same stem cells and progenitor cells, i.e. endothelial progenitor or mesenchymal stem cells, when they were obtained from different tissues. This finding raises questions whether phenotypic differences are due to the source or if it is only caused by different isolation and experimental conditions.[3] The review of literature shows apparently less data about the fetal liver cell development. Pioneer research in this direction was conducted by Professor Kochupillai Vinod.[4] Study of these processes is not only scientifically important but also has vast practical significance, such as transplantation of cell specialized on particular function having potentially high chances of successful treatment.

Thus, human fetal stem (progenitor) cells need additional studies. In particular till date remains unknown fact of dynamic phenotypical changes of cells in different organs and tissues in the duration of gestation period (from 6-20 weeks). Knowledge of these changes (specific design about it) is very important for treatment of patients with stem cells. This is related to those, that phenotype of cells reflects the state of genome and therefore they are the markers for potential treatment features of cells. Therefore, actual problem of regenerative medicine is forming phenotypic map of fetal progenitor cells in dynamics of fetal development. Such maps provide the opportunity to develop treatment algorithm of several human diseases with fetal stem (progenitor) cells according to its phenotypes optimum for each diseases.

Aim

To study the dynamic of CD34-markers expression on liver stem (progenitor) cells in process of human fetus development (from 6-20 weeks gestation).

MATERIALS AND METHODS

Raw Material

Experiments were conducted with the fetal liver cells which were isolated and stored in cryobank of EmProCell Clinical

[1]Research Officer, [2]Honorary Professor and Director

[1,2]Department of Biotechnology, EmProCell Clinical Research Private Limited, MGM School of Biomedical Sciences (MGMIHS), Navi Mumbai, Maharashtra, India

Corresponding Author: AB Padma Priya, Research Officer Department of Biotechnology, C-7/1A, TTC Industrial Area Thane-Belapur Road, Village Pawane, Navi Mumbai-400703 Maharashtra, India, e-mail: priyaepc1@gmail.com

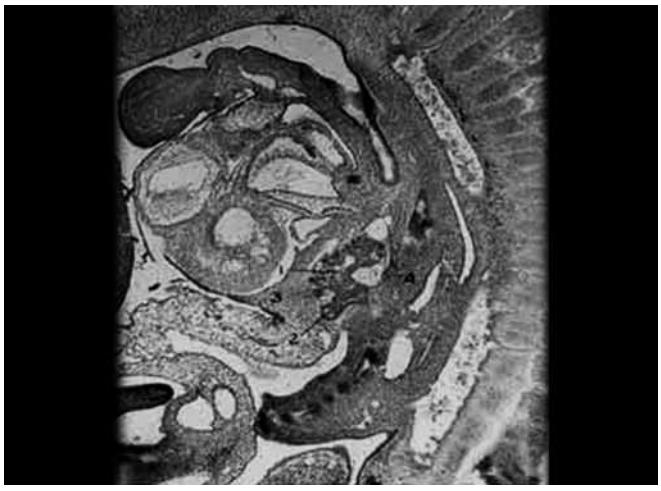

Fig. 1: Sagittal section of human fetus—5.0 mm length (26-27 day of development) ×21: 1—Hepatic folds with entodermal trace and mesenchyme layers; 2—Gallbladder folds; 3—Transverse partition fold; 4—Intestinal tubule

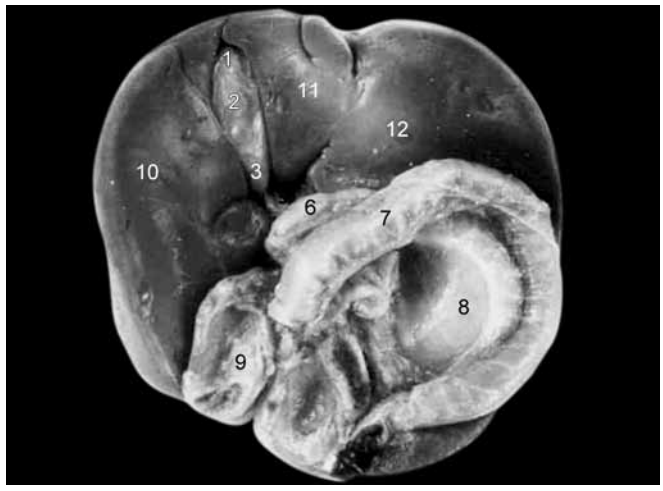

Fig. 2: Human fetal liver 132 mm length (bottom view) ×2.5: 1—Bottom of the gallbladder; 2—Body of the gallbladder; 3—Neck of the gallbladder; 4—Bladder duct; 5—Common hepatic duct; 6—Duodenum; 7—Transverse colon; 8—Stomach; 9—Right adrenal gland; 10—Unnamed hepatic lobe; 11—Square lobe of the liver; 12—Left lobe of the liver

Research Pvt Ltd, based on the approval of ethical committee MGM Institute of Health Sciences from 11.06.2010. Cells were stored in the liquid nitrogen.

Hematopoiesis in the liver takes place extravascularly – by the pathway of capillaries, in-growing along with mesenchyme in the internal hepatic lobule. Source of blood forming which migrates from yolk sac hematopoiesis in the liver is hematopoietic stem cells. Mesenchymal cells located between primary hepatic entodermal traces and endothelial cells of in-growing capillaries (Fig. 1).[5,6]

Liver isolated from the body of the fetus in the sterile condition (Fig. 2), washed from the mixture of blood, pulverized and homogenized. Subsequently from the homogenate liver tissue, stem cells are isolated by the consecutive method of filtration and centrifugation on the gradient of ficoll and verographin.

Analyses were performed on CD34 expression in hematopoietic cells isolated from fetal liver in gestation terms: 6 to 7 weeks (9 samples), 8 weeks (7 samples), 9 weeks (6 samples), 10 weeks (11 samples), 11 weeks (12 samples), 12 weeks (10 samples), 13 weeks (9 samples), 14 weeks (8 samples), 15 weeks (6 samples), 16 weeks (7 samples), 17 weeks (5 samples), 18 weeks (5 samples), 19 weeks (7 samples), 20 weeks (6 samples).

Isolation of Human Fetal Liver Cells

Fetal livers were dissociated in Leffert's buffer with 0.03% collagenase (Cat. no. 2139, Worthington Biochemical Corp., Lakewood, NJ), 5 mM $CaCl_2$ and 500 U/ml DNase (D-5025, Sigma Chemical Co., St. Louis, MO). Dispersed cells were passed through 80 μm dacron, pelleted at 350 gm for 5 minutes at 4°C, and cryopreserved. Cell viability was determined with Trypan Blue exclusion.

Marker for Research

CD34-stem cell marker, adhesion, found on hematopoietic precursors, capillary endothelium and embryonic fibroblasts. CD34 is ligand for CD62 (L-selectin).

Flow Cytometry

Cryopreserved cell samples were thawed and washed from DMSO by taking thawed 1.8 ml of cell suspension of fetal liver progenitor cells and added to 10 ml of PBS. Cells were centrifuged, the supernatant was discarded and the pellet was suspended in 1 ml PBS at 1×10^6 cells/ml. For direct staining, 100 μl of the cell suspension was incubated with 10 μl CD34 (Anti-HPCA-2), clone 8G12 (Becton Dickinson, USA) was added and incubated for 30 minutes at 4°C in the dark. Cells were centrifuged, the supernatant was discarded and the pellet was suspended in 500 ml PBS and immediately analyzed in a flow cytometer 'Accuri C 6' (Becton Dickinson, USA) with the unstained controls.

Statistics

All values are given as mean ±SD. Statistical analysis was performed using Microsoft Excel and statistical package for social sciences (SPSS, Chicago, Inc Version 16).

RESULTS

Altogether 108 determinations were performed. As the result of determining the expression on surface of hematopoietic

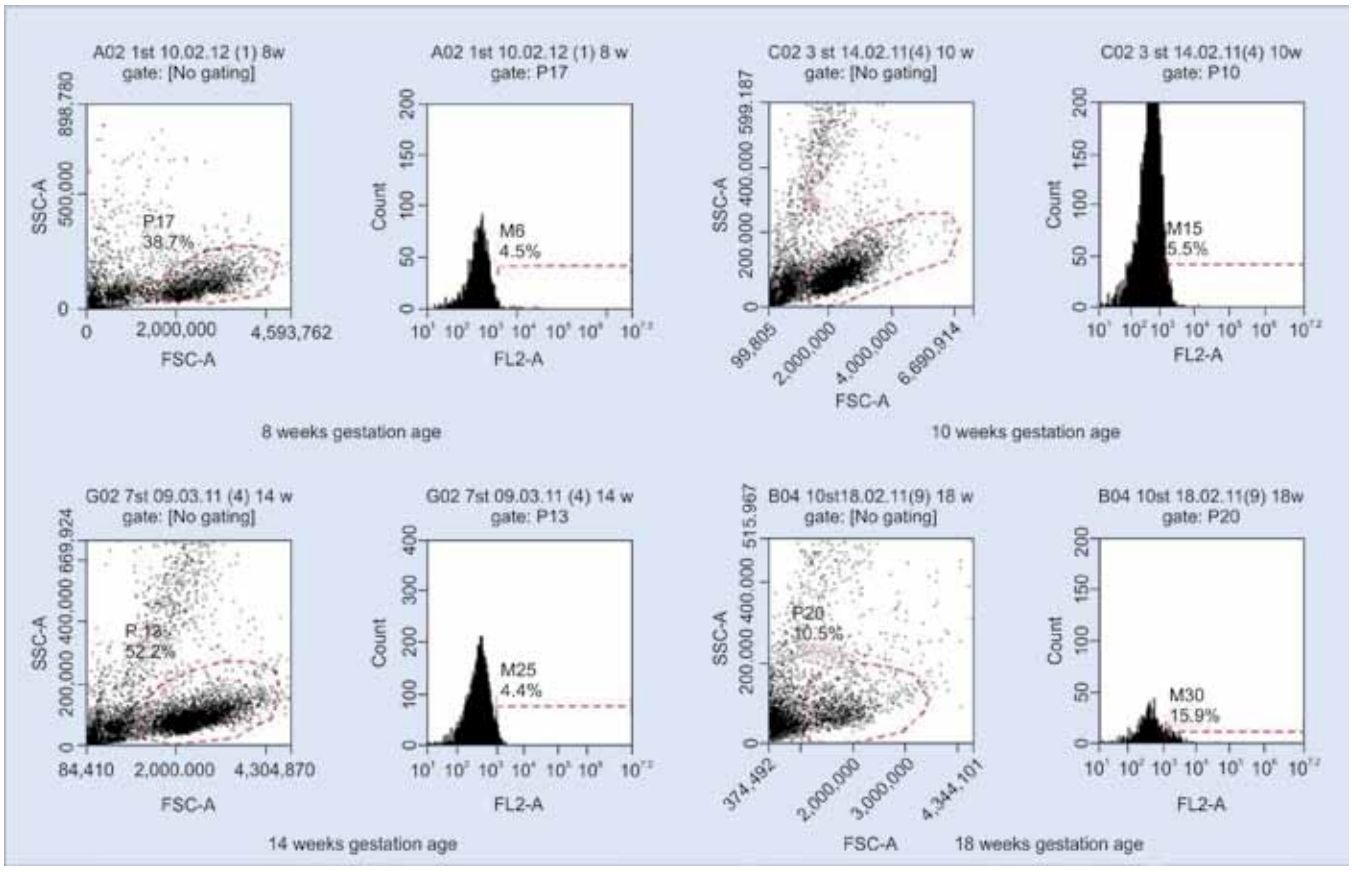

Fig. 3: Hematopoietic stem cells of fetal liver CD34⁺-cells

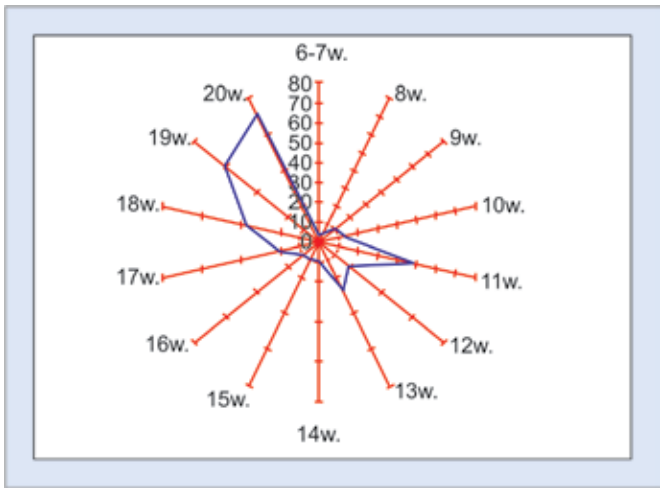

Fig. 4: Absolute amount of CD34⁺-cells of fetal liver in various gestation period (× 10^4/1 ml 10% suspension of liver cells)

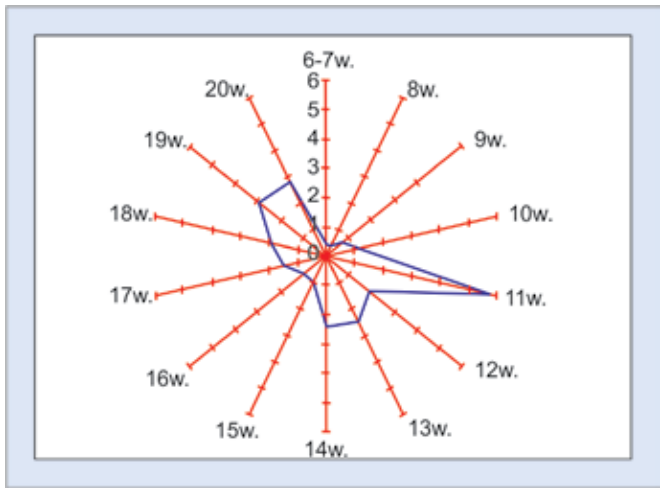

Fig. 5: Percentage of CD34⁺-cells of fetal liver in various gestation period (% from the total amount of cells in 10% suspension of liver cells)

progenitor CD34 mentioned in the Table 1 and Figure 3 (Flow cytometry histograms).

Results show that maximum total amount of fetal liver cells could be isolated in the gestation period 20 weeks, minimum – in the gestation period of 6 to 7 weeks. Maximum absolute quantity of CD34⁺-cells observed in the period of gestation 20 weeks, minimum – in the period of gestation 6 to 7 weeks (Fig. 4). Viability of the cells while using our method of isolation is high and varies from 91.5 to 95.5%. The highest percent of CD34⁺-cells observed in the gestation period 11 weeks, and lowest – in the period of gestation 6 to 7 weeks (Fig. 5).

CONCLUSION

Special feature of fetal liver hematopoietic cells is its ability to create colony, which by their size significantly converts

Table 1: Expression of CD34 on hematopoietic cells of fetal liver of various gestation terms

Gestation terms	*Total amount of cells (×10^6/ml)*	*Amount of CD34$^+$ (×10^4/ml)*	*% CD34$^+$-cells*
6-7 weeks, n = 9 group 1	7.91 ± 1.08	3.38 ± 0.47	0.43 ± 0.02
8 weeks, n = 7 group 2	15.66 ± 2.34 $p_{2-1} < 0.02$	4.63 ± 0.64	0.30 ± 0.01 $p_{2-1} < 0.001$
9 weeks, n = 6 group 3	15.52 ± 1.89 $p_{3-1} < 0.02$	8.87 ± 1.28 $p_{3-1} < 0.001$; $p_{3-2} < 0.02$	0.56 ± 0.020 $p_{3-1} < 0.001$; $p_{3-2} < 0.001$
10 weeks, n = 11 group 4	11.38 ± 1.08	12.61 ± 0.96 $p_{4-1} < 0.001$; $p_{4-2} < 0.001$; $p_{4-3} < 0.05$	1.14 ± 0.04 $p_{4-1} < 0.001$; $p_{4-2} < 0.001$; $p_{4-3} < 0.001$
11 weeks, n = 12 group 5	9.83 ± 1.04 $p_{5-2} < 0.02$; $p_{5-3} < 0.02$	50.85 ± 3.40 $p_{5-1} < 0.001$; $p_{5-2} < 0.001$; $p_{5-3} < 0.001$; $p_{5-4} < 0.001$	5.50 ± 0.30 $p_{5-1} < 0.001$; $p_{5-2} < 0.001$; $p_{5-3} < 0.001$; $p_{5-4} < 0.001$
12 weeks, n = 10 group 6	10.85 ± 1.27	20.14 ± 2.56 $p_{6-1} < 0.001$; $p_{6-2} < 0.001$; $p_{6-3} < 0.01$; $p_{6-4} < 0.02$; $p_{6-5} < 0.001$	1.89 ± 0.07 $p_{6-1} < 0.001$; $p_{6-2} < 0.001$; $p_{6-3} < 0.001$; $p_{6-4} < 0.001$; $p_{6-5} < 0.001$
13 weeks, n = 9 group 7	10.83 ± 1.53	24.02 ± 2.62 $p_{7-1} < 0.001$; $p_{7-2} < 0.001$; $p_{7-3} < 0.01$; $p_{7-4} < 0.001$; $p_{7-5} < 0.001$	2.40 ± 0.21 $p_{7-1} < 0.001$; $p_{7-2} < 0.001$; $p_{7-3} < 0.001$; $p_{7-4} < 0.001$; $p_{7-5} < 0.001$; $p_{7-6} < 0.05$
14 weeks, n = 8 group 8	8.61 ± 1.29 $p_{8-2} < 0.02$; $p_{8-3} < 0.01$	11.36 ± 1.41 $p_{8-1} < 0.001$; $p_{8-2} < 0.01$; $p_{8-5} < 0.001$; $p_{8-6} < 0.02$; $p_{8-7} < 0.001$	1.39 ± 0.09 $p_{8-1} < 0.001$; $p_{8-2} < 0.001$; $p_{8-3} < 0.001$; $p_{8-4} < 0.02$; $p_{8-5} < 0.001$; $p_{8-6} < 0.001$ $p_{8-7} < 0.001$
15 weeks, n = 6 group 9	9.87 ± 1.22 $p_{9-3} < 0.05$	10.57 ± 1.40 $p_{9-1} < 0.001$; $p_{9-2} < 0.01$; $p_{9-5} < 0.001$; $p_{9-6} < 0.02$; $p_{9-7} < 0.01$	1.07 ± 0.04 $p_{9-1} < 0.001$; $p_{9-2} < 0.001$; $p_{9-3} < 0.001$; $p_{9-5} < 0.001$; $p_{9-6} < 0.001$; $p_{9-7} < 0.001$ $p_{9-8} < 0.02$
16 weeks, n = 7 group 10	10.91 ± 1.61	11.40 ± 1.56 $p_{10-1} < 0.001$; $p_{10-2} < 0.01$; $p_{10-5} < 0.001$; $p_{10-6} < 0.05$; $p_{10-7} < 0.01$	1.12 ± 0.20 $p_{10-1} < 0.01$; $p_{10-2} < 0.01$; $p_{10-3} < 0.05$; $p_{10-5} < 0.001$; $p_{10-6} < 0.001$; $p_{10-7} < 0.001$
17 weeks, n = 5 group 11	17.22 ± 2.90 $p_{11-1} < 0.01$; $p_{11-4} < 0.05$; $p_{11-5} < 0.01$; $p_{11-6} < 0.05$; $p_{11-8} < 0.02$; $p_{11-9} < 0.05$	20.54 ± 3.84 $p_{11-1} < 0.001$; $p_{11-2} < 0.001$; $p_{11-3} < 0.02$; $p_{11-4} < 0.02$; $p_{11-5} < 0.001$; $p_{11-8} < 0.05$ $p_{11-9} < 0.05$; $p_{11-10} < 0.05$	1.18 ± 0.03 $p_{11-1} < 0.001$; $p_{11-2} < 0.001$; $p_{11-3} < 0.001$; $p_{11-5} < 0.001$; $p_{11-6} < 0.001$; $p_{11-7} < 0.01$
18 weeks, n = 5 group 12	17.02 ± 2.90 $p_{12-1} < 0.01$; $p_{12-4} < 0.05$; $p_{12-5} < 0.02$; $p_{12-6} < 0.05$; $p_{12-8} < 0.02$; $p_{12-9} < 0.05$	34.44 ± 6.80 $p_{12-1} < 0.001$; $p_{12-2} < 0.001$; $p_{12-3} < 0.01$; $p_{12-4} < 0.001$; $p_{12-5} < 0.05$; $p_{12-6} < 0.05$; $p_{12-8} < 0.01$; $p_{12-9} < 0.01$; $p_{12-10} < 0.01$	2.01 ± 0.09 $p_{12-1} < 0.001$; $p_{12-2} < 0.001$; $p_{12-3} < 0.001$; $p_{12-4} < 0.001$; $p_{12-5} < 0.001$; $p_{12-8} < 0.001$ $p_{12-9} < 0.001$; $p_{12-10} < 0.01$; $p_{12-11} < 0.001$
19 weeks, n = 7 group 13	20.59 ± 2.69 $p_{13-1} < 0.001$; $p_{13-4} < 0.01$; $p_{13-5} < 0.001$; $p_{13-6} < 0.01$; $p_{13-7} < 0.01$; $p_{13-8} < 0.01$; $p_{13-9} < 0.01$; $p_{13-10} < 0.01$	60.03 ± 3.98 $p_{13-1} < 0.001$; $p_{13-2} < 0.001$; $p_{13-3} < 0.001$; $p_{13-4} < 0.001$; $p_{13-6} < 0.001$; $p_{13-7} < 0.001$ $p_{13-8} < 0.001$; $p_{13-9} < 0.001$; $p_{13-10} < 0.001$; $p_{13-11} < 0.001$; $p_{13-12} < 0.01$	3.12 ± 0.27 $p_{13-1} < 0.001$; $p_{13-2} < 0.001$; $p_{13-3} < 0.001$; $p_{13-4} < 0.001$; $p_{13-5} < 0.001$; $p_{13-6} < 0.001$ $p_{13-7} = 0.05$; $p_{13-8} < 0.001$; $p_{13-9} < 0.001$; $p_{13-10} < 0.001$; $p_{13-11} < 0.001$; $p_{13-12} < 0.01$
20 weeks, n = 6 group 14	25.23 ± 3.01 $p_{14-1} < 0.001$; $p_{14-2} < 0.05$; $p_{14-3} < 0.05$; $p_{14-4} < 0.001$; $p_{14-5} < 0.001$; $p_{14-6} < 0.001$; $p_{14-7} < 0.001$; $p_{14-8} < 0.001$; $p_{14-9} < 0.001$; $p_{14-10} < 0.01$	71.73 ± 6.24 $p_{14-1} < 0.001$; $p_{14-2} < 0.001$; $p_{14-3} < 0.001$; $p_{14-4} < 0.001$; $p_{14-5} < 0.01$; $p_{14-6} < 0.001$; $p_{14-7} < 0.001$; $p_{14-8} < 0.001$; $p_{14-9} < 0.001$; $p_{14-10} < 0.001$; $p_{14-11} < 0.001$; $p_{14-12} < 0.01$	2.91 ± 0.12 $p_{14-1} < 0.001$; $p_{14-2} < 0.001$; $p_{14-3} < 0.001$; $p_{14-4} < 0.001$; $p_{14-5} < 0.001$; $p_{14-6} < 0.001$; $p_{14-8} < 0.001$; $p_{14-9} < 0.001$; $p_{14-10} < 0.001$; $p_{14-11} < 0.001$; $p_{14-12} < 0.001$

Note: p_{x-y}: Level of statistical significance of various parameters in corresponding groups; n: Number of observation

into similar while growth of hematopoietic stem cells of the cord blood or bone marrow, consequently this is related to all types of colony.[7] This fact evidences about the high proliferative potential of hematopoietic cells of fetal liver. Unique properties of hematopoietic precursor cells of fetal liver – much shorter than in comparison with other sources of cell cycle,[8] that has greatest significance from the viewpoint of effective repopulation of the hematopoietic organs while transplantation. Analysis of the content of hematopoietic suspension, obtained from sources of mature organism evidences about those, that on all stages of ontogenesis of the nuclear cells favorably represents final cell differentiation, quantity and phenotype which depends on donor's ontogentic growth of the hematopoietic tissues. In particular, mononuclear cells suspension of the bone marrow and cord blood consisting more than 50% from mature cells of lymphoid series, whereas in hematopoietic tissue of fetal liver consists of less than 10% of lymphocytes. Besides, cells of myeloid lines in embryonic and fetal liver represents beneficial by erythroid series, at times, such as in cord blood and bone marrow heaps up the granulocyte-macrophage elements.[9]

Significant, that fetal liver contains complete set of most early hematopoiesis precursors: erythroids, granulopoietic, megakaryopoietic and multilinear colony forming cells. It is most primitive precursors—long-term culture-initiating cells (LTC-IC) capable to proliferate and differentiate *in vitro* during 5 and more weeks, similarly stores functional activity after grafting in recipient's organism while allogenic and even in xenogenic transplantation of immune-deficient animals.[10-12]

Conscripted above information evidences about, that fetal liver in initial embryogenesis distinguishes not by just increase in contents of early precursor cells of hematopoiesis, but its hematopoietic cells characterizing mostly wide spectrum of differentiation in various cell lines. This specialty of functional activity of hematopoietic stem cells of fetal liver can have determined clinical significance; however its qualitative characterization allows anticipating defined therapeutically effect in transplantation even in fewer amounts of cells, obtained in the early gestation period.[13]

The study Vali SM, Vishwakarma SK, Bardia A, Tiwari SK, et al (2014), was focused to identify the highest percentage of stem cells population within different gestation aged human fetal liver using CD133. Enriched CD133$^+$-cells were found to co-express other stem cell markers, such as CD49f, CD34, CD29, CD90 and most interestingly embryonic stem cells markers SOX-2 and OCT-4. This analysis represents the existence of other stem cell subpopulations in CD133$^+$ enriched cells. Most of the CD133$^+$ cells of gestation age between 10 and 13 week showed highest co-expression for SOX-2 and OCT-4 which revealed the property of embryonic like cells within the human fetal liver.[14]

Fetal liver distinguishes from other sources of hematopoietic stem cells in mostly high content like committed, as in early hematopoietic precursor cells. Approximately 30% CD34$^+$-cells of fetal liver have phenotype CD38$^-$. At the same time, the amount of lymphoid precursor cells (CD45$^+$) in the early period of hematopoiesis in liver, consists of not more than 4%.[15] In the culture with growth factor, cells of fetal liver with phenotypes CD34$^+$CD45$^-$Ra^{low}CD71^{low} forms 30 times more colony, than analogical cord blood cells and 90 times greater than in hematopoietic stem cells of the bone marrow. Mostly expressed in indicated sources difference in the content of early hematopoietic precursor cells, forming mixed colony—amount of CFU-GEMM in fetal liver exceeds as such in cord blood and bone marrow in correspondingly to 60 to 250 times.[16] Till 18th week of embryonic development (commencement period of hematopoiesis in bone marrow) in hematopoietic function involved more than 60% of liver cells. However till 13th week of human fetal development, there is absence of thymus and correspondingly thymocytes. Therefore, transplantation of hematopoietic cells of fetal liver from 6 to 12 weeks of gestation significantly reduces risk of developing reaction 'graft *vs* host' and does not require any selection of histocompatible donor,[17] as such allows comparatively easy to achieve the hematopoietic chimerism.[16]

Thus, obtaining results allow making preliminary conclusion, that optimal period for isolation of fetal liver hematopoietic CD34$^+$-cells are 11 and 18 to 20 weeks periods of gestation age.

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10.5005/jp-journals-10036-1010

ORIGINAL ARTICLE

Comparative Study of Serum Malondialdehyde Levels as a Marker of Oxidative Stress in Patients of Pregnancy-induced Hypertension and Controls

[1]Dhananjay V Bhale, [2]Manjusha D Hivre, [3]Roshan K Mahat, [4]Ashlesha A Bujurge

ABSTRACT

Hypertensive disorders are the most common medical complications of pregnancy with a reported incidence ranging between 5 and 10%. In pregnancy-induced hypertension, many complex homeostatic modifications occur, some are harmful to the mother and fetus, while others are beneficial.

The objective of this study was to determine the serum malondialdehyde (MDA) in pregnancy-induced hypertension (PIH) and to compare them to that of normal pregnant women.

Materials and methods: The study was carried out in the department of biochemistry which included total 30 patients of PIH age group of 20 to 40 years and age and sex matched controls. Serum MDA was estimated by method of Nourooz-Zadeh J et al using trichloroacetic acid and thiobarbituric acid. Mean and standard deviation were calculated for serum MDA. Statistical analysis was done using SPSS no. 17 and student t-test.

In the present study, statistically significant increase in levels of lipid peroxidation MDA was observed PIH as compared to those in normal pregnant controls.

Keywords: Malondialdehyde, Oxidative stress, Pregnancy, Hypertension.

How to cite this article: Bhale DV, Hivre MD, Mahat RK, Bujurge AA. Comparative Study of Serum Malondialdehyde Levels as a Marker of Oxidative Stress in Patients of Pregnancy-induced Hypertension and Controls. MGM J Med Sci 2014;1(2):53-55.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Hypertensive disorders are the most common medical complications of pregnancy, with a reported incidence ranging between 5 and 10%.[1] The incidence varies among different hospitals, regions and countries. In India, the incidence of preeclampsia is reported to be 8 to 10% of the pregnancies.[2] Hypertension in pregnancy strikes mostly the primigravidae after 20th week of gestation and frequent occurrences are seen near term. It contributes significantly to the cause of maternal and perinatal mortality and morbidity.[3]

Pregnancy-induced hypertension (PIH) includes a group of hypertensive disorders, gestational hypertension which is without edema and proteinuria, preeclampsia and eclampsia with edema and proteinuria. In PIH, many complex homeostatic modifications occur, some are harmful to the mother and fetus, while others are beneficial. In health, oxidation by free radicals and neutralization by antioxidants remain in balance. When the reactive oxygen species (ROS) are in abundance, oxidative stress occurs which is thought to be the causative factor in PIH.[4]

Oxidative stress describes the damage that occurs when reactive oxygen species (ROS) overwhelm the antioxidant defenses of the host. Oxidant stress may play an important role in the pathogenesis of hypertension in pregnancy and may be a final common pathway leading to tissue damage.[5] Malondialdehyde (MDA) is an aldehyde considered to be the terminal compound and the most important marker for monitoring lipid peroxidation and oxidative damage induced by ROS which is strongly associated with development of serious disease, it is also considered as a thiobarbituric reactive substance.[6,7]

MATERIALS AND METHODS

Pregnant women from MGM Medical College and Hospital, Aurangabad, were selected for the study from April 2012 to March 2013. The study was carried out in the department of biochemistry which included total 30 patients of PIH age group of 20 to 40 years. Selection cases: selection cases of PIH were done after assessing for BP > 140/90 mm Hg, proteinuria, edema and within 28 to 42 weeks of gestation. Age matched 30 normal pregnant women with blood pressure <140/90 mm Hg without edema or proteinuria and within 28 to 42 weeks of gestation constituted the control group.

Exclusion Criteria

Illness like anemia, diabetes mellitus, essential hypertension, renal insufficiency, cardiovascular disease which by themselves are known to alter free radical status were excluded from study.

[1]Professor and Head, [2]Assistant Professor, [3,4]Postgraduate Student

[1-4]Department of Biochemistry, MGM Medical College Aurangabad, Maharashtra, India

Corresponding Author: Dhananjay V Bhale, Professor and Head, Department of Biochemistry, MGM Medical College Aurangabad, Maharashtra, India, e-mail: dr.bhale@gmail.com

Collection of Blood Sample

Five milliliter venous blood was collected with the informed consent of all patients. It was taken from both normal as well as study groups for determination of oxidative damage in terms of lipid peroxidation product—MDA. After clot formation, the tubes were centrifuged at 4000 rpm for 10 minutes. Serum thus separated was analyzed immediately for MDA. Serum MDA was estimated by method of Nourooz-Zadeh J et al.[8] Statistical analysis was done using SPSS version 16 and student t-test.

RESULTS

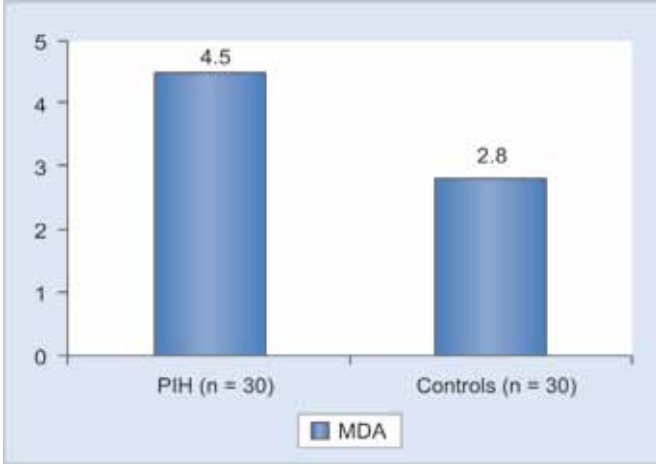
There was highly significant increase in serum level of MDA in hypertensive pregnant women. This because MDA considered to be the most sensitive and final stage of peroxidation and it considered as a marker of pro-oxidant level and indicator of oxidative stress, and it is the end product of lipid peroxidation.

The values obtained on analyzing specimens collected from PIH and normal pregnant groups are tabulated (Table 1). The mean values and standard deviation also have been calculated for comparative study of PIH and normal pregnant groups. The values of subject and controls groups are also graphically represented for comparison. The graphs were plotted using values of all the study parameters. The graphs show significantly decrease of hemoglobin level in subjects were observed compared to the controls. Malondialdehyde

Table 1: The comparable values of MDA in PIH and normal pregnant women

Women in different groups	*MDA (nmol/ml)*
Normal pregnant	2.8 ± 0.5
Pregnancy-induced hypertension (PIH)	4.5 ± 0.8*

*p < 0.05 in comparison with normal nonpregnant women



Graph 1: Comparisons of MDA in PIH with normal pregnant women (controls)

significantly increases in PIH as compared to normal pregnant women (Graph 1).

DISCUSSION

Reactive oxygen species functions as signal transducers in normal physiology, however, their overproduction may result in numerous human health problems. Although the body's own defense mechanism plays a crucial role to control the levels of these free radicals, the levels of antioxidants that counterbalance these oxidative radicals get impaired themselves. The present study was planned to detect lipid peroxidation products, i.e. MDA in PIH.

In the present study, the lipid peroxidation product like MDA levels has been measured in plasma of hypertensive pregnant women. It was found that higher O_2 free radical production, evidenced by increase levels of MDA in hypertensive pregnant women. The present study shows that there is significant difference between PIH and normal pregnant regarding serum MDA (*see* Table 1).

Rise in MDA could be due to increased generation of ROS due to the excessive oxidative damage generated in the hypertensive patients.[9] These O_2 species in turn can oxidize many other important biomolecules including membrane lipids. The lipid peroxides and free radicals may be important in pathogenesis of PIH.[10]

In similar previous study was done on pregnant women with PIH, it was found that there was a significant increase in erythrocytes MDA levels, activates of SOD and GP level.[9] In contrast to the present study, some studies have reported that there are no evidences of increased lipid peroxidation in PIH.[11]

CONCLUSION

On the basis of the results of the present study, it may be concluded that PIH is associated with generation of free radical. Oxidative stress, therefore, has the potential for being used as a marker for PIH. However, further studies are needed to assess the oxidative stress in PIH.

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10.5005/jp-journals-10036-1011

REVIEW ARTICLE

Maternal Morbidity and Estimates from Community Studies in India

Prakash Prabhakarrao Doke

ABSTRACT

First phase of implementation of national rural health mission was completed with 11th plan. Reviews are regularly conducted to monitor the achievements of goals which include reduction of maternal mortality ratio, which is an emerging priority. Due to inherent difficulties in definition, data compilation studies are infrequent. Maternal mortality to morbidity ratio varies from 5 to 223. The morbidities range from mild to severe almost near miss case. The criteria for inclusion of a patient in severe acute maternal morbidity on organ/system failure/dysfunction seem to be objective but availability of diagnostic facilities is the limiting factor. The simple criterion based on some diseases or conditions is widely accepted. Usually magnitude is recorded high when disease or condition criteria are used and low when failure or dysfunction criteria are used. Community-based studies are scarce. National level surveys provide limited information. In such type of studies, morbidities are self-reported and hence the magnitude is very high. The district level household survey-3 recorded morbidity in 93.3% women. Very few studies were carried out before 2001. Studies in this millennium have been deliberated. Women having some postnatal depression ranged from 11 to 33%.

Keywords: Maternal morbidity, Community study, India.

How to cite this article: Doke PP. Maternal Morbidity and Estimates from Community Studies in India. MGM J Med Sci 2014;1(2):56-64.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

The fifth millennium development goal only mentions maternal mortality and reproductive health. National rural health mission clearly targets re-education in maternal mortality. The latest available data about maternal mortality ratio (MMR) in India pertains to years 2007 to 2009. Special bulletin on maternal mortality is issued by sample registration system provides of all the three statistics measuring maternal mortality. The MMR in the country for that period was recorded as 212/lakh live births, maternal mortality rate was 16.3 per lakh of women in 15 to 49 years age group and life time risk of dying maternal death was estimated as 0.6. The targeted goal of MMR > 100 was achieved by the state of Kerala in 2004 to 2006. In 2007 to 2009 Tamil Nadu also achieved the target and Maharashtra was a little more than the target. The MMR is declining continuously. Various activities initiated in national rural health mission like accredited social health activists (ASHA), janani suraksha yojana (JSY) and janani shishu suraksha karyakram (JSSK), training in basic emergency obstetric care, comprehensive emergency obstetric care, skilled birth attendance and life saving anesthetic skill to doctors and nurses are helping to accelerate the pace. Planning for assessment and tackle the maternal morbidity at least in few states like Kerala, Tamil Nadu and Maharashtra and subsequently across the country is the need of the day.

For various reasons there is no universally agreed definition of maternal morbidity. Conceptually any departure, subjective or objective, from a state of physiological or psychological well-being during pregnancy, childbirth and the postpartum period may be considered as maternal morbidity.[1] In 1989, WHO defined the term as, morbidity in a woman who has been pregnant (regardless of the site or duration of the pregnancy) from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes. Similar to maternal mortality, the period from pregnancy to 42 days after giving birth or abortion is considered for maternal morbidity. The maternal morbidities can be acute, or chronic, lasting for months or even years. The morbidities range from mild or severe. Many of these conditions that cause difficulty in pregnancy, and aggravate existing morbidities can also lead to more severe consequences for women. Department of reproductive health and research of world health organization was compelled to define the term more clearly as present estimates of maternal morbidity estimations are not based on well-documented methodologies.[2]

Historically, maternal hospitalization has served as a proxy for complications of pregnancy. The available data indicates that about 8 to 27% of women are hospitalized at least once during pregnancy.[3] The most common reasons for hospitalizations during pregnancy include: preterm labor, vomiting, genitourinary complications and hypertensive disorders.[3] While postpartum admissions were mainly due

Professor

Department of Community Medicine, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India

Corresponding Author: Prakash Prabhakarrao Doke Professor, Department of Community Medicine, MGM Medical College and Hospital, Kamothe, Navi Mumbai, Maharashtra India, Phone: 02227437907, Fax: 02227431723, e-mail: prakash.doke@gmail.com

to puerperal sepsis, malaria, pneumonia. At least 1.7% of postpartum needed hospitalization.[4] Use of only hospitalization data without exact assessment of clinical and overall status may not lead to precise identification of maternal morbidity. Hospitalization alone does not indicate severity and hence it is certainly an overestimate of the incidence of severe morbidity. Maternal morbidity is probably the best suited example to explain the iceberg phenomenon and morbidity pyramid. The tip of the iceberg or the apex of the pyramid is maternal death and the broad base represents normal pregnancy. The morbidity has very wide range of conditions included in the definition. For health status of pregnancy, there is a continuum of morbidity beginning with health and normal pregnancy and moving along the spectrum of morbid events to death. The encompassed set of conditions broadly defines major categories along the continuum. While the two extreme ends of the continuum are easily identified and understood, locating intermediate points along the range of the continuum is far more difficult. Specifically, there are no clear thresholds beyond which a woman can be reliably categorized as a severe morbidity *vs* a near miss case. The severity of morbidity is truly a continuous variable, and as with any attempt to transform a continuous measure into a discrete one, there will be loss of certain information. This particularly will happen when women with unique constellations of clinical and nonclinical factors are combined into a morbidity group. Despite the loss of information, however, categorization is certainly essential for facilitating development of targeted interventions. It is proposed that this continuum can be partitioned into meaningful clinical and epidemiologic ranges that permit an analysis of factors, including preventability factors that may differentiate deaths, near misses and other severe morbidities. The morbidities also include mild to moderate conditions which may lead to psychological and social consequences later in her life.

CLASSIFICATION

The maternal morbidities can be classified by different ways depending upon the drive behind it. The maternal morbidity presents four patterns in context to the gestational phase. The first pattern of diseases is observable only during pregnancy and the puerperium. The second includes diseases starting during pregnancy or the puerperium, but continuing beyond it. The third pattern of disease is associated with pregnancy but not temporally located within it. The last pattern belongs to the underlying disease exacerbated by pregnancy or puerperium.

The obstetricians' simple way of classification of obstetric morbidities is immediate, early and late conditions on the basis of occurrence of the condition in time frame. The most common morbidity conditions are mentioned below:

1. *Immediate*: Perineal tears, loss of sphincter control, uterine perforation, nonunited episiotomy/gapping, persistent perineal pain, retention of urine, eclampsia, etc.
2. *Early*: Fistulae, puerperal psychosis, infections, breast abscess, etc.
3. *Late*: Prolapse, cystocele-rectocele, dyspareunia, cervical incompetence, LSCS—future obstetrics handicap, incisional hernia, chronic pain in abdomen, secondary infertility, Rh—sensitization, obesity, depression- diffidence—if baby is lost, etc.

Maternal morbidity is differentiated from gynecological and contraception morbidities and termed as obstetric morbidity. The obstetric morbidity is further classified as direct obstetric, indirect obstetric and psychological morbidity.[5]

The criterion of severity of maternal morbidity is also very frequently used for classification. By severity criteria the morbidity may range from clinical insult, mild morbidity, moderate morbidity, severe acute maternal morbidity (SAMM), near miss cases. The problem of precision and objectivity in conceptually well-accepted definition persists in the concept of SAMM also. Following three criteria are used to classify the conditions under SAMM:

- Based on the disease/disorder that caused it
- Based on management, such as hysterectomy or admission to intensive care unit, need for massive blood transfusion (three and more), need for operative intervention to control hemorrhage, etc.
- Based on failure of specific body organs.

Inclusion in SAMM on clinical criteria seems to be more appealing to clinicians, because it focuses on immediate causes of maternal mortality. The diagnosis is comparatively easy. Following well-defined diseases like hypertensive disorders in pregnancy, severe hemorrhage, severe sepsis, and uterine rupture are considered as SAMM. When the definitions based on clinical signs and symptoms are used several difficulties arise. These definitions require the consensus of clinicians on criteria of severity, which can be difficult to obtain given the diversity of clinical experience. As for example, severe vaginal bleeding has been defined as blood loss >1500 ml if measured or hemorrhage leading to abnormalities of coagulation;[5] whereas others have suggested hypovolemic shock requiring blood transfusion to be considered as severe vaginal bleeding,[6] and severe vaginal bleeding is also defined as resulting in to hypovolemia and requiring 5 units blood.[7] Management based criterion is more objective but consists of many subcomponents. In a recent world health organization systematic review of maternal morbidity and mortality, transfer to an ICU was taken as an indicator for assessing the prevalence of SAMM worldwide.[8] Definition using organ failure criteria seems to be more attrac-

tive. Drawbacks in accepting this criterion include difficulty in diagnosis of organ dysfunction as it needs highly technical laboratory and hemodynamic investigations, which are often lacking in developing countries like complete blood count/ central venous pressure/multipara monitors/arterial blood gas. There is, therefore a clear need to set uniform criteria to classify patients as SAMM. This standardization could be made for similar settings separately. Still an organ-system dysfunction/failure approach is the most clinically and epidemiologically sound as it is least open to bias, and thus could permit developing summary estimates.[9] Stones et al[10] were the first to use the term 'near miss morbidity', to define a narrow category of morbidity encompassing 'potentially life-threatening episodes'. During an international seminar held in Morocco, a near-miss case was defined as "any pregnant or recently delivered or aborted woman whose immediate survival is threatened and who survives by chance or because of the hospital care received. Although it narrows down to few severe cases, sometimes SAMM are considered synonymous. Many other term are very frequently used obstetrics or maternal complications and various grades of severity, absolute maternal indications, etc. Inconsistencies still continue although are getting reduced.

At national and international level a good amount of awareness and discussion about classification and data availability is generated about severe and hospitalized patients. At the same time, a comparative vacuum is felt about availability of information about acute mild and moderate morbid conditions. Equally gap also exists about chronic morbid conditions. These acute mild/moderate conditions and chronic conditions lead to maternal disabilities decreasing the quality of life of the unfortunate women.[11] This is in contrast to the fact that the women in general usually have longer life expectancy than males. It is well-known that the health of women during pregnancy or childbirth further impacts the health and development of the next generation and the well-being of the family—both economically and socially—through impoverishment, violence, stigmatization, isolation, divorce, and remarriage of spouse.[12] These disabilities are tragic on two counts: they occur in the process of giving life, and they are almost entirely preventable.[10]

Magnitude of the Maternal Morbidity

Maternal morbidity is difficult to measure, for several reasons. The foremost reason is uncertainty about the definition of maternal morbidity particularly conditions which constitute a large spectrum and varies widely according to researchers. Criteria to diagnose the diseases could also vary. Although maternal mortality is a clear-cut condition, maternal mortality survey is not easy to perform. Surveys to estimate the prevalence of maternal morbidity are even more difficult to conduct. The other strong difficulty is several maternal morbidities are difficult to diagnose, and require pelvic examination, which is seldom possible in surveys (privacy, shyness about sexual and reproductive matters). Thus, very little information is available on morbidity, especially in the developing world. The importance of maternal morbidities can be only perceived when underlying factors for underreporting are considered. Patients have no complaints or the complaints are very mild and vague, nor are the sufferings revealed. Mother accepts the morbidity as consequence of labor. Even in medical fraternity there is denial mode to accept the varied aspects like psychological problems and their magnitude of the problem. As a net result, the maternal morbidity is usually detected and diagnosed late.

A systematic review clearly has shown how the magnitude of the maternal morbidity varies according to criteria for identification of cases. Prevalence varies between 0.80 and 8.23% in studies that use disease-specific criteria, while the range is 0.38 to 1.09% in the group that use failure of organ/ system dysfunction based criteria and included unselected group of women. Rates are within the range of 0.01 and 2.99% in studies using management-based criteria.[8]

In a systematic review in India SAMM was found to be 7.1% and case fatality ratio 13.8%. Incidence of SAMM ranges from 0.07 to 8.2%, case-fatality ratio 0.02 to 37%. There is a big difference between case-fatality ratio in developing (South Africa 1:5; India and Niger 1:11) and developed countries (UK 1:118; France 1:222).[13] A very comprehensive review revealed vital information about morbidity and is briefed here.[14] Worldwide it is estimated that about 1.4 million women experience acute obstetric morbidity (near-miss) events, 9.5 million women experience other complications and 20 million women suffer from long-term disabilities. Anemia is the commonest morbid condition among pregnant women. World Health Organization in 2008 estimated that about 42% of pregnant women suffer from anemia. Malaria consortium in 2009 and WHO in 2010 estimated that in sub-Saharan Africa malaria cause up to 400,000 cases of severe maternal anemia per year. Almost 90% of anemic women reside in Asia or Africa. UNFPA estimated that about 20 to 30% of perinatal women in developing countries suffer some mental health problem. Around 186 million ever-married women in the age group of 15 to 49 years in the developing countries (excluding China) were infertile in 2002 (Rutstein and Shah-2004). About 25% of ever-married women of reproductive age in these countries and 30% of women with secondary infertility are in sub-Saharan Africa. Global estimates for fistula vary widely. About 2 million women worldwide are facing the problem, with 50,000 to 100,000 new cases occurring annually. Out 654,000 cases from

Africa 262,000 emanate from sub-Saharan Africa. Genital and uterine prolapse is observed in 2 to 20% of women of reproductive age group by Columbia university in 2009. Uterine rupture is estimated to occur in the developed world, one in 1,000 for scarred uteri to less than one in 10,000 for unscarred uteri and approximately 10 times higher in developing countries. The prevalence of severe maternal morbidity ranged from 0.07 to 8.23% and the case-fatality ratio from 0.02 to 37%. Studies estimating the incidence of severe maternal morbidity have used different definitions and ways of identification. Severe hemorrhage, sepsis and hypertensive disorders of pregnancy are the commonly used 'near-miss' conditions.[15] Data from low income countries is given in Figure 1.

The compiled information from selected studies across the world about the ratio of maternal morbidity to maternal mortality is given in Table 1.[24] Obstetricians from many hospitals carry out descriptive and analytic studies about maternal morbidity and are frequently published. For describing the conditions observed in Indian hospitals, pooled recent data from one hospital from Delhi and three hospitals from Maharashtra[25-28] is presented here. It indicates that pregnancy induced hypertension including eclampsia contributes maximum (35-77%) to severe acute maternal morbidity. Hemorrhage including resultant shock was observed in 6 to 35% cases. Puerperal sepsis was reported in 1 to 19% SAMM cases. Obstructed labor accounted for 4 to 9.5% severe morbidities. In one hospital other medical conditions were also frequently seen in 25.7% cases. Resuturing, first trimester complications and burst abdomen were other conditions recorded. Severe acute maternal morbidity was recorded in 2.1 to 3.3% deliveries.

The geographical and even cultural characteristics of neighboring countries are similar to Indian condition. In Bangladesh in a field study, the commonest postnatal complications were weakness, weight loss, palpitations, discharge nonhemorrhagic or hemorrhagic discharge, pelvic pain, giddiness, headache and anxiety. The percentage of these complications ranged from 95.6 to 28.6%.[29] Highest proportions women reported having prolonged labor, abnormal bleeding, fever, pre-eclampsia-toxemia, retained placenta and leaking membrane.[30]

Community Studies

Although large field studies are rarity may be carried out in a systematic method. A field based study was carried out in six West African countries to validate the definitions adopted and to report frequency of severe maternal morbidity (Prual). In India only two large scale data source are available which emanate from the rounds of national level surveys. Latest in the series are national family health survey-3 (NFHS-3) (2005-2006)[31] and district level household survey-3 (DLHS-3) (2007-2008).[32] The results of earlier rounds from have been reviewed from various angles. In these surveys, the morbidities are self-reported. This characteristic poses two basics problems; one is precision and second comparability. In NFHS-3 past history about two symptoms pertaining to two major post-natal morbidities were asked. Women reported massive vaginal bleeding in 12% of births and a very high fever in 14% of births. The determinants of these symptoms are given in Table 2.

Postdelivery complications observed in DLHS-3 are given in Table 3. There were only two postpartum conditions common in both the national level surveys. The range of women who had excessive vaginal bleeding was 12.4 to 21.8%. The second common condition was high fever; where the recorded proportion ranged from 13.5 to 55.4%. The DLHS-3 survey also included complications during delivery. There was very wide state to state variation. Complications during pregnancy were 57.8 and 80.2% had

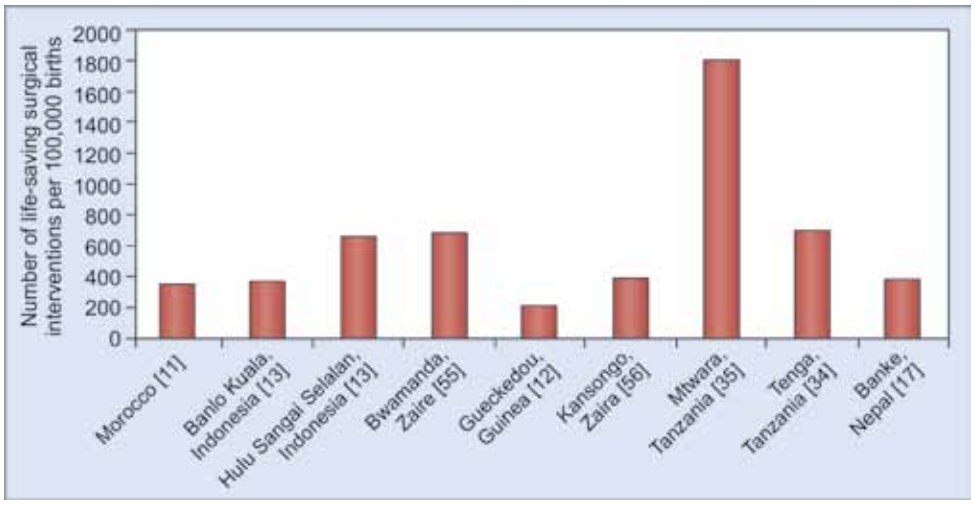

Fig. 1: Life-saving surgical interventions per 100,000 births (source)[15]

Table 1: Maternal morbidity and mortality ratio

Study	*Country*	*Cases*	*SS*	*Preval. (%)*	*Deaths*	*Mb/Mr*
Disease-specific criteria						
Prual 1998[7]	Niger	232	4081	5.68	21	11
Filippi 1998[16]	Benin	353	4291	8.23	30	12
Sivalingam 1999[17]	Malaysia	122	9933	1.23	10	12
Prual 2000[18]	West Africa	1174	19 694	6.17	41	29
Khosla 2000[19]	India	224	5124	4.37	31	7
Waterstone 2001[20]	UK	588	48 865	1.2	5	117
Girard 2001[6]	France	223	27 872	0.8	1	223
Organ-system based criteria						
Mantel 1998[8]	South Africa	147	13 429	1.09	30	5
Cochet 2003[21]	South Africa	131	15 978	0.82	16	8
Kaye 2003[22]	Uganda	87	980	10.61	17	5
Brace 2004[23]	Scotland	196	51 165	0.38	4	49
Mixed criteria						
Sahel 2001[24]	Morocco	76	5686	1.34	5	15

some maternal complication and are given in Table 4.[33] The highest proportion of complications during pregnancy was 75.4% reported from Bihar. Highest complications in delivery (83.5%) were in Jharkhand. The highest proportion of 57.4% postdelivery morbidities was in Bihar. Bihar was also the state to record some maternity complication in 93.3% women. In the DLHS-3 also provided information about fistula and infertility. Five questions on obstetric fistula had been incorporated in the DLHS-3, based on the study on chronic obstetric morbidities. In India 8.25% women reported primary or secondary infertility. The proportion of women having fistula was 1.5%.

Few field studies are also had been conducted in India. The noteworthy and real community studies which were carried out in Alwar in Rajasthan, second in South India, third in Gadchiroli district Maharashtra.[34-36] The fourth study was carried out in Union Territory of Puducherry and surrounding South Arcot district was one of the sites for estimating prevalence of maternal morbidity in four developing countries.[5]

All these studies were conducted before 2000. Apart from these three field studies, few studies carried out in this millennium provide very valuable information and the findings are briefed here. A total of 4,975 women, representing 87.1% of all expected deliveries in a population of 58,000, were examined in their first postpartum week during January 2007 to December 2010. Hemoglobin was tested for 77.1% of women (n = 3,836) who had a postnatal visit. The most common morbidity was postpartum anemia, 7.4% of women suffered from severe anemia and 46% from moderate anemia. Other common morbidities were fever (4%), breast conditions (4.9%) and perineal conditions (4.5%). Life-threatening postpartum morbidities were detected in 7.6% of women 9.7% among those who had deliveries at home and 6.6%

Table 2: Symptoms of postpartum complications (NFHS-3)

Characteristic		*Massive vaginal bleeding*	*Very high fever*	*Number of women*
Residence				
Urban		10.1	8.7	10,626
Rural		13.2	15.2	29,051
Age at birth				
<20		13.3	13.9	6,881
20-34		12.2	13.3	30,716
35-49		10.8	15.7	2,080
Birth order				
	1	13.1	12.3	10,457
	2-3	12	12	18,207
	4-5	12.2	16.6	6,955
	6+	12.2	18.1	4,058
Place of delivery				
Public sector health facility		11.2	9.6	7,540
NGO or trust hospital/clinic		10.3	7.7	190
Private sector health facility		12.3	9.4	8,727
Own home		12.7	16.7	19,403
Parents' home		13.2	14.9	3,552
Other home		6.1	11.1	180
Other 1		17.7	14	85
Assistance during delivery				
Doctor		11.7	10.2	19,937
ANM/Nurse/Midwife/LHV		11.8	14.9	9,117
Other health personnel		18.6	21.9	414
Dai/TBA		16.7	17.3	458
Other 1		13.7	18.3	9,751
Total		12.4	13.5	39,677

among those who had institutional deliveries. None had a fistula. Overall 67.6% women had some complication.[37] Follow-up of 430 women up to 6 to 8 weeks and 375 women up to 1 year was completed. Depression was noticed in one-third women and suicidal tendency in 4.8% women who had severe complications.[38] Depressive disorder was detected in 59 (23%) of the mothers at 6 to 8 weeks after childbirth; 78% of these patients had had clinically substantial psychological morbidity during the antenatal period. More than one-half of

Table 3: Type of delivery complications (DLHS-3)

Background characteristics	*Any delivery complication*	*Premature labor*	*Excessive bleeding*	*Prolonged labor*	*Obstructed labor*	*Breech presentation*	*Convulsion/ high BP*	*Other*	*Number of women*
Age group									
15-19	66.6	48.6	0	38.8	72.1	8.1	7.9	1.4	14,006
20-24	62.5	48.8	0	34.9	68.8	8.1	7.6	1.4	73,455
25-29	60.1	49	0	33.6	67.7	8.3	7.6	1.5	72,061
30-34	59.7	48	0	32.4	68.8	8.7	8.5	1.4	35,246
35+	59.4	47.8	15.2	32.5	69.6	7.4	8.4	1.3	20,280
No. of living children									
0	73.2	54.5	21.2	38.4	59.4	19.4	15	2.6	819
1	62.9	48.6	14.5	37.1	65.9	9.3	8.2	1.9	59,993
2	58.7	49	15	32.4	66.2	8.2	7.6	1.5	59,470
3	60.1	48.4	15.2	33.1	70.1	7.7	7.7	1.3	38,057
4+	62.6	48.3	14.8	33	74	7.1	7.7	1	56,709
Residence									
Rural	62.4	49.1	15.4	34.6	70.2	7.9	7.9	1.2	1,74,913
Urban	58	47.4	13.3	32.8	64.7	9.1	7.8	2.1	40,135
Number of ANC visits									
0	62.8	51.5	15.3	34.6	71.2	7.6	8.2	0.8	60,258
1	66.7	51.3	15.9	36.8	74.7	8	8.1	0.9	12,140
2	66.1	46.1	12	32.3	75.7	6.6	6.2	1	41,957
3+	57.9	47.7	15.8	34.3	63.6	9.3	8.3	2	1,00,693
Delivery									
Normal	60.6	49.2	14.8	33.4	70.5	6.7	7.3	1	1,93,550
Cesarean	64.2	43.6	14.4	36.6	53.4	20	12.1	5.4	17,511
Instrument or assisted	76.3	48.2	18	48.8	64.5	15.8	10.8	2.1	3,927
Place of delivery									
Government	60	49.3	16.5	38	62.3	9.2	8.7	1.7	54,699
Private	60.4	48.3	14.2	35.4	62.7	12.3	9.2	2.9	38,659
Home	62.1	48.4	14.3	31.7	74.2	6.1	6.9	0.8	1,20,072
Other	63.1	51.2	18.2	37.7	66.8	8.4	9.7	1.4	1,618
India	61.2	48.6	14.9	34.1	68.7	8.2	7.9	1.4	2,15,048

the patients remained ill at 6 months after delivery. Economic deprivation and poor marital relationships were important risk factors for the occurrence and chronicity of depression. The gender of the infant was a determinant of postnatal depression; it modified the effect of other risk factors, such as marital violence and hunger. Depressed mothers were more disabled and were more likely to use health services than nondepressed mothers.[39] In other parts of India the proportion postpartum depression was about 11%.[40, 41]

In the state of Maharashtra one study was conducted in Nashik district with financial support from UNFPA.[42] Information about reproductive morbidities was collected. Obstetric history of 4862 deliveries revealed that in 90.5% deliveries there was no complication. Among those who had some complication, the commonest was prolonged labor (56.7%), followed by PPH (17.1%), perineal tear (16.5%). Detailed history of induced abortion was asked to women who had undergone abortion. The complications reported by the women were lower abdominal pain (28.6%), fever (25.7%), excessive bleeding (22.8%). Nonspecific symptom complexes like low backache, lower abdominal pain, vaginal discharge and menstrual irregularities were observed in more than 10% women, in that order. On clinical examination, the proportion of women having low backing was 37%, symptoms of prolapse, secondary infertility, secondary amenorrhea and urinary incontinence were observed in that order. A total of 1,560 women were interviewed in houses 12% of them reported some morbidity. Among the reporting women 625 complained prolapse of pelvic organs, 22% had symptoms of chronic pelvic inflammatory disease, 15% secondary infertility and 1% fistula. Among respondents of house hold surveyed women about 36.6% women who had prolapse and equal proportion having urinary incontinence sought treatment. For secondary infertility only 17.1% women sought treatment.

The study carried out in Andhra Pradesh in two districts, one developed and one less developed district.[43] The study revealed a high prevalence of maternal morbidity in rural

Table 4: Postdelivery complications by background characteristics

Background characteristics	*Any post-delivery complication*	*High fever*	*Lower abdominal pain*	*Foul smelling vaginal discharge*	*Excessive bleeding*	*Other*	*Number of women*
15-19	38.4	58.0	53.8	20.3	23.7	53.2	14,006
20-24	34.4	54.7	56.4	18.6	22.5	51.1	73,455
25-29	33.3	53.6	57.1	18.3	21.6	51.8	72,061
30-34	35.5	56.4	57.9	18.7	21.1	52.4	35,246
35+	38.0	60.7	57.5	20.2	20.1	53.4	20,280
No. of living children							
0	44.9	55.9	58.8	21.4	31.2	48.7	819
1	31.2	52.3	52.4	17.5	23.0	49.5	59,993
2	30.8	51.0	57.1	17.9	22.6	50.3	59,470
3	35.8	54.9	59.2	19.0	21.6	52.8	38,057
4+	42.6	62.1	58.9	20.6	20.2	54.9	56,709
Residence							
Rural	37.4	57.0	57.5	19.6	22.1	52.6	1,74,913
Urban	28.2	50.1	54.5	16.3	21.0	49.5	40,135
Delivery							
Normal	34.7	56.5	56.8	19.3	21.6	52.0	1,93,550
Cesarean	34.1	46.7	57.5	13.5	23.3	49.6	17,511
Instrumental/assisted	43.8	47.5	56.8	19.6	24.9	56.7	3,927
Place of delivery							
Government	30.7	48.2	56.6	16.9	23.8	51.2	54,699
Private	28.3	50.3	53.9	16.2	22	49.4	38,659
Home	39.3	59.8	57.7	20.3	20.9	52.8	1,20,072
Others	39	56.4	55.4	19.9	26.4	55.2	1,618
Conduction of last delivery							
Doctor	37.6	57.0	56.4	20.6	26.4	55.5	3,733
ANM/Nurse/Midwife/LHV	33.8	56.0	55.1	17.5	22.3	50	7,770
Other	37.0	42.5	51.6	17.8	23.8	50.2	595
Dai	40.9	60.0	59.4	22	20.8	53.2	72,379
Relatives/Friends	37.6	61.3	54.4	17	20.5	52	33,678
Others	41.2	53.4	59.3	20.9	21.8	56.7	2,466
No one	34.8	55.8	53.7	21	24.4	57.8	1,003
India	34.8	55.4	56.8	18.8	21.8	51.9	2,15,048

areas of Andhra Pradesh. The details are given in Table 5. Especially in the less developed district, nearly 95% of the women experienced at least one of the morbidities and in the developed district it is 61%. 'Life-threatening' and 'serious' morbidities are experienced by 39 and 54% in the less developed; 15 and 46% of women in developed district respectively. Highest proportion of women reported antenatal morbidities, followed by postnatal and intranatal in that order. The distribution of proportion is different from the proportion observed in DLHS-3 where the proportions were 58.3% in antenatal, 61.2% intranatal and 36.8% postnatal. Highest proportion of women reported to have suffered from serious complications, followed by life-threatening complications and mild ones in that order. After implementation of JSY it was observed that there was increase in incidence of maternal morbidity. This was assumed due increased awareness seeking healthcare services at enhanced rate.[44]

Table 5: Maternal morbidity in rural Andhra Pradesh

Morbidities	*Mahbubnagar*	*Guntur*
Women suffering from antepartum morbidities		
Life-threatening	3.7	1.2
Serious	77.7	49.6
Mild	6.3	7.2
Any	87.7	57.9
Total women	1258	419
Women suffering from intrapartum morbidities		
Life-threatening	36.7	14
Serious	6.7	9.4
Any	43.4	23.4
Total women	1111	351
Women suffering from postpartum morbidities		
Life-threatening	19.4	7.7
Serious	41.2	7.4
Mild	0.4	2.8
Any	61	27
Total women	1111	351

CONCLUSION

Large number of women experience maternal morbidities. Apart from usual conditions depression, fistula and prolapse are also observed. A robust system of surveillance is the need of the day. Along with maternal death audits need of review of all obstetric admissions is also emerging.

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10.5005/jp-journals-10036-1012

REVIEW ARTICLE

Cervical HPV Infection in Indian Women: Screening and Immunization as Preventive Strategies

[1]Lynette J Menezes, [2]Seung Eun Jang, [3]Daniel J Ross, [4]Alexander D Glaser, [5]Rojan Varghese

ABSTRACT

Invasive cervical cancer (ICC) is the second leading cause of cancer related mortality among women in India. Human papillomavirus (HPV), the etiological agent of cervical cancer is widely prevalent worldwide. Persistent HPV infection, particularly with HPV 16, is essential for progression to cervical cancer. Human papillomavirus 16 and 18 are the most common genotypes detected among Indian HIV-infected and uninfected women, although their relative contributions vary. HIV-infected Indian women experience a higher risk for HPV infection compared to the general population. Although cervical screening and vaccination to protect against HPV infection are the two main strategies for prevention, there are significant challenges to their implementation in India. Scaling up of cervical screening using simple, rapid tests followed by colposcopy and treatment within a minimal number of visits is essential to prevent loss to follow-up. Increasing the uptake of the HPV vaccine combined with cervical screening can greatly reduce the burden of ICC in India.

Keywords: Cervical cancer, Human papillomavirus, Cervical screening, Human papillomavirus vaccination.

How to cite this article: Menezes LJ, Jang SE, Ross DJ, Glaser AD, Varghese R. Cervical HPV Infection in Indian Women: Screening and Immunization as Preventive Strategies. MGM J Med Sci 2014;1(2):65-75.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Invasive cervical cancer (ICC) is the fourth leading cause of cancer among women worldwide and the second leading cause of cancer related mortality among women in India (Fig. 1).[1] Nearly nine out of 10 ICC deaths (87%) occur in the developing world; at 67,000 deaths annually, India accounts for 29% of these ICC deaths.[1] The etiology of cervical cancer has been clearly linked to infection with the human papillomavirus (HPV); and nearly 100% of cervical cancer cases are attributed to HPV infection. Additionally, HPV causes 88% of anal cancers, 43% of vulvar cancers, 70% of vaginal cancers, 50% of penile cancers,[2] and 70% of oropharyngeal cancers,[3] representing nearly 4.8% of all cancers worldwide.[2] Globally, an estimated 50 to 80% of men and women will acquire an HPV infection in their lifetime, making it the most widely prevalent sexually transmitted infection (STI).[4] Among HIV-infected individuals, studies worldwide demonstrate that HIV-infected women have a 2-25-fold risk for ICC compared to the general population[5] and ICC is classified as an AIDS-defining illness.[6] This paper describes the epidemiology of cervical HPV infection and ICC including risk factors among women in India with a special focus on HIV-infected women. We also examine strategies for ICC prevention, specifically screening and vaccination.

HUMAN PAPILLOMAVIRUSES (HPVs)

Of the more than 100 HPV genomes that are fully sequenced, nearly 50% have been isolated from the anogenital tract.[7] Human Papillomavirus is a non-enveloped DNA virus that has a predilection for the skin and mucosal epithelial tissue.[7] Human papillomaviruses are further classified into low-risk and high-risk based on their ability to integrate into the host genome and produce malignant lesions. There are 13 HPV genotypes HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 that are designated high-risk because of strong evidence of their carcinogenic potential.[8] All of these have been isolated in varying proportions from ICC cases across the world. Human papillomavirus 16 and 18 are the most potent carcinogenic types and account for 70% of all cervical cancers globally.[4]

EPIDEMIOLOGY OF HPV INFECTION

In 2012, an estimated 528,000 women had cervical cancer and 266,000 women died from the disease.[1] Globally, the annual age standardized incidence of ICC is 14/100,000 women; 22/100,000 women in India; and incidence rates greater than 30/100,000 among women in Africa (Fig. 2).[1] Two recent meta-analyses of studies worldwide provide information on HPV prevalence among women with normal cytology and those with abnormal cytology. Among >1 million cytologically normal women from 194 studies worldwide,

[1]Assistant Professor, [2,5]Research Assistant,
[3,4]MS II MD Candidate

[1,2,5]Division of Infectious Disease and International Medicine University of South Florida, Florida, USA

[3,4]Morsani College of Medicine, University of South Florida Florida, USA

Corresponding Author: Lynette J Menezes, Assistant Professor Division of Infectious Disease and International Medicine University of South Florida, 1 Tampa General Circle, Suite G318 Tampa, FL 33606, USA, Phone: 813-8448037, Fax: 813-8447605 e-mail: lmenezes@health.usf.edu

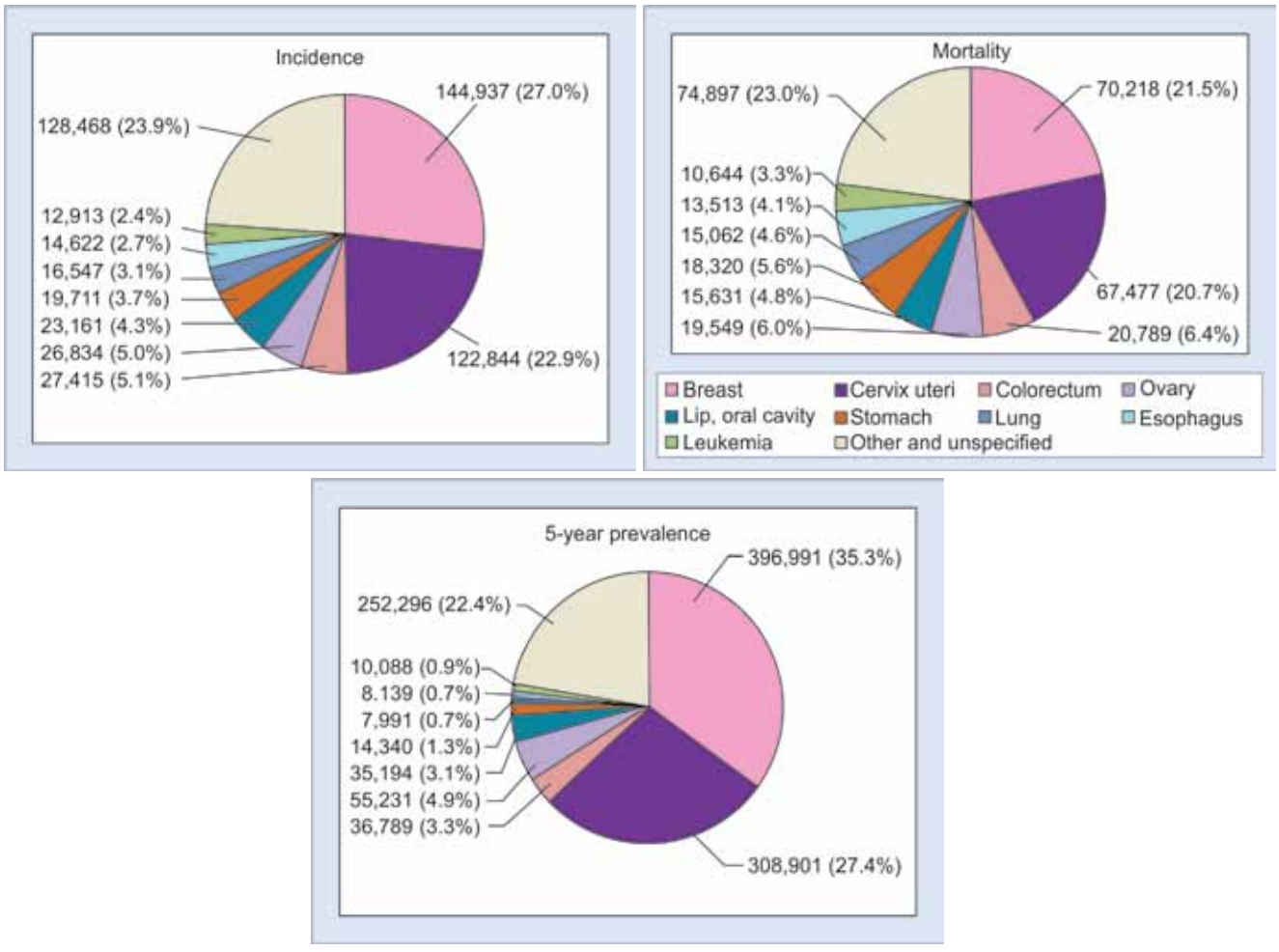

Fig. 1: Incidence, mortality and 5-year prevalence of various cancers among Indian women (Globocan 2012 with permission)[5]

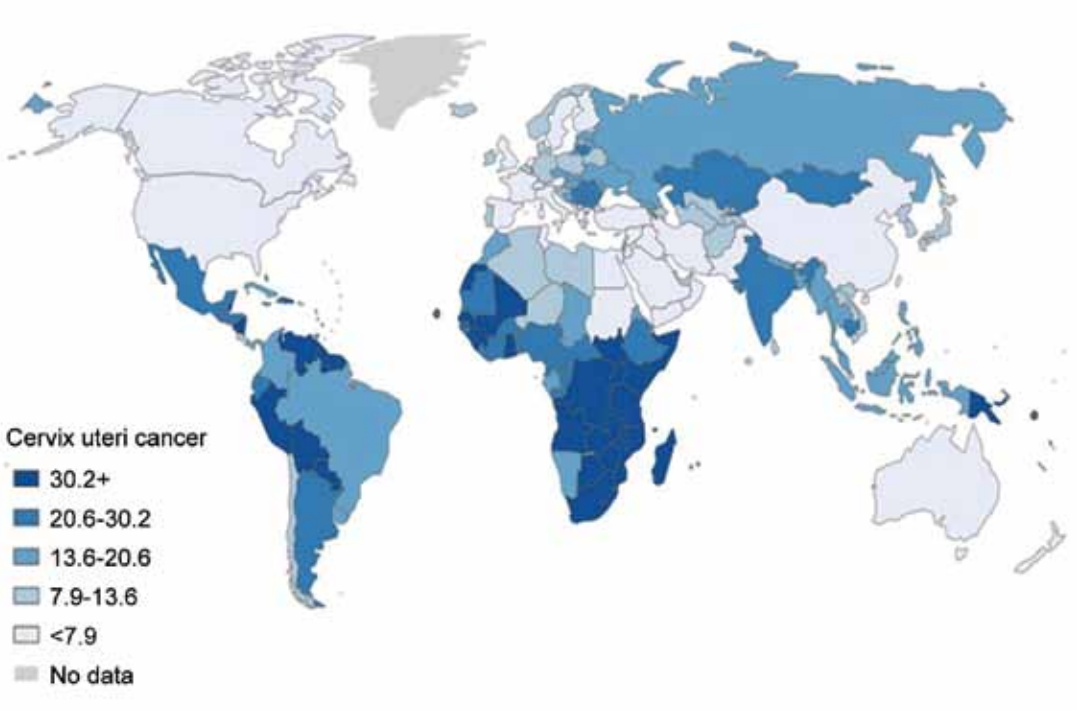

Fig. 2: Age standardized incidence of cervical cancer worldwide in 2012 (Globocan 2012 with permission)[1]

HPV prevalence was 11.7% and ranged from 1.6 to 41.9%.[9] Human papillomavirus 16 (3.2%) and 18 (1.4%) were the most prevalent genotypes, and about 3.2% of women tested harbored multiple HPV infections.[9] An estimated 7.9% of Indian women had an HPV infection (4.8%-36.8%).[9,10] In the second meta-analysis, among 115,789 high-risk HPV women with normal and abnormal cervical cytology, HPV prevalence rose with severity of cervical lesions from 73% in women with CIN1 to 93% in women with CIN3 with a sharp rise in HPV 16 prevalence from CIN1 to CIN3.[11] This rise is reflected in Indian women as well; women with cervical disease in one study had a higher proportion of any HPV (normal cytology: 7.6%; CIN1: 42.3%; >CIN2: 87.5%), and HPV 16 infection (normal cytology: 28.6%; CIN1: 36.4%; >CIN2: 74.3%), and this proportion increased with severity of disease.[12] Human papillomavirus infection also differs over the life span. Although younger women tend to have a higher prevalence of HPV infection in most populations, prospective data clearly indicate that 90% of women clear these asymptomatic infections within 2 years.[13-15] Approximately, 4 to 10% of women with prevalent infections experience persistent carcinogenic infections that result in malignant cervical disease.[16]

HUMAN PAPILLOMAVIRUS GENOTYPE DISTRIBUTION

Indian women from the general population harbor a wide range of genotypes. Human papillomavirus 16 and 18 are the predominant genotypes that are detected in women with normal and abnormal cytology. Human papillomavirus 16 and 18 combined prevalence ranges from 2.0 to 10.1% among women with normal cytology.[12,17-22] Other high-risk genotypes that were commonly detected in women from some of these studies included HPV31, 33, 35, 39, 45, 51, 52, 56 and 59.[12,19,20] Among women with high-grade cervical disease, HPV 16 and 18 combined prevalence ranged from 74 to 97% with >70% of the fraction attributed to HPV 16 in most studies.[12,23-27] Other high-risk genotypes that were frequently detected in women with ≥ CIN2 were 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59.[12,23-27] Multiple HPV infections were also common in women with cervical abnormalities. The only 24 months prospective study of HPV infection in young women from a low-income community in Delhi found an any genotype cervical HPV incidence rate of 5.0 per 1000 women months with HPV 16 having the highest incidence rate of 3.0 per 1000 person months.[19]

CERVICAL HPV INFECTION AMONG HIV-POSITIVE WOMEN

Worldwide studies have documented that compared to HIV-negative women, HIV-infected women experience a 2-5-fold risk of acquiring a cervical HPV infection, have higher HPV incidence and persistence rates, show a shorter time interval for development of cervical lesions, experience recurrent cervical disease and faster progression to invasive cervical cancer.[28-31] Information regarding HPV infection among Indian women is limited in comparison to the developed world and there is a lack of prospective data. A large cross-sectional study of 1,109 HIV-infected women in Maharashtra reported an HPV prevalence of 44.8%.[32] In other smaller cross-sectional studies of HIV-positive women from Pune, North India, West Bengal and Tamil Nadu and one 12-months prospective report from Mumbai, HPV (any type) prevalence ranged from 20 to 56% (Table 1).[33-38] These reports are 3 to 8 times higher than the HPV prevalence in the general population of Indian women. Similar to studies worldwide, cytologically normal HIV-infected Indian women have a higher HPV prevalence than cytologically normal HIV-negative women.[32,39]

Human papillomavirus genotypic distribution in HIV-positive Indian women is similar to studies in other parts of the world although the relative contributions may vary. Human papillomavirus 16 is the most prevalent type; other common high-risk genotypes include 18, 31, 33, 35, 51, 56, and 68.[32,37] HIV-positive Indian women also had multiple high-risk HPV infections and a higher prevalence of non-HPV16/18 infections.[36,37] Among HIV-infected women with cervical intraepithelial neoplasia (CIN), HPV 16 was the most commonly detected genotype—31.9% in CIN1 and 69.8% in CIN2/3.[32] There was some variation in the detection of cervical lesions across studies. Prevalence of CIN1 ranged from 3.96 to 36.7% and CIN 2+ ranged from 4.71 to 11.2% (*see* Table 1).[32,36,37,40]

RISK FACTORS FOR HPV INFECTION

Age, Sexual Behavior and STIs

As anogenital HPV infection is transmitted by sexual intercourse, sexual behavior patterns among women and their partners often dictate women's risk for HPV exposure and acquisition. Data from many studies indicate that younger women are at greater risk for HPV infection and early age at first sexual intercourse is a risk factor for HPV acquisition.[41-44] However, studies have also shown that this risk is potentially influenced by other sexual behaviors. Kahn et al. found that risk of HPV infection at early sexual debut was mediated by other risky behaviors including higher number of sexual partners, history of STIs, alcohol/drug use related to sexual behaviors, and higher number of a partner's sexual partners.[43] It has also been suggested that the increased risk may be due to biological factors such as an immature cervix with metaplastic epithelium, which is vulnerable

Table 1: Prevalence of HPV and cervical abnormalities among HIV-positive women in India

Source	*Location*	*Sample size*	*Population*	*HPV(%)*	*LSIL(%)*	*HSIL(%)*	*CIN1(%)*	*CIN2(%)*	*CIN3⁺(%)*
Aggarwal et al 2012[33]	North India	130	Women attending ART clinic	20†	0.77	2.30	—	—	—
Isaakidis et al 2013[34]	Mumbai	95	Women attending ART clinic	32	14	5	8.40	5.30	2.10
Joshi et al 2005[35]	Pune	287	Women attending voluntary counseling testing clinic	33*	4.18º	0	—	—	—
Joshi et al 2012[40] and Joshi et al 2014[32]	Pune	1109	Women in Pune, Maharashtra	45	4.44	1.76	3.96	1.71	3.10
Mane et al 2012[37]	Pune	278	Women attending ART center & through community outreach	53	32	2.52	36.70	6.50	4.70
Peedicayil et al 2009[36]	Tamil Nadu	75	Women attending a multidisciplinary HIV clinic	39	1	13	—	10	—
Sarkar et al 2011[38]	West Bengal	93	Women attending pre-ART clinic and reproductive and child healthcare clinic	56	—	—	—	—	—

*Testing for HPV16/18 only; †Testing for high-risk HPV only; ºIncludes LSIL and ASCUS

to HPV infection.[45,46] Several recent studies in India that looked at the association of age and HPV infection found that HPV prevalence was constant across all ages.[20,21,47] In these studies, age at first sexual intercourse and young age at marriage (surrogate marker for first sexual intercourse) were not associated with HPV infection.[20,21,47] Indian women mostly report low number of sexual partners and no history of other sexually transmitted infections, which might explain this difference from other reports worldwide. In one study, consistent with studies in other nations, husband's sexual activity including extramarital sex and reported history of sexually transmitted infections was significantly associated with HPV infection and risk for ICC among Indian women.[47] Coinfection with HIV (See previous section) and/or other STIs is also a strong risk factor for ICC. Data indicate that certain STIs, such as *Chlamydia trachomatis* and herpes simplex virus type 2 (HSV-2) increase HPV persistence as well as influence the development of high-grade cervical lesions and invasive cancer.[48,49] Some researchers suggest that this high-risk is in part, due to cervical inflammation produced by these STIs, possibly resulting in genotoxic damage by reactive oxidative metabolites.[48,50] As in HIV and other STIs, circumcision is a cofactor in reducing HPV infection. Castellsague et al found that monogamous women had a reduced risk for cervical cancer if their male partners were circumcised.[51] In addition, a recent trial in Rakai, Uganda demonstrated that female partners of circumcised males had a lower HPV prevalence and a lower rate of newly detected high-risk infections.[52]

High Parity, Smoking, Oral Contraceptives and Socioeconomic Status

Other contributing cofactors in cervical carcinogenesis are high parity, smoking, and long-term use of oral contraceptives (OC). HPV infection in women with higher number of pregnancies is more likely to progress to ICC.[53,54] Likewise, multiparous Indian women had a higher risk for cervical cancer compared with nulliparous women.[47,55] Data from many studies indicate that smoking not only influences HPV persistence and increases the risk for CIN3 and ICC but also there is a clear dose-response relationship.[54,56-58] It is unclear whether the increased risk is due to carcinogens

in cigarettes that cause DNA damage or because smoking has a negative impact on the host immune response to viral infection.[59-61] In studies, assessing smoking and ICC risk, Indian women do not report smoking but one study found a two-fold risk for ICC with reported paan chewing.[47]An analysis of 35 studies among women with and without cervical cancer showed an enhanced ICC risk with recent and current use of OCs.[62] In addition, a more recent study by Luhn et al found that high parity, smoking and long-term OC use resulted in an elevated risk for CIN3 *vs* <CIN2 suggesting that smoking and hormone-related factors play a role in the progression of HPV infection to precancerous lesions.[54]

Among Indian women, another factor associated with an increased risk for HPV infection in India and subsequent development of ICC is low socioeconomic status.[63] One case control study by Franceschi et al found that surrogate markers of poverty or low socioeconomic status, such as poor hygienic conditions, low education, paan chewing and poor nutrition were associated with higher risk of HPV infection and higher ICC risk.[47]

Risk Factors for HIV-infected Women

Data from a few studies on HIV-infected women in India indicate an increased HPV risk associated with multiple sexual partners,[37] parity[34] and young age at first sexual intercourse.[36] Declining CD4 counts at study enrollment and nadir CD4 < 200 cells/μL were also significantly associated with HPV infection.[34,37] Worldwide, published reports on the effect of antiretroviral therapy (ART) on HPV risk and cervical cancer are inconclusive.[64] Likewise, in India, Isaakidis et al reported a higher odds of HPV infection among HIV-infected women receiving ART for <12 months compared to ≥12 months (OR = 3.57, p = 0.025), while Joshi et al did not find any effect of ART duration on HPV risk; and Mane et al reported a higher odds of HPV 16 infection (OR = 3.47, CI: 1.47-8.59) as well as more severe CIN among ART-experienced women. It has been postulated that the increased survival time due to ART may allow the development of cervical disease as well as other cancers in HIV-positive patients.[64,65]

PREVENTION OF INVASIVE CERVICAL CANCER

Pap Cytology, Visual Inspection with Acetic Acid (VIA) and HPV DNA Testing

Invasive cervical cancer is a preventable disease. Cervical cancer screening followed by treatment of abnormal lesions, and HPV vaccination, remain the two key modalities for ICC prevention. In the developed world, women can be screened by (1) cytology using the conventional Papanicolaou (Pap) test or the newer liquid-based, thin layer cytology,[66] and (2) high-risk HPV DNA testing (for women older than 30) as cotesting. The employment of extensive cytology screening to detect abnormal lesions early has resulted in a remarkable decline in ICC incidence worldwide.[67] However, developing countries, such as India have not been able to successfully implement Pap smear screening because of a weak health infrastructure for adequate collection and transport of specimens, lack of competent cytopathologists, inadequate laboratory infrastructure, inability to manage follow-up visits and other barriers.[68,69] In addition, cytology-based screening is not especially sensitive and requires repeated screening or cotesting with HPV DNA to be efficacious for reducing ICC risk, thus making it a less cost-effective option in developing countries.[32]

An alternate screening technique,visual inspection of the cervix after application of acetic acid (VIA) or Lugol's iodine (VILI) has gradually gained acceptance in resource-constrained settings such as India. VIA/VILI are simple to conduct and allow for same day 'screen and treat' approaches in non-urban or low-resource settings where loss to follow-up remains a critical issue in treating women early.[69] Two large-scale randomized control trials of VIA screening among 80,000 women in Tamil Nadu and 150,000 women in Mumbai that included colposcopy and directed biopsy of positive cases followed by treatment, showed a 35% and 31% reduction in ICC mortality.[70,71] Overtreatment of women without precancerous lesions using cold coagulation or cryotherapy is of concern in a VIA one visit 'screen and treat approach'.[69,72] A few recent studies have also evaluated a 'see and treat' approach, which combines VIA with colposcopy/directed biopsy and treatment with loop electrosurgical excision procedure (LEEP) in one visit with inconsistent results.[72,73] This approach requires experienced colposcopists that could make accurate diagnoses to prevent overtreatment.

Human papillomavirus DNA testing has recently been found to be a valuable alternative tool to Pap cytology under specific conditions. Data from a large population-based trial in Osmanabad, India demonstrated that HPV DNA screening of women 30 years and older, at least once in their lifetime can result in a 36% reduced lifetime risk of cervical cancer at a cost of <$500 per life saved.[74,75] Several other published reports also indicate that HPV DNA testing is superior to cervical cytology and VIA screening in reducing ICC risk among women older than 30 years.[76,77] Human papillomavirus DNA testing is highly sensitive but has a low specificity, and is not recommended among younger populations and HIV-infected women, given the high HPV prevalence in these populations. In addition, HPV DNA tests are expensive, require trained technical staff, and results are not available quickly.[69] The care HPV test, a less expensive

option, has shown favorable results with good sensitivity and specificity and is currently being marketed in some developing countries. The equipment is portable, provides results rapidly and can be performed with simple training and without expensive infrastructure.[76]

National cervical screening guidelines in India that were developed in 2005 with assistance from WHO and IARC have not been implemented widely.[78] These guidelines recommend screening women between the ages of 30 and 59 at least once in their lifetime at a primary health center using VIA and if indicated, a follow-up single visit at the district hospital to include colposcopy and treatment when necessary.[78] These guidelines are a minimum for those settings in India that have limited resources. Table 2 compares guidelines by the American Society for Colposcopy and Cervical Pathology (ASCCP)[67] and WHO.[79] Of note, ASCCP recommends that HIV-infected women should be screened more often with two Pap smears 6-months apart during the first year after diagnosis, and if normal, then annual screening thereafter.[80] Implementing frequent screening for HIV-infected Indian women is feasible through creative utilization of the existing infrastructure during regular care visits.

BARRIERS TO CERVICAL SCREENING

Cervical screening rates in India are extremely low. In a large population study of 100,800 women in Maharashtra, only 8 women reported ever being screened prior to the study.[81] A WHO household survey in 2001-2002 found an overall 2.6% rate of Pap smear screening among urban and rural women.[10] In rural Kerala, 6.9% of women in one study reported being screened.[82] Community participation was noted as the key barrier to screening women in Andhra Pradesh.[68] Women did not perceive a need to seek medical attention in the absence of symptoms. Other common reasons cited by women were fear/anxiety of medical providers, fear of pelvic exam, pain, discomfort, embarrassment, fear of cancer diagnosis, fear of community perception and gossip, since ICC is associated with sexual activity, and not knowing where to go for the test.[68,82] Lack of support from husband and other family members were also important reasons for low participation in screening.[68,82] Self-collection of samples for HPV screening improved participation rates from 53.8% (clinician collected) to 71.5% in a rural setting.[83] Currently, there is no national policy on cervical screening in India and therefore no significant investment has been made to implement nationwide screening. Developing countries, such as Mexico, Thailand and Brazil have implemented national cervical screening initiatives that have been designed to meet the needs of their unique populations.[72] India can learn from these successful initiatives.

HUMAN PAPILLOMAVIRUS VACCINATION

Two HPV vaccines Gardasil®, a quadrivalent vaccine to protect against infection from HPV genotypes 6, 11, 16, and 18 and Cervarix®, a bivalent vaccine to protect against infection from HPV genotypes 16 and 18 are expected to

Table 2: Summary of cervical cancer screening guidelines by the World Health Organization (WHO)*[79] and American Society for Colposcopy and Cervical Pathology (ASCCP)[67]

Population	*WHO**	*ASCCP*
Age <21 years	No screening for women <30 years unless HIV+ or living in high HIV prevalence area	No screening
Age 21-29 years	No screening for women <30 years unless HIV+ or living in high HIV prevalence area	Cytology screening only every 3 years
Age 30-65 years	Prioritize women 30-49 years Screening interval with VIA/cytology should be 5 years (not less) Screening interval with HPV testing should be 10 years (not less)	Cytology and HPV co-testing every 5 years (preferred) Cytology screening alone every 3 years (acceptable)
Age >65 years		No screening, if previous history of negative screening Women with prior history of ≥ CIN2 must continue routine screening for at least 20 years
After hysterectomy		No screening for women without cervix and previous negative screening for CIN2
HPV vaccinated		Same as age-specific recommendations for unvaccinated women

VIA: Visual inspection with acetic acid; CIN2: Cervical intraepithelial neoplasia grade 2; ICC: Invasive cervical cancer; HPV: Human papillomavirus; *WHO guidelines are 'minimum guidelines' for countries that do not have national programs for cervical screening, specifically in resource-limited settings[78]

prevent up to 70% of all cervical and anal cancer cases caused by HPV 16/18 infections and >95% of genital warts (quadrivalent vaccine) in both women and men globally.[16,104,105] The two vaccines approved by the WHO are typically recommended for girls 9 to 26 years in a series of three doses over 6 months.[16] Data from clinical trials and other follow-up studies have demonstrated the safety and tolerability of both vaccines showing high immunogenicity, low adverse events and sustained protection of up to 8.4 years.[16,84] Recently, the quadrivalent vaccine was found to be safe and immunogenic for HIV-infected children[85] and women, although women with CD4 counts <200 cells/µl and HIV viral load >10,000 copies/ml had slightly lower seroconversion rates.[86] There is growing evidence from countries that have implemented HPV vaccination among girls and young women that the vaccines have had a significant impact on reducing genital warts[87-89] and decreasing incidence of high grade cervical lesions.[90,91] Clinical trial data of the much anticipated nonavalent vaccine which protects against nine high-risk HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 indicate that the vaccine has the same efficacy as the quadrivalent vaccine against HPV 16 and 18 and has a 97% efficacy in preventing cervical disease from the additional five HPV types.[92] It is estimated that the nonavalent vaccine will prevent up to 90% of cervical cancers.[93]

BARRIERS TO HPV VACCINATION

Although Gardasil and Cervarix have been licensed by the Drug Controller General of India and recommended by the Indian Academy of Pediatrics, Committee on Immunization and the WHO,[94] the vaccine has not been introduced into India's national immunization schedule. Human papillomavirus vaccine uptake in India has been slow, encountering significant challenges as in other countries, including the need for three doses, high vaccine costs, poor awareness about the vaccine and its benefits, safety concerns, strong cultural beliefs that adolescent females are not sexually active and therefore fear of encouraging promiscuity, and lack of physician recommendations.[95-97] Currently, the vaccine is only available through private providers because, in April 2010, the Indian government halted two vaccine feasibility studies due to demands from advocacy groups about adverse events related to the vaccine as well as other alleged ethical violations. An extensive inquiry determined that the deaths of seven girls who were vaccinated were not linked to the vaccine.[94,98] However, the resultant public distrust and concerns about the vaccine have not been addressed[99] preventing any further evaluation of implementation strategies through the national public health system. The cost of the HPV vaccine is a significant barrier and although the cost has been reduced from $ 100 to 4.50 per dose for GAVI eligible countries,[100] the vaccine is still expensive for low-resource countries.

Increasing vaccine uptake in India will require that the delivery of HPV vaccine becomes a priority on the government's agenda, by developing a national policy for preventing ICC that is lacking. Australia and Scotland have implemented successful national HPV immunization campaigns for girls 9 to 12 years and catch up vaccinations for adolescents and young adults through schools, community clinics and general practitioners.[101,102] The South African government has announced that starting in 2014, it will begin to provide around 500,000 HPV vaccines to 9 to 10 year old girls.[103] India has been successful in their national immunization campaigns for other childhood diseases and can learn from other countries as well to implement such campaigns. It would be essential to first address public concerns about the vaccine, gain public trust, garner support from all stakeholders including women activists, media, schools, community leaders and particularly physicians that are a highly valued resource by the Indian population.

In summary, Indian women continue to share a significant burden of invasive cervical cancer. Human papillomavirus infection is widely prevalent among Indian women, with HIV-infected women at higher risk for cervical disease. Human papillomavirus 16 is the predominant genotype in both HIV-infected and uninfected women. Cervical screening rates are extremely low, and modest improvements to screening participation rates have the potential to significantly reduce ICC burden. Implementing Pap cytology nationwide as the main cervical screening modality is not feasible because of the substantial infrastructure investment and quality control needed to screen accurately. VIA might be a better option in the short-term, if VIA can be standardized with well-trained staff to increase specificity. The long-term goal must include the development of rapid, inexpensive screening tests requiring low-resources and able to detect HPV DNA or biomarkers that can predict precancerous lesions in women. New screening and treatment algorithms using such tests will allow the scale up of prevention programs in countries that share a large burden of ICC. Lastly, a national public policy regarding cervical screening of women and HPV vaccination for girls and young women in India is integral to the scale up of both primary and secondary prevention programs and must become a priority.

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10.5005/jp-journals-10036-1013

REVIEW ARTICLE

Childhood and Adolescent Onset Type 1 Diabetes in India

[1]Anandakumar Amutha, [2]Thai Kalpana, [3]Viswanathan Mohan

ABSTRACT

According to International Diabetes Federation, there are 382 million people with diabetes globally. While the majority of this is constituted by type 2 diabetes, numbers of type 1 diabetes are also increasing. This paper reviews the clinical and epidemiological features and management issues in children and adolescents with type 1 diabetes.

Keywords: Type 1 diabetes, Children and adolescents, Management, Complications, Epidemiology, India.

How to cite this article: Amutha A, Kalpana T, Mohan V. Childhood and Adolescent Onset Type 1 Diabetes in India. MGM J Med Sci 2014;1(2):76-83.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Recently, physicians and pediatricians are facing fresh challenges due to new epidemics affecting children's physical and mental health. Earlier, infectious diseases like viral infections, mumps, chicken pox, pneumonia, diarrhea, nutritional deficiencies dominated childhood diseases. Today these are being replaced by noncommunicable diseases like overweight/obesity and diabetes.[1-3]

Diabetes mellitus is one of the commonest endocrine and metabolic diseases of childhood. Till recently, diabetes in children (defined as onset below 12 years) and adolescents (defined as onset between 12 and 19 years) was almost exclusively type 1 diabetes (T1DM) and this has changed, as there is increased recognition of a number of different forms of 'nontype 1 diabetes' in the young. This includes type 2 diabetes (T2DM), maturity onset diabetes of young (MODY), fibrocalculous pancreatic diabetes (FCPD) and diabetes due to genetic disorders. This review will focus exclusively on the epidemiology, clinical profile, management and complications of childhood onset type 1 diabetes with special reference to published studies from India.

[1]Research Associate, [2]Consultant Pediatric Diabetologist [3]Chairman and Chief

[1]Department of Epidemiology, Madras Diabetes Research Foundation, Chennai, Tamil Nadu, India

[2,3]Department of Diabetology, Dr Mohan's Diabetes Specialities Centre, Chennai, Tamil Nadu, India

Corresponding Author: Viswanathan Mohan, Chairman and Chief, No. 6B Conran Smith Road, Gopalapuram, Chennai Tamil Nadu, India, Phone: +91-4443968888, e-mail: drmohans@diabetes.ind.in

Epidemiology

T1DM is a disorder that arises following the autoimmune destruction of insulin-producing pancreatic β-cells.[4] The disease is most often diagnosed in children and adolescents, usually presenting with a classic triad of symptoms, (i.e. polydypsia, polyphagia, polyuria) along with severe hyperglycemia, necessitating the need for exogenous insulin replacement on a lifelong basis.

T1DM probably accounts for 5 to 10% of all diagnosed diabetes. About 40 to 60% of persons with T1DM are younger than 20 years of age at onset, thus making diabetes one of the most common severe chronic diseases of childhood affecting 0.3% of the general population by the age of 20 years and 0.5 to 1% during the lifespan.[5] The worldwide prevalence of T1DM is 0.1 to 0.3%, with 78,000 new cases every year, especially among young individuals (<5 years). Some 79,100 children under 15 years are estimated to develop T1DM annually worldwide.[6]

According to the reports of SEARCH group[7] the incidence of T1DM peaks around the age of 10 years and is highest among non-Hispanic Whites followed by non-Hispanic Blacks, Hispanics, Asia and Pacific Islanders and American Indian/Alaskan Natives. The South-East Asia Region (SEAR) has a high prevalence of T1DM in children, with an estimated 77,900 children affected. In 2013, alone an estimated 12,600 children under the age of 15 in SEAR developed T1DM.[6]

India due to its sheer size (1.2 billion people) accounts for most of the children with T1DM in the SEAR. The incidence rate for T1DM in India was frequently used in extrapolation for other countries in the region and therefore the estimates in India are of great significance. In the 1990's, Menon et al[8] had done an overview of childhood onset diabetes mellitus in India. Prevalence of juvenile diabetes (onset below 15 years) among all diabetes hospital/clinic based data was presented and the prevalence ranged from 0.8 to 3.61% during the period from 1964 to 1989.

After a long gap of two decades, this review tries to fulfill the lacunae by presenting the incidence and prevalence/percentage of T1DM reported in India so far in Table 1. In a population based study conducted in South India for a period of 1991 to 1994, the incidence for the 4 years period was 10.5/100,000/year (CI 5.0) for children up to 15 years of age.[9] Similarly, a study from Karnal district in 2008, showed a prevalence of 18.3/100,000 in the 0 to 14

Table 1: Incidence and prevalence/percentage of type 1 diabetes reported in India

Author name	*Place*	*Year or period of study*	*Number of T1DM in children reported and given as % where applicable*	*Total sample studied*	*Age at diagnosis*	*Ref. no.*
Incidence of T1DM						
Bai et al	Chennai	1991		10513	School children	11
Ramachandran et al		1991-1994	10.5/100,000 person-years	IDDM registry	<15 years	9
Kalra et al	Karnal	2008	3.82/100,00 24.22/100,000	Endocrine center registry	0-6 years 5-15 years	10
Prevalence/percentage of T1DM (clinic based)						
Verma IC	New Delhi	1980-84	44 (80.0)	55	5-12 years	12
Venkataraman et al	Chennai	1979-89	126 (7.88%)	160	<20 years	13
Mohan et al		1990	165 (63.9)	258	<20 years	14
Ramachandran et al		1991	0.26/100 (30 children)	116, 486	<15 years	15
Ramachandran et al		2000	617	-	<20 years	16
Kumar et al		1991-2001	8 (0.01%)	70000	≤1 year	17
Mohan et al		2007	286 (65.9%)	434	<16 years	18
Ganesh et al		2003-2007	4 (0.05)	83	≤1 years	19
Varadarajan et al		1999-2010	350 (81%)	432	<12 years	20
Amutha et al		1992-2009	940 (68.5)	1372	≤19 years	21
Varadarajan et al		1999-2012	40 (7.9)	506	≤1 year	22
Kota et al	Hyderabad	1997-2011	260	-	10.5 ± 7.2 years	23
Sahay et al		1999-2002	28 (59.6)	47	<20 years	24
Abraham et al	Central Kerala	1985-1989	39 (67%)	58	<20 years	25
Bhadada SK et al	Chandigarh	2002-2008	189	-	10.8 ± 7.3	26
Unnikrishnan et al	Multicentric study	2006-2008	535 (89%)	603	<20 years	27
Bhatia et al	Lucknow	2004	130 (81%)	160	<18 years	28
Balasubramanian et al		10 years period	55 children	-	<20 years	29
Singh et al		1992-1997	83 (57.2)	145	13.8 ± 7.3	30
Samal et al	Cuttack	1983-1988	54 (60%)	90	<15 years	31
Mazumder et al	Kolkata	2004-2006	41 (70.7)	58	<18 years	32
Kumar P et al	Karnataka	1995-2008	134 (43%)	311	9-14 years	33
Zargar et al	Srinagar	1990-1999	84 (90.3)	93	<20 years	34

years age group.[10] Clinic based data show that more than 60% of the T1DM patients registered were childhood and adolescent onset T1DM patients.

Etiology and Pathogenesis of T1DM

The precise cause of T1DM is unknown but there are a number of possible contributory factors and some of them were discussed below.

Genetic Factors

T1DM tends to run in families. Epidemiologic studies have shown that brothers and sisters of children with T1DM have a higher chance of developing the disease (6% in siblings *vs* 0.4% in the general population) among the relatives of T1DM patients, underlying the role of genetic factors as a cause of T1DM.[35] Twin studies of T1DM from a large Finnish cohort of 22,650 twin pairs, 228 of which had at least one twin with T1DM (44 monozygotic (MZ), 183 dizygotic (DZ), and 1 of unknown zygosity), demonstrated a 27.3% MZ pair-wise concordance, and a 3.8% DZ concordance.[36]

Since, the 1970s it has been acknowledged that genes belonging to the human leukocyte antigen (HLA) system on chromosome 6 constitute the most important genetic risk factor.[37-39] The chromosomal locations of these 'diabetes genes' are called inherited susceptibility loci. There are now at least 18 insulin-dependent diabetes mellitus (IDDM) susceptibility loci (IDDM 1 to IDDM 18).[40] HLA make up the human major histocompatibility complex (MHC), which presents antigens to the immune system, but now more than 40 additional loci are known to significantly affect T1D risk.

Recently, genome-wide association studies (GWAS) have been used to identify genetic loci-associated T1DM. In contrast to the traditional methods of using a candidate gene approach, GWAS scans the whole genome for single nucleotide polymorphisms (SNPs) that occur more frequently

in people suffering from T1DM. The associated SNPs then are used to mark the susceptibility loci. By using the SNP typing technology, a number of additional susceptibility loci were discovered for T1DM, namely: CLEC16A, CI1QTNF6, UBASH3A, CD226, PTPN2, CTSH, SH2B3, ERBB3, PRKCQ, TAGAP, IL-2RA, TNFAIP3, BACH2, IL-7R, IL-2, CCR5, IFIH1, IL-18RAP, RGS1, IL-10, IL-19, IL-20, GLIS3, CD69 and IL-27.[41-43]

Viral Infections and Toxins

Epidemics of enteroviral infections in the autumn and winter months are associated with an increase in the incidence of T1DM. Several viruses (e.g. coxsackie B, enteroviruses, rubella, mumps and cytomegalovirus) have been implicated in the etiology of T1DM.[44] Also, T cells target the envelope proteins (VP1, VP2 and VP3) of coxsackie virus B4, but the T cell proliferative response was reduced markedly in T1DM patients compared with control subjects, which eventually results in destruction of beta cells.[45] Possible mechanisms for their effect include molecular mimicry in which the immune response to the infection cross reacts with islet antigens. Alternatively viral infections including those occurring antenatal may have more direct effects on β-cells. Ingestion of the rodenticide vacor is also known to be associated with development of T1DM.

Environmental Factors

Among the various environmental factors, exposure to antigenic substances early in life is thought to contribute to T1DM.[44] Undissolved gluten causes subclinical inflammation of intestinal mucosa, which raises the proportion of aggressive T cells. The functional state of beta cells also plays a role in the pathogenesis of T1DM, and food intake with a high glycemic index increases the insulin demand and forces the beta cell to produce more insulin, which accelerates its destruction. This observation has inspired the 'Accelerator hypothesis', which states that increased weight gain in youngsters might accelerate T1DM development.[46]

Nutrition and Dietary Factors

Breastfeeding appears to provide protection against the risk of developing T1DM.[47] Available evidence to date shows that lack of breastfeeding is a possible modifiable risk factor for the manifestation of both T1DM and T2DM. The benefits of breastfeeding have been attributed to bioactive substances, which promote the maturation of the immune system, reduce insulin resistance, and prevent excessive weight gain during childhood.[48]

Early introduction of Cow's milk appears to be a risk factor for the development of T1DM.[49] Many new patients with T1DM have IgG antibodies to bovine serum albumin, a protein in Cow's milk with similarities to the islet cell antigen. This protein may stimulate autoantibody production leading to islet cell destruction as a result of molecular mimicry.

Breastfeeding may be viewed as a surrogate for the delay in the introduction of diabetogenic substances present in formula or early childhood diet. Circumstantial evidence suggests a connection between T1DM and consumption of foods and water containing nitrates, nitrites or nitrosamines.[50-52]

Pancreatic β-cell Reserve—C-peptide Assay

It is known that at the time of T1DM diagnosis, 80 to 90% of the pancreatic islet β-cells are destroyed. C-peptide determination[53] is used to better understand the course of T1DM. It was shown that young children with classical ketosis prone insulin dependent diabetes also had residual insulin secretion.[54] Very young children especially those with onset after infections tend to have less C-peptide.

In recent years, C-peptide determinations have gained lot of interest. Efforts to preserve residual insulin secretion have increased dramatically in the last few years.[55] The heterogeneity of diabetes at clinical onset along with the increasing incidence in children and adolescents[56] makes it of interest to test if C-peptide may improve the classification of newly diagnosed children. Katz et al[57] reported fasting C-peptide levels of 0.38 ± 0.37 ng/ml can distinguish T1DM from T2DM with 83% sensitivity. In our study,[21] we found that a combination of clinical criteria and C-peptide criteria is largely helpful for classification of our children with diabetes and this also has been reported by Ludvigsson et al.[58]

Antibodies

Several autoantibodies have been identified in newly diagnosed cases of T1DM. Currently, four major antibodies namely (the 65 kDa form of glutamic acid decarboxylase (GAD65), insulinoma antigen 2 (IA-2), insulin auto, antibodies (IAA) and zinc transporter 8 (ZnT8) have been shown to be found in T1DM and approximately 94% of all T1DM patients have least one of these antibodies at clinical onset.[59]

Monitoring these autoantibodies is currently the most reliable biomarker in the prodromal phase of T1D, since their appearance typically precedes overt T1D onset for years or even decades.[60,61] This provides a window for therapeutic intervention, and as a measure of treatment efficacy.[62-64] Most important, the prevalence of multiple types of autoantibodies identifies individuals with the highest risk of progression to clinical disease in those in the prediabetes stage of T1DM.

Clinical Features of T1DM

1. Abrupt onset of severe symptoms (polyuria, polydipsia and/or weight loss).
2. Presence of ketosis or ketoacidosis.
3. Severe diabetes with markedly elevated glycated hemoglobin levels (HbA1c).
4. Usually patients are nonobese or even lean.
5. Family history of diabetes in parents is usually absent.
6. C-peptide test shows absence or very low pancreatic β-cell reserve.
7. GAD, IA2, zinc transporter or other islet cell antibodies may be present.
8. Patients require lifelong insulin from time of onset for survival and to maintain good health and for control of hyperglycemia.

Management of T1DM

The basic elements of T1DM management are insulin administration, nutrition management, physical activity, self, monitoring of blood glucose (SMBG), and the avoidance of hypoglycemia. In T1DM, since the pancreas can no longer produce insulin, patients are required to take insulin daily, either by injection or via an insulin pump. Other routes of delivering insulin are currently being investigated.

Children are now being treated with basal bolus regime or an insulin pump. Basal bolus regime—this is the most physiological way of matching the insulin secretion in our body by insulin injections. In this, children receive a basal insulin dose with long acting insulin analog and premeal boluses are given by rapid acting insulin analogs just before meals. The total insulin dosage in children is 0.5 units/kg/day to 1.0 units/kg/day with up to 2.0 units/kg/day during puberty period.[65]

Premeal boluses are calculated more accurately by carbohydrate (CHO) counting, insulin to carbohydrate ratio (ICR) and correction bolus.

Carbohydrate counting is a meal planning wherein the patient identifies the CHO in the meal, estimates the total CHO amount in the meal and calculates the insulin to balance the CHO using ICR (insulin to CHO ratio) thereby controlling postprandial glucose levels more accurately. It is done by two methods, CHO exchange (1CHO serving = 15 gm carb portions) and CHO gram counting (food is weighed and CHO is calculated).

Insulin to carbohydrate ratio is the amount of insulin required to cover a specified number of CHO grams. This is calculated by 500/300 rule [500/total daily dose of insulin (TDD) for children aged 5 years and above and 300/TDD for preschool children].

Correction bolus is the amount of extra, fast acting insulin added to or subtracted from a bolus to correct a blood glucose that is above or below target (90-140 mg). This is calculated by [(Current blood glucose – Target blood glucose)/insulin sensitivity factor (ISF)]. ISF is how much 1 unit of insulin will lower the blood glucose by. This is calculated by 1500 or 1800 rule (1500/TDD for short acting insulin and 1800/TDD for rapid acting insulin).[66]

Further adjustment of insulin or food intake may be made based on anticipation of special circumstances, such as increased exercise and intercurrent illness. Children on these regimens are expected to check their blood glucose levels (self monitoring of blood glucose) routinely before meals and at bedtime.[67]

Insulin pumps are being more commonly used because of their unique ability to continuously infuse insulin, closely mimicking that of physiological secretion from a normal pancreas. The insulin pump separates the insulin used as background, or basal insulin, from the insulin needed for meal and corrections boluses and therefore insulin can be more exactly matched to the metabolic need achieving better glycemic control. Scientific evidence from published studies have proven added benefit of insulin pumps in improving quality of life and normalizing sugars. The success of insulin pump therapy depends on selection of the right candidate, extensive education, motivation, and implementing the sophisticated programs with skill.[68]

Advantages of Insulin Pump

- Improvement in HbA1c
- Reduction in blood sugar fluctuations
- Reduction in major and minor hypoglycemic episodes
- Reduction in total daily dose of insulin
- Improvement in quality of life.

Disadvantages of Insulin Pump

- Cost of pumps and consumables is beyond the reach of the common individual
- There is a risk of infection if the cannula is not changed once in every 3 days
- Overeating and frequent bolusing could result in weight gain and misuse of an insulin pump
- Improper use of insulin pump boluses can lead to insulin stacking and low sugar.[68]

Complications of Diabetes

Acute Complications

Acute complications of T1DM include diabetes ketoacidosis (DKA), hypoglycemia and infections. An estimated 26% of the patients have at least one episode of severe hypoglycemia

within the initial 4 years of diagnosis, with little relation to demographic or socioeconomic factors. The incidence of severe hypoglycemic episodes varies between 6 and 20/100 patient-years depending on age, geographic location and intensity of insulin treatment.[69]

Diabetic ketoacidosis in children continues to be an important cause of morbidity and mortality. Malnutrition also increases the risk of diabetic ketoacidosis-related complications.[70] Boys and girls were equally affected. Newly diagnosed diabetics constituted more than 50% of total DKA admission.[71] Management requires careful replacement of fluid and electrolyte deficits, intravenous administration of insulin, and close monitoring of clinical and biochemical parameters directed toward timely detection of complications, including hypokalemia, hypoglycemia and cerebral edema.[72,73]

Chronic Complications

Long-term complications may be microvascular (retinopathy, nephropathy and neuropathy) or macrovascular (ischemic heart disease, peripheral vascular disease). Microvascular complications may develop in puberty or early adult hood whereas macrovascular complications affect in later years. The longer the duration of diabetes, the greater the risk of complications which increases significantly following puberty. The risk of developing complications may also be increased by poor glycemic control, hypertension, dyslipidemia and behavior, such as smoking in addition to genetic factors.

Background diabetic retinopathy in childhood may rarely progress to proliferative retinopathy later in life. This can be successfully treated in its early stages with laser photocoagulation therapy. Cataracts may also occur in T1DM patients but is very rare under the age of 20 years. The prevalence of retinopathy in adolescents varies from 18 to 47%. More than 90% of patients with T1DM will eventually develop some degree of retinopathy. A pilot study done by SEARCH group estimated, the prevalence of diabetic retinopathy among those with T1DM was 17% which was similar to that reported from Australia [74] with similar duration. The SEARCH for diabetes in Youth study[75] reported a high prevalence of elevated albumin creatinine ratio (22.2%) in youth with T2DM, well over twice the percentage for participants with T1DM (9.2%).

A cohort of 354 patients with T2DM, age of onset between 15 and 30 years (T2DM15-30), were compared with 470 patients with T1DM with a similar age of onset (T1DM15-30) to study the clinical and mortality outcomes. No significant differences were found between T1DM and T2DM with regard to prevalence of retinopathy or renal function assessed by eGFR, but a marked excess of macrovascular disease was found in the T2DM15-30 cohort, with a higher prevalence of ischemic heart disease (12.6 *vs* 2.5%, p, 0.0001), stroke (4.3 *vs* 0.7%, p = 0.002), and the composite end point of any macrovascular disease despite having shorter duration of diabetes and remarkably similar glycemic exposure as T1DM 15 to 30 cohort.[76]

Prevalence of diabetes complications in T1DM reported from India is outlined in Table 2.

Most of the available data are from clinic based studies and the prevalence or percentages represents against their total patients registered from those particular clinics in India. The age ranges studied are usually inconsistent. There is also a lack of uniformity in classification of diabetes types. Some of the adolescents who were originally diagnosed as having T1DM were later found to have T2DM and *vice versa*. Some of the children and adolescents were not able to be classified due to lack of unavailability of GAD antibody and C-peptide assays. Another problem is migration of patients to other centers.

Table 2: Diabetes complications in T1DM reported from India

S. no.	*Author name*	*Year or period of study*	*Age at onset in years/duration of diabetes in years*	*Retinopathy n (%)*	*Nephropathy n (%)*	*Neuropathy n (%)*	*Ref. no.*
1.	Venkataraman et al	1979-1989	<20 years/ 6 to 9 years	7/126 (5.6%)	5/126 (4%)	19/126 (15.1%)	13
2.	Sharma et al	1991	–	15/35 (42.8%)	–	–	77
3.	Ramachandran et al	2000	≤20 years/ 11-15 years	23/74 (31.1)	16/74 (21.6%)	19/617 (3.0%)	16
4.	Bhatia et al	2004	<18 years/ >5 years	22%	18%	–	28
5.	Unnikrishnan et al	2006-2008	<20 years/ <7 years	27/535 (5%)	29/535 (5.4%)	32/535 (6%)	27
6.	Kumar et al	1995-2008	<25 years	14/166 (8.4%)	20/230 (8.6%)	12/230 (5.2%)	33
7.	Amutha et al	1992-2009	<20 years/ 5-14 years	38/171 (22.2%)	9/183 (4.9%)	5/139 (3.6%)	21

The Indian Council of Medical Research recently set up a national registry of diabetes in the young (onset <25 years of age). This shows that private diabetes centers have more cases of young-onset T2DM, whereas government hospitals mostly deal with T1DM. This is probably a socio-economic issue as the free supply of insulin would attract type 1 patients to government hospitals, whereas the more affluent with obesity-related T2DM would visit private diabetes centers.

In spite of a number of studies describing the prevalence, distribution and possible causes of diabetes, many government and public health planners still remain largely unaware of the current magnitude and in particular the increases in young diabetes and its serious complications. Special efforts must be made to collect data, especially in those countries where diagnosis may be missed.

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10.5005/jp-journals-10036-1014

REVIEW ARTICLE

Cutaneous Adverse Drug Reactions

[1]Shylaja Someshwar, [2]Hemangi R Jerajani

ABSTRACT

Cutaneous adverse drug reaction is one of the most common manifestations of drug allergy. As the knowledge of the morphology of drug induced cutaneous lesions helps in the early identification of even a serious drug reaction, it is mandatory for the treating physician to pick up early signs of these reactions followed by a prompt withdrawal of the suspected drug. The paper discusses the clinical presentation and management of these including severe cutaneous adverse drug reactions. It emphasizes on need of a great amount of skill for its identification and management.

Keywords: Adverse drug reaction, Hypersensitivity reaction, Exanthema, Erythroderma.

How to cite this article: Someshwar S, Jerajani HR. Cutaneous Adverse Drug Reactions. MGM J Med Sci 2014;1(2):84-94.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Cutaneous adverse drug reaction is defined as an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.[1]

Adverse drug reactions (ADRs) are responsible for about 3% of all hospital admissions and between 10 and 20% of hospital inpatients develop ADRs.[2] The ready visibility of skin signs makes it easy to detect a drug reaction earlier so as to discontinue the drug in question. Skin manifestation is also the commonest presentation of drug allergy[3,4] emphasizing the importance of recognition and withdrawal of the causative drug which at times may be life saving.

The presentation varies from mild in the form of a skin rash alone to severe having multisystem involvement in addition. It poses diagnostic difficulties because of its varied clinical presentation and also because of the need to find out the causative drug out of the many taken by the patient.

[1]Associate Professor, [2]Professor and Head

[1,2]Department of Dermatology, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India

Corresponding Author: Shylaja Someshwar, Associate Professor, Department of Dermatology, 201, Pramukh CHS Plot No. 64-B, Sector-21, Kharghar, Navi Mumbai-410210 Maharashtra, India, e-mail: shaila38@yahoo.co.in

Women are more likely than men to develop ADRs.[5]

Patients with acquired immunodeficiency syndrome have an increased risk of developing drug reactions. The reasons may be multifactorial which include changes in the drug metabolism, oxidative stress, cytokine profiles and immune hyperactivation.[6] The risk increases as they also receive multiple drugs for various associated ailments.

Rougeau proposed criteria[7] which help to diagnose cutaneous adverse drug reactions:

a. Other causes for the eruption as viral exanthema should be excluded.
b. A temporal relationship between the drug and onset of rash should exist.
c. Improvement should be noted following drug cessation.
d. Reactivation upon challenge should be noted.
e. Cutaneous reaction is known to be associated with the drug.

MECHANISM OF DRUG ALLERGY

Drug reactions are of two types—Allergic and more commonly nonallergic.

Nonallergic Reactions

Nonallergic reactions are usually dose dependent and predictable and normally result from the known pharmacological actions of the drug. Rarely they can be unpredictable in the form of idiosyncratic or hypersensitive reactions which are dose independent and are unrelated to the pharmacological actions of the drug. This may also have a genetic basis though not all of them have a genetic influence. Genetic factors are known to affect the pharmacokinetics and pharmacodynamics of the drug. The metabolic pathways most subject to genetic influence include oxidation, hydrolysis and acetylation.[8] Thus, genetic variations in all these areas may underlie intolerance and idiosyncrasy.[9-11]

Drug reactions are also known to occur more commonly with certain HLA types emphasizing the importance of genetic factors in the pathogenesis of drug reactions.

Allergic Reactions

On the other hand, allergic reactions require a prior immune stimulation by the drug in question. They can be divided into four types (Coombs and Gell).

Hypersensitivity Reactions

Type 1: This is an IgE dependent reaction wherein the drug or its reactive metabolite binds to IgE present on the surface of basophils or mast cells and cause degranulation of these cells with the resultant release of vasoactive mediators like histamine, prostaglandin D2, leukotriene C4, eosinophil and neutrophil chemotactic factors, platelet activating factor and bradykinin which clinically results in urticaria, angioedema or systemic anaphylactic reactions.

The most common causes of IgE–mediated drug-induced hypersensitivity are antibiotics (especially the penicillins) and anesthetic related drugs, particularly muscle relaxants.[12]

Type 2: Here there is a complement mediated cytolysis leading to cell damage after the antibody binds to the surface of the cell. An example is the thrombocytopenic purpura that may result from antibodies to quinidine-plateletconjugates.[13,14]

The other examples of this type of reaction are drug induced pemphigus, bullous pemphigoid and linear IgA disease. Drug induced pemphigus is divided into the following two types:[15]

1. Drug dependent pemphigus wherein exogenous factors such as thiol (_SH) containing drugs (e.g. D-penicillamine, captopril) cause pemphigus by binding with the plakoglobin and thus altering the immunogenicity. Thiols can also alter the immune system directly by its action on the T cells.
2. True (drug-triggered) pemphigus wherein in a genetically predisposed individual, nonthiol group drugs (e.g. penicillin, cephalosporins) trigger pemphigus by the virtue of amide group present.

Type 3: Serum sickness is the prototype of this kind of reaction wherein there is formation of antigen-antibody complexes and subsequent activation of complement cascade and inflammatory response. Here the antigen antibody complexes are present in the circulation with antigen excess. The immune complexes get deposited in the skin, gastrointestinal tract and kidneys. It can manifest in various forms like urticaria and anaphylaxis or vasculitis both as a result of anaphylotoxins C3a and C5a generated during the process of complement cascade activation. Another example of this type of hypersensitivity reaction is Arthus reaction which is a localised form occurring at the injection site.

Type 4: In recent years increasing evidence indicates that drug specific T cells play a cent role in the pathogenesis of these exanthema.[16-19] T cells (both CD4 and CD8) produce various cytokines which are responsible for the various manifestations. Earlier for the delayed hypersensitivity reactions, a hapten-prohapten model was believed to be the only mechanism involved wherein a chemically reactive small molecule (hapten) required binding with a larger molecule to be able to be recognized by the immune system or a chemically inactive molecule (prohapten) after metabolism becoming active and then being recognized by the immune system.[20-22] Lately, it was also demonstrated that the inert drug itself and not a metabolite was recognized by T cells.[23] There is also an upregulation of major histocompatibility complex (MHC) class II expression on keratinocytes.

CLINICAL PRESENTATION AND DIAGNOSIS OF VARIOUS DRUG REACTIONS

As the clinical patterns of drug reactions are very variable, it is a great task for the clinicians to diagnose and manage these reactions. It is also mandatory to differentiate mild from a severe reaction thus requiring an astute clinical awareness of the various clinical patterns. The common clinical manifestations include maculopapular rash, purpura, bullous lesions, erythema multiforme, fixed drug eruptions, and more serious forms like exfoliative dermatitis, acute generalized exanthematous pustulosis, toxic epidermal necrolysis and Steven Johnson's syndrome (SJS). Chronic onset drug-induced disorders include pigmentary changes, drug-induced

Table 1: Agents commonly implicated in drug induced skin lesions[24]

Lesion(s)	*Agents*
Urticaria	Aspirin; NSAIDs; angiotensin-converting enzyme inhibitors; penicillin; cephalosporins; opiates; peptide hormones; radiocontrast dyes; vaccines
Maculopapular eruptions	Aspirin; NSAIDs; ampicillin; anticonvulsants; barbiturates; isoniazid; phenothiazines; quinolones; sulfonamides; thiazides; co-trimoxazole
Vesiculobullous eruptions	Aspirin; NSAIDs; barbiturates; furosemide; griseofulvin; penicillamine; penicillin; sulfonamides; thiazides
Pemphigus	Penicillamine; gold; levodopa; heroin; penicillin; rifampin; phenylbutazone
Photosensitivity	Amiodarone; chlorpromazine; furosemide; quinolones; sulfonamides; tetracycline; thiazides
Fixed drug eruptions	Acetaminophen; anticonvulsants; barbiturates; metronidazole; oral contraceptives; penicillin
Vasculitis	Allopurinol; cimetidine; gold; phenytoin; quinolones; propylthiouracil; thiazides; NSAIDs
Stevens-Johnson syndrome; toxic epidermal necrolysis	Sulfonamides; co-trimoxazole; tetracyclines; barbiturates; thiacetazone; phenytoin; carbamazepine; phenylbutazone

autoimmune bullous diseases, pseudo lymphoma, lichenoid and acneiform eruptions.

A knowledge of the specific morphology of the skin rash associated with a particular drug helps in suspecting and timely withdrawal of the drug in question. Table 1 shows drugs commonly implicated in skin lesions.[24]

Drug Induced Urticaria and Angioedema

Urticarial reaction which consists of pruritic erythematous edematous usually evanescent and sometimes persistent wheals (Fig. 1) may also be drug induced apart from other causes, is classical of IgE mediated type 1 hypersensitivity reaction. It may also occur as a 'pseudoallergic' reaction due to direct release of inflammatory mediators because of the direct binding of the drug to mast cell or basophils. Angioedema, caused by the same pathogenic mechanism involves deep dermis and subcutaneous tissue. It presents mainly as asymptomatic or painful swelling which are less or nonitchy (Fig. 2). In the most severe form it may present with laryngeal edema, hypotension or bronchospasm. Penicillin is one of the most common causes for this kind of reaction the others being nonsteroidal anti-inflammatory drugs and sulphonamides. Along with these, radiocontrast media, animal sera, blood products can also cause both reactions.

Skin prick tests, enzyme linked immunosorbent assay (ELISA) and the radiosorbent test (RAST) may be useful in the diagnosis.

Histopathological examination of urticaria shows a normal epidermis with venular dilatation with edema in the dermis and superficial and deep dermal mononuclear infiltrate admixed with eosinophils and neutrophils. In angioedema, the infiltrate and edema extend to the subcutis.

Exanthematous Eruption

Exanthematous eruptions, sometimes referred to as morbilliform or maculopapular, are the most common form of drug eruptions, accounting for approximately 95% of skin reactions.[25] This manifests usually as symmetrical blanching, erythematous, papular eruption of sudden appearance with or without systemic features (Fig. 3). Mucous membrane involvement is rare. Systemic manifestations when present may include lymphadenopathy, fever, eosinophilia and organ dysfunction. Penicillins, sulphonamides, phenylbutazone, phenytoin, carbamazepine and gentamicin are the common causative drugs. In patients with concomitant infectious mononucleosis, the risk of developing an exanthematous eruption while being treated with an aminopenicillin (e.g.: ampicillin) increases from 3 to 7% to 60 to 100%.[26] Histopathology shows sparse perivascular infiltrate of lymphocytes with or without eosinophils.

The main differential diagnosis is viral exanthems. Viral exanthems are commonly accompanied by fever, lymphadenopathy and the rash usually starts on the face and later progresses to involve the trunk. Continuation of the drug may lead to erythroderma. The rash usually fades with desquamation or hyperpigmentation.

Fixed Drug Eruptions

Fixed drug eruptions (FDE) commonly present as eythematous or dusky red macules progressing to edematous plaques occurring anywhere on the body with or without constitutional symptoms (Fig. 4). Genitals, hands and feet are the favored sites. Local burning or stinging sensation may be present. It can develop from few minutes to few hours after the drug intake. Widespread and bullous lesions are known to occur when severe. A peculiar feature of this is the residual slate gray hyperpigmentation which on rechallenge become active with or without the development of new lesions.

Histopathology shows necrotic keratinocytes, superficial and deep dermal perivascular infiltrate of lymphocytes, eosinophils and occasional neutrophils. Melanophages when present give a clue to the diagnosis.

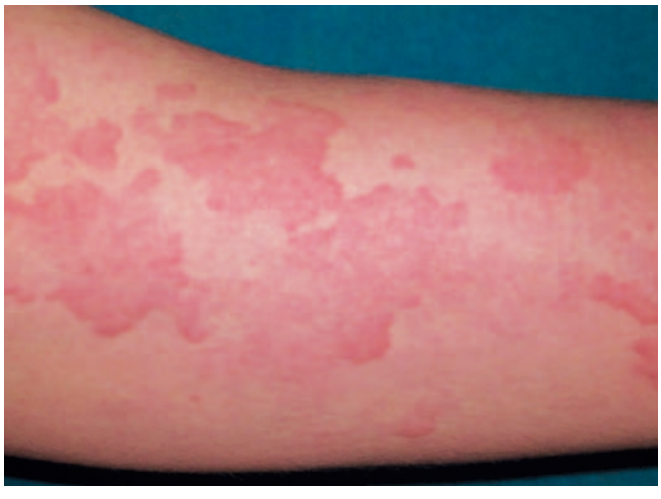

Fig. 1: Drug induced urticaria

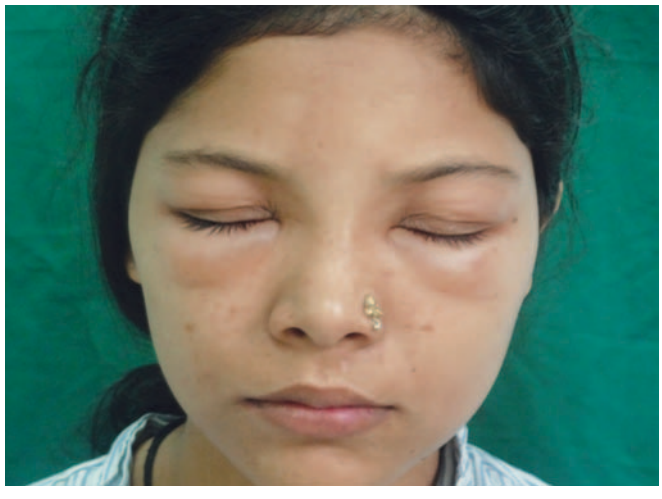

Fig. 2: Angioedema

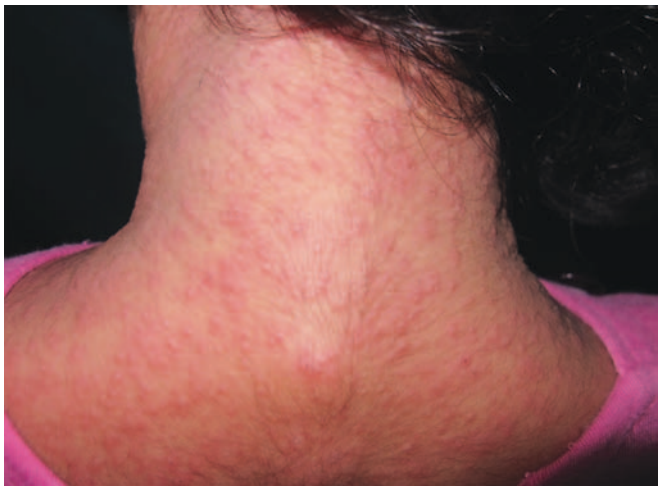

Fig. 3: Drug induced exanthema

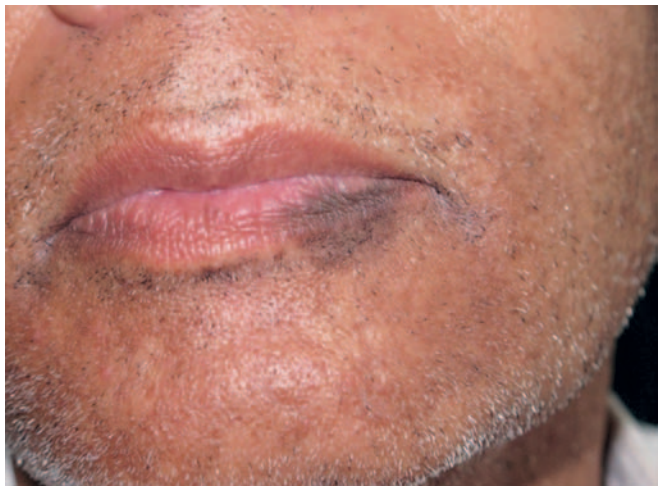

Fig. 4: Fixed drug eruptions

Sulphonamides, tetracyclines, barbiturates, carbamazepine, phenolphthalein and NSAIDs are the common culprit drugs.[27]

Drug Induced Lichenoid Eruptions

Though clinically resemble classical lichen planus with violaceous pruritic papules and plaques on the trunk and extremities, drug induced lesions are more eczematous and may be extensive (Fig. 5). There may also be sparing of mucous membranes.

Histologically lichenoid drug eruption may have focal parakeratosis, cytoid bodies in the stratum corneum and granulosum along with the presence of eosinophils and plasma cells in the inflammatory infiltrate and perivascular inflammatory infiltrate in the deep dermis apart from the classical features of lichen planus.

The drugs implicated are penicillamine, beta blockers, captopril, antimalarials, phenothiazines, NSAIDs, sulfonylureas and antitubercular drugs among the common ones.

Drug Induced Photosensitivity Reactions

It is defined as a reaction on the photoexposed areas often sparing upper eyelids, retroauricular and submental areas following drug intake (Fig. 6).

It can be divided into phototoxic and photoallergic reaction. The differences are listed in Table 2. Photoallergic reaction represent a T-cell mediated reaction in which ultraviolet light alters either the hapten or the avidity with which the hapten combines with the carrier protein to form a complete photoantigen.[28]

Drug Induced Vasculitis

Classically affecting small vessels, it presents clinically with palpable purpura commonly on the lower extremities. Other

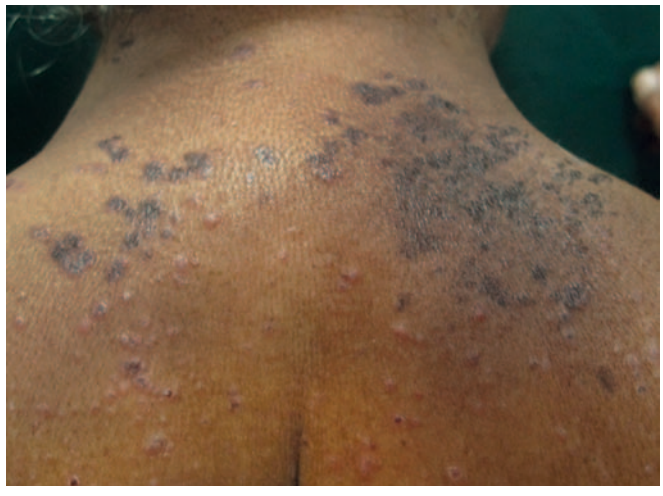

Fig. 5: Drug induced lichenoid eruption

manifestations include nodules, ulcers, urticarial lesions and hemorhagic bullae. Systemic involvement is common with involvement of liver, kidney, gut and central nervous system and can be life-threatening.[29]

Drugs that are associated with vasculitis include propylthiouracil, hydralazine, granulocyte-macrophage colony -stimulating factor, allopurinol, cefaclor, minocycline, penicillamine, phenytoin, isotretinoin and anti-TNF agents.[30]

Other causes of vasculitis have to be ruled out. Tissue eosinophilia and positive perinuclear staining ANCA against myeloperoxidase may point to the diagnosis.[31]

Withdrawal of the drug and systemic corticosteroids are the mainstay of treatment.

Drug Induced Pseudolymphoma

Named so because of its resemblance to lymphoma clinically presenting as red papules, plaques or nodules which may be solitary or multiple with or without lymphaedenopathy developing months to years after the administration of the

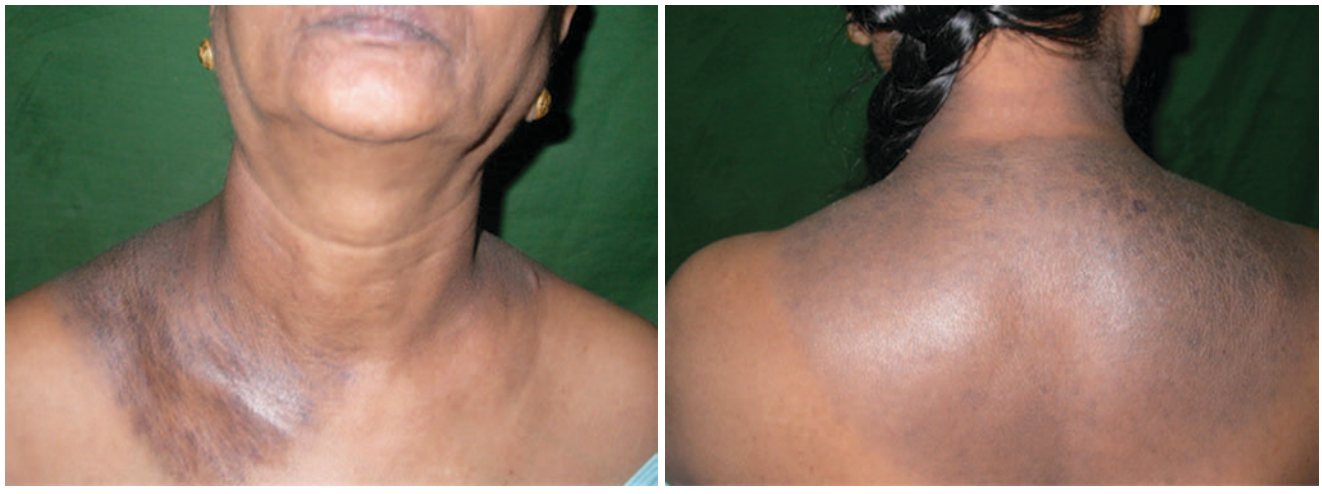

Fig. 6: Photoallergic reaction to thiazide diuretics

Table 2: Differences between phototoxic and photoallergic reaction

Phototoxic reaction	*Photoallergic reaction*
Predictable	Unpredictable
Occurs with the first exposure to a certain amount of the drug with the required intensity of sunlight	Occurs after a sensitization phase and is a type 4 hypersensitivity reaction
Clinical manifestations is an exaggerated sunburn (Fig. 6)	It is an allergic reaction which is eczematous and pruritic
Usually confined to the sunexposed area	Lesions can be seen beyond the sunexposed parts
Causative drugs are commonly tetracyclines, quinolones, amiodarone, psoralens, methotrexate, voriconazole and furosemide (frusemide), coal tar	Causative drugs are sulphonamides, thiazide diuretics, NSAIDs, phenothiazine, antimalarials, calcium channel blockers Topical photoallergens include topical anesthetic drugs, antihistamines, PABA containing sunscreens
Histopathology is that of a sunburn reaction	Histopathology is like an allergic contact dermatitis

drug in question. They can also have hepatosplenomegaly, fever and arthralgia.

The drugs commonly associated with the development of this condition include barbiturates, carbamazepine, hydantoin, ACE inhibitors and D-penicillamine.

Histopathological examination shows dense infiltrate of polyclonal lymphocytes in the dermis often indistinguishable from mycosis fungoides. Peripheral blood eosinophilia may aid in diagnosing the condition.

Complete recovery usually follows withdrawal of the drug.

Drug induced Acneiform Eruptions

Papulopustular acne like eruptions with same sites of involvement as acne but absent comedones is the hallmark of this condition (Fig. 7). Lesions are usually monomorphic Common drugs implicated in the causation are corticosteroids, iodides, bromides, oral contraceptives, isoniazid.[32] Epidermal growth factor receptor antagonists used in oncology are also responsible for acneiform eruptions. Folliculitis occurs in 43 to 85% of patients who take these drugs; this applies to all epidermal growth factor receptor antagonists.[33]

Withdrawal of the drug with antiacne treatment results in gradual disappearance of lesions.

Drug Induced Lupus

Drug induced lupus commonly presents with absent skin lesions, but there are other systemic features of lupus like fever, weight loss, arthralgia and respiratory manifestations. Renal involvement seems to be rarer compared to classical SLE. The common drugs associated with lupus are beta blockers, anticonvulsants, procainamide, hydralazine, lithium, isoniazid, minocycline.

Immunological abnormalities commonly present are positive ANA with homogenous pattern, antihistone antibodies and anti single stranded DNA antibodies.

A genetic basis has been described as demonstrated by HLA DR4 association in 73% of hydralazine induced lupus and 70% of patients with minocycline induced lupus.[34]

Acute Generalized Exanthematous Pustulosis (AGEP)

It is a peculiar kind of drug eruption with the following proposed diagnostic criteria:[35,36]

a. An acute pustular eruption

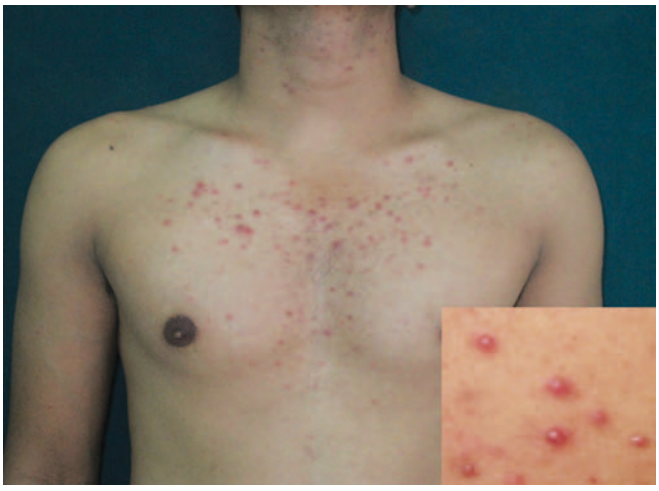

Fig. 7: Steroid induced acne

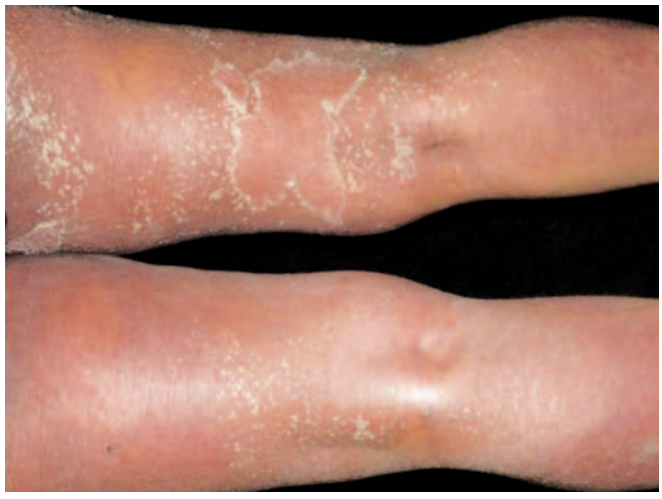

Fig. 8: Acute generalized exanthematous pustulosis (AGEP)

b. Fever of >38°C
c. Neutrophilia with or without mild eosinophilia
d. Subcorneal or intraepidermal pustules on skin biopsy
e. Spontaneous resolution in <15 days.

AGEP is usually due to penicillins or macrolides, especially ampicillin/amoxicillin and clavulanic acid, pristinamycin, quinolones, (hydroxy) chloroquine, anti-infective sulphonamides, terbinafine, diltiazem, carbamazepine and spiramycin, metronidazole.[37-41]

The pustules which are numerous, sterile and non follicular commonly appear with fever on the flexures, trunk and upper extremities appearing within a few hours of ingestion of the offending drug. Associated features may be fever, facial and hand edema, vesicles and EM like lesions (Fig. 8). Leukocytosis may also be noted.

Histopathological examination shows subcorneal and intraepidermal pustules, dermal edema and a perivascular lymphohistiocytic infiltrate.

The main differential diagnosis of a generalized pustular drug eruption is pustular psoriasis[42] which may be difficult to differentiate with the help of histopathological examination alone.

Exfoliative Dermatitis (Erythroderma)

It is defined as an inflammatory skin reaction involving more than 90% of the body surface area. Apart from other causes, it may also occur secondary to drug intake.

Clinically it presents as redness and exfoliation generalizing rapidly to involve extensive areas of the body. Patient has systemic manifestations like fever with chills, lymphaedenopathy and anorexia. The possible complications include hypoproteinemia, hypo or hyperthermia, fluid and electrolyte loss, high output cardiac failure and septicemia (Fig. 9).

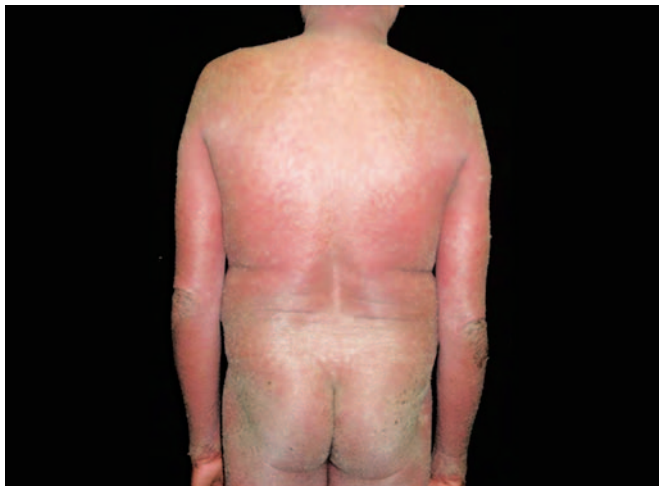

Fig. 9: Drug induced erythroderma

The most common causes of erythroderma is a pre existing skin disease. Common drugs implicated in the causation are penicillins, sulphonamides, NSAIDs, chloroquine, phenytoin, isoniazid among others.

Skin biopsy often helps in differentiating drug induced from other causes of erythroderma showing the classical features of the pre-existent skin disease. Drug induced erythroderma may show nonspecific subacute or chronic spogiotic dermatitis.

Erythema Multiforme, Toxic Epidermal Necrolysis (TEN) and Steven Johnson Syndrome (SJS)

Erythema multiforme (EM) is caused mainly due to infections the commonest being herpes virus. Drugs which are implicated in the causation of both EM and SJS are beta lactam antibiotics, barbiturates, carbamazepine, sulphonamides, lamotrigine, leflunamide, macrolides, NSAIDs, phenothiazines, etc.

With a prodrome of fever and flu-like symptoms it presents with classical target lesions comprising of three zones of central purpura or dusky red erythema, a middle zone of edema and an outer zone of erythema mainly distributed on the extremities more than the trunk (Fig. 10). Sometimes only two zones can be appreciated. As the name suggests it may also have different morphology of lesions including papules and vesicles.

In a typical target lesion, the histological changes include vacuolar degeneration of the lower epidermis and individual necrotic keratinocytes with perivascular lymphohistiocytic infiltrate and dermal edema. Epidermal changes may be very subtle to severe necrosis in bullous lesions.

There may also be involvement of mucous membranes and when extensive, the condition may be named Erythema multiforme major or Steven Johnson syndrome (SJS).

Steven Johnson syndrome is commonly associated with fever, myalgia, arthralgia with more extensive mucosal (oral, genital, conjunctival, nasal cavity, urethral) and facial lesions (Fig. 11). Involvement of trunk also is present with target like lesions. Skin involvement is limited to 10% of the body surface area. Though this syndrome is distinct from toxic epidermal necrolysis (TEN), there is an overlap in a considerable number of patients when skin involvement ranges between 10 and 30% of the total body surface area. When it exceeds 30% it is termed TEN (Fig. 12).

Steven Johnson syndrome and TEN are mainly the result of drugs in contrast to EM. The common culprit drugs include sulfonamides, penicillins, cephalosporins, isoniazid, NSAIDs, anticonvulsants, antiretroviral drugs like abacavir and nevirapine, antifungals like terbinafine and griseofulvin.

Toxic epidermal necrolysis is a medical emergency with a high mortality rate with full thickness skin necrosis along with severe involvement of mucous membranes (oropharynx, eyes and genitals). The estimated incidence ranges from 0.4 to 1.2 per million population per year.[43]

Patients with HIV infection, systemic lupus erythematosus and bone marrow transplant recipients seem to be predisposed to this disorder.[44,45]

Toxic epidermal necrolysis presents with a prodrome of fever, nausea, vomiting, sore throat, chest pain, arthralgia, myalgia and burning sensation in the skin followed by dusky red ill defined erythema, areas of target like lesions progressing to form denuded areas. The progression may take few hours to 3 to 4 days. Nikolsky sign is positive. The simultaneous involvement of multiple mucosae like conjunctivae, nasopharynx, esophagus and anus increases the morbidity and mortality.

The acute complications of this condition include dehydration, electrolyte loss and septicemia along with or without multisystem involvement in the form of pneumonia, nephritis, hepatic and myocardial damage. The chronic complications of SJS and TEN include fibrosis and strictures.

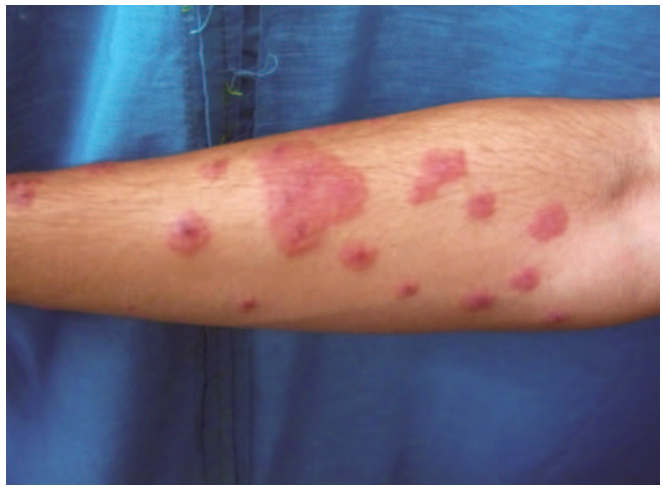

Fig. 10: Erythema multiforme

Fig. 11: Steven Johnson syndrome

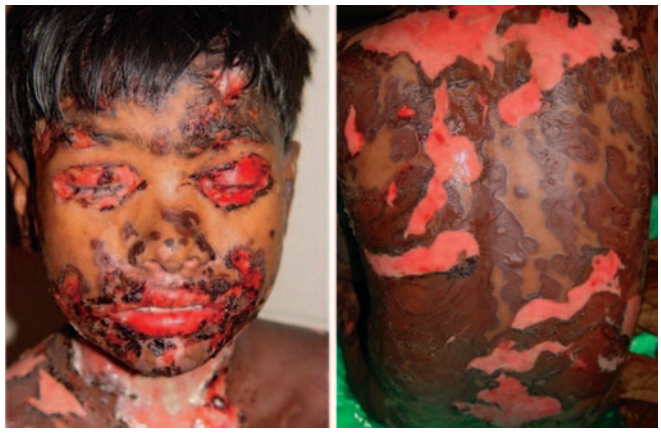

Fig. 12: Toxic epidermal necrolysis

Identification of the causative drug is often difficult. In general, most drugs causing TEN have been given in the previous 1 to 3 weeks. Drugs started less than 7 days or more than 2 months before the onset of the reaction are unlikely to be responsible.[46]

Histopathological examination of skin sections show epidermal spongiosis and exocytosis with perivascular mononuclear infiltrate in early lesions to complete epidermal atrophy in a case of established TEN.

The pathophysiology of these reactions is not fully understood yet. Various theories have implicated the involvement of immunological mechanisms in particular those mediated by memory cytotoxic T cells.[47] Although it was originally classified as a type IV delayed hypersensitivity reaction, it now appears that the immunological mechanisms governing the SJS reaction are initiated by the Fas antigen, a cell surface molecule that can mediate apoptosis[48,49] leading to widespread keratinocyte apoptosis and subsequent epidermal necrosis. Perforin released from natural killer T cells is also believed to initiate keratinolysis.[50]

Clinicians use the SCORTEN score (TEN specific severity of illness score)[51] (Table 3) to determine the severity of the illness where important indicators like heart rate, renal function and age are taken into account.

Management requires multidisciplinary skilled approach like in case of burns with a specialist team. Maintaining the fluid and electrolyte balance, nutritional support, close monitoring to identify and treat sepsis, taking care of the denuded areas are to be given utmost importance. The role of systemic corticosteroids in the management has always been controversial. Intravenous Ig has been shown to be beneficial.[44,52]

Bullous Drug Eruptions

Blistering drug eruptions consist of drug-induced pemphigus and pemphigoid, linear IgA bullous dermatosis and pseudoporphyria cutanea tarda.[53,54]

Some causes of blistering drug eruptions are given in Table 4.[55]

In pseudoporphyria, porphyria like bullous eruptions are seen on the extremities following the causative drug intake. These patients do not have derangement in porphyrin metabolism unlike in patients with porphyria cutanea tarda.

Table 3: SCORTEN score[51]

Parameter	1 point awarded for each parameter; SCORTEN derived by totalling scores
Age >40 years	
Presence of a malignancy	
Epidermal detachment >30%	
Heart rate >120/min	
Bicarbonate >20 mmol/l	
Urea >10 mmol/l	
Glycemia >14 mmol/l	
SCORTEN	Probability of death (%)
0-1	3
2	12
3	35
4	58
More than 5	90

In drug induced bullous pemphigoid, tense bullae similar to bullous pemphigoid in a younger age group with usually absent anti BMZ antibodies with a history of a known drug causing BP like eruptions help in pinpointing the diagnosis (Fig. 13).

The commonest type of presentation of drug induced pemphigus is like pemphigus foliaceus and erythematosus with superficial blisters. Most patients have circulating autoantibodies with the same antigenic specificities as in other forms of pemphigus.[56,57] Patients of pemphigus with drugs containing thiol group have a good prognosis on withdrawal of the drug compared to those with nonthiol group induced pemphigus.

Histopathological examination cannot distinguish drug induced from nondrug induced pemphigus.

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

In its complete form, DRESS also known as drug induced hypersensitivity syndrome (DIHS) is typically characterized by a severe skin eruption, lymphadenopathy, fever, hepatitis,

Table 4: Drug induced bullous diseases[55]

Type of eruption	*Causative drugs*
Pemphigus	Captopril, cephalosporins, penicillin, penicillamine, piroxicam, gold/ sodium aurothiomalate
Bullous pemphigoid	Furosemide, ACE inhibitors (captopril, enalapril), penicillin, penicillamine, chloroquine, sulfasalazine
IgA bullous dermatosis	Captopril, ceftriaxone, co-trimoxazole, furosemide, G-CSF, interleukin-2, lithium, NSAIDs, penicillin, rifampicin, vancomycin
Pseudoporphyria cutanea tarda	NSAIDs, tetracycline, thiazides, furosemide

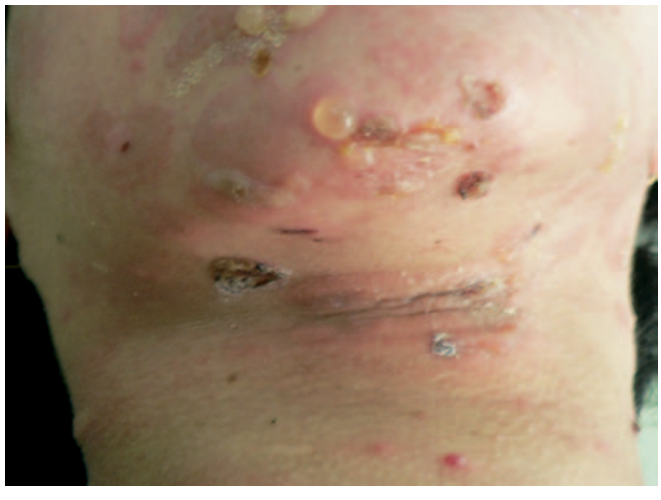

Fig. 13: Drug induced bullous pemphigoid secondary to carbamazepine

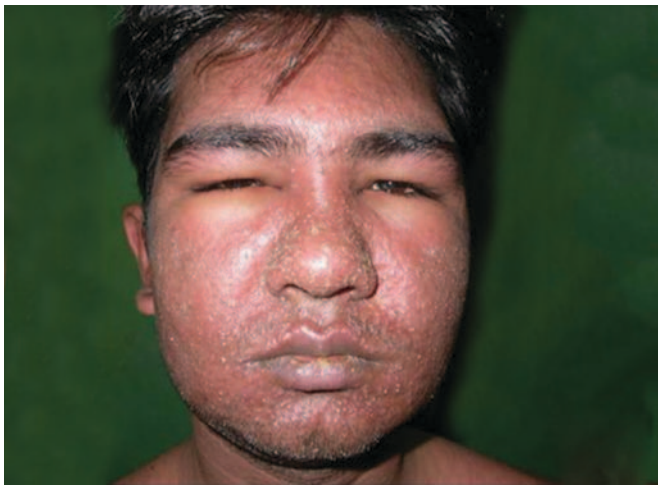

Fig. 14: Drug hypersensitivity with Dapsone

arthralgias, pulmonary infiltrates, interstitial nephritis and hematological abnormalities.[7,9,58]

The incidence of DRESS is estimated at between 1 in 1000 and 1 in 10 000 exposures to antiepileptic drugs.[59] The other drugs which my cause this pattern of reaction include sulphonamides, minocycline, dapsone, carbamazepine and allopurinol.

The pathomechanism of the condition is not well understood and seems to be multifactorial. Clinically a generalized erythematous exathematous rash appears 2 to 6 weeks after the drug intake and is usually associated with fever. Infiltrated papules coalescing to form erythroderma along with vesicles and pustules may also occur. Edema of the face is characteristic (Fig. 14). Lymphaedenopathy, interstitial nephritis and hepatitis are the common associations. Patients with DRESS may develop a worsening of the clinical picture once the initial reaction starts subsiding. This is due to reactivation of members of the herpes virus family, HHV6 and HHV7 in particular, but EBV and/or CMV as well.[60,61] Eosinophilia which is an essential criteria is often associated with atypical lymphocytosis. Liver function tests may be deranged in a considerable number of individuals.

RegiSCAR group has given the diagnostic criteria for the diagnosis[62] (Table 5).

Early withdrawal of the drug is mandatory. Systemic corticosteroids are given when there is a visceral involvement.

Table 5: Regi-SCAR group criteria for diagnosis of DRESS[63]

Features	*No*	*Yes*	*Unknown*
Fever >35.50°C	–1	0	–1
Enlarged lymph glands (>2 sites, >1 cm)	0	1	0
Atypical lymphocytes	0	1	0
Eosinophilia	0	–	0
700-1499 or 10-19.9%	–	1	–
>1500 or >20	–	2	–
Skin rash	0	–	0
Extent >50%	0	1	0
At least 2 of purpura, edema, purpura, scaling	–1	1	0
Biopsy suggesting DRESS	–1	0	0
Internal organ involvement	0	–	0
One	–	1	–
2 or more	–	2	–
Resolution in more than 15 days	–1	0	–1
At least 3 biological inv done and negative to exclude alternative diagnosis	0	1	0
Final score:<2 = no case, 2-3 = possible case, 4-5 = probable case,>5 = definite case			

SEVERE CUTANEOUS ADVERSE DRUG REACTIONS (SCAR)

Certain life-threatening drug reactions like SJS, TEN, drug hypersensitivity reactions (DHR), DRESS and AGEP are classified as SCAR as they are: (a) severe, (b) unpredictable and (c) drug induced.[63]

MANAGEMENT OF CUTANEOUS DRUG REACTIONS

- Withdrawal of the offending drug is the single most important most effective measure to be done immediately.
- Notification of the reaction to the concerned regulatory authority is a mandatory measure.
- Substitute of the essential drug of a different group to be introduced with careful observation. Take utmost care not to give a drug with a potential to cross react with the offending drug.
- Before considering on intradermal, patch or prick tests, the risk assessment has to be done as it may prove fatal as the patient is re-exposed to the drug. They can develop a generalized rash or even anaphylaxis. At the same time it is necessary to find out the culprit drug out of the many and also to find out the safe alternative which can be given to the given condition. Appropriate controls are necessary to avoid false positive results.
- Blood drug levels may be measured when over dosage is suspected or when the patient is comatose to arrive at the diagnosis.
- The knowledge of the known side effects of the drug helps in the identification of the drug wherever possible.
- Most of the reactions subside with withdrawal of the causative drug and symptomatic treatment with antihistaminic (H1 receptor blocker) drugs and topical calamine lotion. Topical corticosteroids may sometimes be necessary.
- Subcutaneous injection of adrenaline and systemic corticosteroids in case of severe angioedema and anaphylaxis.
- In case of photosensitivity reactions, additional sunprotection, use of broad spectrum sunscreens, topical corticosteroids and systemic antipruritic drugs are given.

- Severe drug reactions require hospital admission.
- In severe reactions systemic corticosteroids may be life saving.

CONCLUSION

Identification and management of cutaneous drug reactions need a great amount of skill. The enormous number of new drugs released into the market along with multiple drugs taken by the patient for various ailments requires the clinician to have a thorough knowledge regarding the possible side effects of the drug and the cross reactions which may occur.

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10.5005/jp-journals-10036-1015

CASE REPORT

The Effect of Parental Communication on the Belief System of Teenage Girls: A Case Study

Swati Shiradkar

ABSTRACT

Healthy development during adolescent age is very important. The major issue is experimentation to understand the base of thinking direction of this age group. The questions were given to participants in a workshop. The answers analyzed. Total 48 female students between age group 14 and 16 responded. Fifty percent wanted economical independence but 30% have it. Majority of those who wanted this independence felt that friendship between boys and girls is necessary and they found communication with parents difficult, shared feelings with friends. Improvement in communication between children and parents will help in solving issues about irresponsible behavior of the children.

Keywords: Economical independence, Behavior of teenagers, Communication.

How to cite this article: Shiradkar S. The Effect of Parental Communication on the Belief System of Teenage Girls: A Case Study. MGM J Med Sci 2014;1(2):95-98.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

Since past decade awareness about adolescent health and psychological issues has increased worldwide. Studies show that most of the health related issues observed in adults have roots in their adolescent age. Healthy development during adolescent age contributes toward good mental health which helps to prevent psychological problems.[1,2] Communication between parents and teenage children is the crucial factor that shapes child's life toward adulthood. However, various changes that occur during adolescence interfere with effective communication between parents and children.[3]

This paper presents the research based on the data that was collected during a workshop aimed at teenage girls between ages of 14 and 16 from various schools in Aurangabad, Maharashtra. A questionnaire was developed to aid in the collection of necessary data. The data obtained was statistically analyzed in order to understand trends in the parent-child interactions. This would help to identify important issues to focus on during a parenting workshop that was conducted at MGM Medical College at later point of time. This paper presents a discussion on trends observed in parent-teenager interactions and how it affects the behavior of teenagers.

Professor and Head

Department of Obstetrics and Gynecology, MGM Medical College, Aurangabad, Maharashtra, India

Corresponding Author: Swati Shiradkar, Professor and Head Department of Obstetrics and Gynecology, MGM Medical College, Aurangabad, Maharashtra, India, e-mail: swati.shiradkar@gmail.com

RESEARCH METHODS

A workshop for teenage female students from different schools was conducted at Aurangabad, Maharashtra. At the end of the workshop, students were asked to fill out a survey form. The survey included questions about the opinion of subjects about issues, such as pocket money, friendship between girls and boys, type of family they desire (nuclear or joint), whether their mother should be a housewife or a working woman, etc. The questions were also aimed at getting information about the subject's communication between family members and friends.

Forty-eight subjects from different schools that attended a workshop were selected for statistical analysis. In this way, random sampling of population was achieved. The data was analyzed using a statistical software. The purpose of the study and procedure of survey was explained to subjects. So, consent of each student was sought before they became part of this study.

Background of the Selected Student Population

All the female students selected for this research came from well educated families. These students were in 8th and 9th standard (ages 14-16). Participant students belonged to middle or upper middle class on socioeconomic scale.

STATISTICAL DATA ANALYSIS AND DISCUSSION

Data obtained from 48 subjects was used as an input to determine trends between different variables. A mosaic plot is a powerful graphical tool which allows to examine relationship among two or more variables. Mosaic plot is basically a square with length one. The square is divided horizontally into bars whose widths are proportional to probabilities of first categorical variable. Then each bar is

vertically divided proportional to probabilities of second categorical variable.[4]

The Figure 1 shows a mosaic plot between variables 'should pocket money be given' and 'do you get pocket money'. The subjects who said 'yes' to the former question are represented by the blue area while those who answered 'no' are represented by the red area. It can be seen that the opinion about if the pocket money should be given is exactly 50% divided. However, only about 30% of the subjects actually received pocket money. Majority of the subjects who received pocket money agreed with the idea of pocket money. On the other hand, majority of subjects who did not like the idea of pocket money, did not get it. This indicates that the parental decision to offer pocket money to their teenagers is capable of shaping their opinion about the idea of pocket money. However, there are some external factors like interaction with friends that are seen to influence the subjects opinion about pocket money and therefore we have found non-negligible number of teenagers who agreed to the idea of pocket money eventhough they actually did not get it.

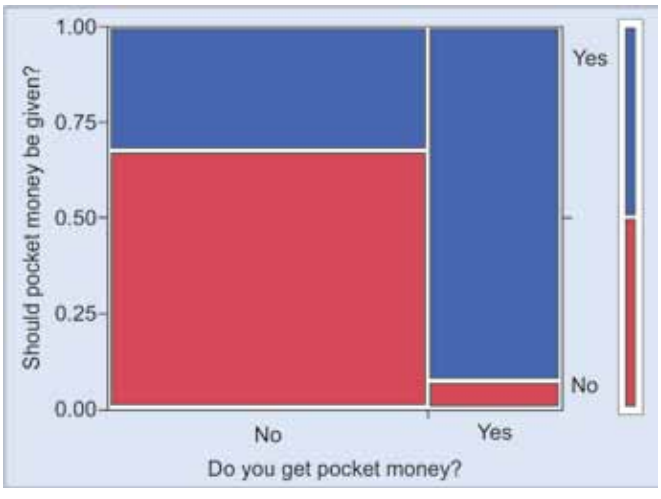

Fig. 1: Mosaic plot of variables 'should pocket money be given' *vs* 'do you get pocket money'

In order to further understand how various factors in parent-teenager interaction affect the teenager's opinions, we have used the question 'is friendship between girls and boys necessary' as a pivotal variable. The two adjacent mosaic plots in Figure 2 show the distribution of variables 'should pocket money be given' and 'do you get pocket money' *vs* 'is friendship between girls and boys necessary'. It is seen that 19% subjects believed that girl-boy friendship is not necessary, 25% were unsure and 56% answered yes. The horizontal axes of the mosaic plot are accordingly scaled. Interestingly, it is seen that as one moves from answers 'no' to 'unsure' to 'yes' to the girl-boy friendship question, the fraction of subjects who agreed to the idea of pocket money increases as 22.2, 41.7 and 63% respectively. Also, 89% of the subjects who felt it was not necessary to have friendship between girls and boys, actually did not get the pocket money. This indicates that as the idea of having friendship with people of opposite sex becomes more and more acceptable to the teenagers, they are more likely to have a positive opinion about pocket money (feeling the need to be in control of their finances).

Figure 3 shows the mosaic plot between the variable 'do you have free communication with parents' *vs* 'is friendship between girls and boys necessary'. It is seen that 67% of the subjects had answered 'yes' to the question about free communication with parents while 14% were unsure, and 19% had actually said 'no'. Interestingly, 89% of the subjects who did not feel that the friendship between girls and boys is necessary, had free communication with their parents. Additionally, no subject who had answered 'no' to the necessity of girl-boy friendship had admitted to having

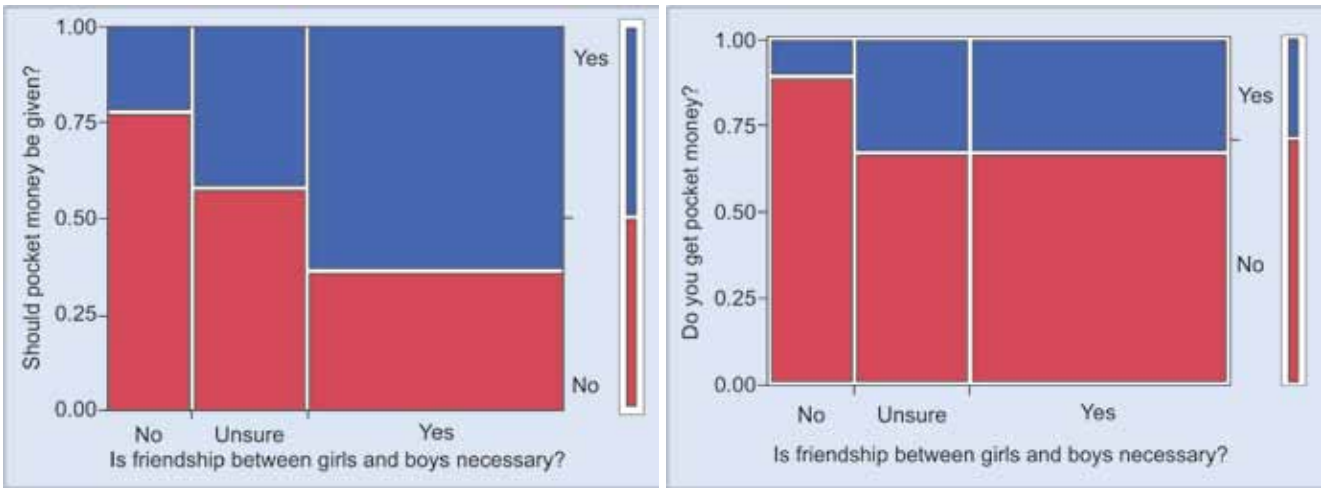

Fig. 2: Mosaic plot of variable 'should pocket money be given' *vs* 'is friendship between girls and boys necessary (left)'

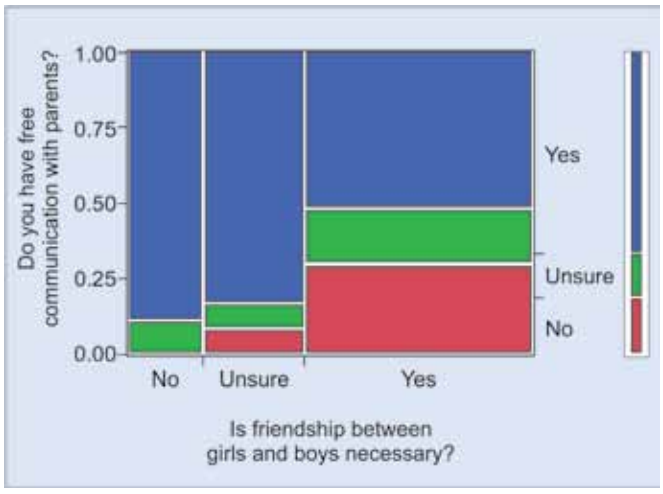

Fig. 3: Mosaic plot of variable 'is friendship between girls and boys necessary?' *vs* 'do you have free communication with parents?'

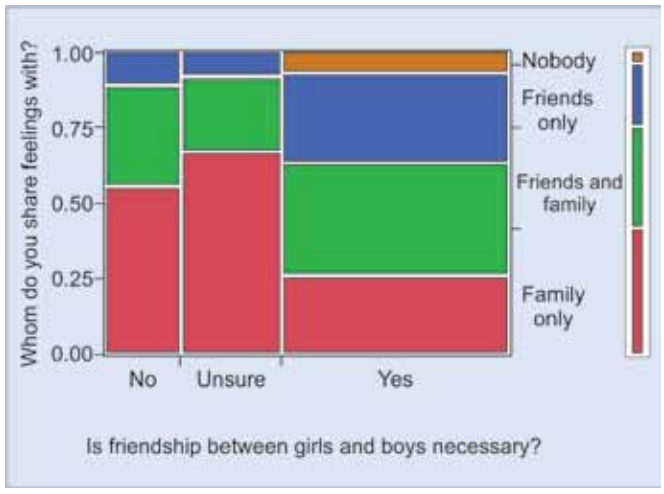

Fig. 4: Mosaic plot of variable 'whom do you share your feelings with? *vs* 'is friendship between girls and boys necessary'?

poor communication with parents. This clearly indicates that parents are playing a major role in shaping the teenagers beliefs about friendship with people of opposite sex. And especially when the teenager thinks that it is 'not necessary' to have a friendship with people of opposite sex, this opinion is largely formed from their interactions with their parents. However, about 51% of the subjects who answered yes to the girl-boy friendship question also admitted to having free communication with parents. This indicates that not all parents are discouraging their teenagers from developing friendship with the people of opposite sex.

Figure 4 shows the mosaic plot between the variable 'Whom do you share your feelings with' and 'is friendship between girls and boys necessary'. It is seen that 41.7, 33.3, 20.8 and 4.2% subjects admitted to share their feelings with family members only, friends and family members, friends only and nobody, respectively. It is seen that as the subjects tend to share more and more of their feelings with friends, they tend to become open to the idea of having friendship between girls and boys. It should be noted that 4.2% of the subjects denied sharing feelings with anybody, but answered yes to the idea of having friendship between girls and boys. Also, as the subjects tend to share their feelings with family members only, their tendency to did not like the idea of girl-boy friendship or be unsure about it increases. This indicates that probably majority of the parents of these teenagers are not encouraging friendship between people of opposite sexes.

Other Findings

This section discusses some of the qualitative findings that were not addressed in the statistical analysis section. When asked if you would like your mother to be a housewife or working, 48% answered housewife, while 35% answered working, and the rest were unsure or answered both. Majority of the subjects who had answered housewife for their mother's occupation gave a reason that having mother at home is helpful for them for emotional support and studies, also it creates less tensions at home. The subjects that answered they would like their mother to be a working woman, said so, because they feel proud, it would make her confident and explore new avenues.

When asked about what kind of family they would like, 50% answered joint family, 33% answered nuclear while 17% were unsure. The subjects that answered joint family pointed out the benefits of joint family, such as guidance from elders and joy of being together. The subjects that chose nuclear family was because of comfort, privacy and freedom.

CONCLUSION AND FUTURE WORK

This study helped to get an overview of how communication between parents and adolescents shapes thought process of adolescents. It was found that the opinion of teenagers about issues, such as friendship with opposite sex, pocket money, etc. is strongly determined by their interactions with parents. However, in order to understand trends in greater detail, the relevance and clarity of survey instrument (questionnaire) needs to be further improved.

ACKNOWLEDGMENTS

The author is thankful for the participants of this survey, MGM Medical College for the support and Sayli Bhide, University of Central Florida, USA, for the statistical analysis and help in preparation of this manuscript.

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10.5005/jp-journals-10036-1016

CASE REPORT

Plexiform Neurofibroma from Palmaris Longus with Carpal Tunnel Syndrome

[1]Ashok M Ghodke, [2]Alfven E Vieira, [3]Rohit V Delat, [4]Apoorv Dua

ABSTRACT

Plexiform neurofibromas (NF) involving the palmaris longus tendon are rare diseases difficult to diagnose when the classical manifestations, e.g. skin pigmentation, sub cutaneous nodules, lisch nodules, family history, etc are absent. We report a case of 26 years male with plexiform NF of palmaris longus tendon which is a relatively rare site. Plexiform NF commonly involve the cranial nerves.

Keywords: Plexiform neurofibroma (NF), Palmaris longus tendon, Median nerve.

How to cite this article: Ghodke AM, Vieira AE, Delat RV, Dua A. Plexiform Neurofibroma from Palmaris Longus with Carpal Tunnel Syndrome. MGM J Med Sci 2014;1(2):99-100.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Plexiform neurofibroma (NF) is a benign tumor arising from axon, schwann cell or fibroblast and eventually leads to enlargement of involved nerve trunk.[1] Neurofibromatosis is a group of autosomal dominantly inherited disorder arising from neural tissue. There are two types. Neurofibroma-1, being the most common type (90% of the cases) and affects 1 in 3,000 newborns with 50% mutation and almost 100% penetrance.[1,2] The genetic abnormality of NFI is mapped to chromosome 17q11.2. Neurofibroma-2 is much less common and affects 1 in 40,000 individual, the genetic mutation of NF-2 is mapped to chromosome 22[1] in which bilateral acoustic neuromas are present leading to hearing loss starting as early as the teen age years.[1,2]

Plexiform NF is common over the branches of trigeminal and cervical nerves over the face and relatively less common in extremities.[2,3] Some authors have reported an incidence of 0.8% for NF in the hands and from 10 to 15% for NF-1.[3] We are reporting a rare case of plexiform NF arising from nerve branches supplying palmaris longus tendon.

[1,3]Assistant Professor, [2]Professor and Head, [4]Resident

[1-4]Department of Orthopedics, MGM Medical College and Hospital, Navi Mumbai, Maharashtra, India

Corresponding Author: Ashok M Ghodke, Assistant Professor Department of Orthopedics, MGM Medical College and Hospital Sector-1, Kamothe, Navi Mumbai-410209, Maharashtra, India Phone: +91-9820415223, e-mail: ghodke.ashok@gmail.com

CASE REPORT

A 26-year-old man came to our institute with chief complaint of tingling sensation and numbness in left index, middle and ring finger since 1 year. It was associated with a painless swelling (4 × 3 cm) over volar aspect of wrist just proximal to proximal wrist crease. On examination, there was a 1×1 cm size swelling, smooth, well defined, firm, and mobile in direction of tendon, with feel of bag of worm. No skin pigmentation, nodules, iris nodule or hearing problem were noted. Family history was not significant.

X-ray was normal. Electromyogram (EMG) and nerve conduction velocity (NCV) showed median nerve compression at the site of scar mark. Intraoperatively there was a swelling on palmaris longus tendon measuring 5 × 3 cm compressing the median nerve. The swelling was resected and sent for histopathological examination (Fig. 3). Postoperatively median nerve function was normal. And symptoms reduced after surgery. Histopatholgy report shows a well circumscribed tumor compromising of both the neural and fibrous tissue. The individual neural cells are elongated with oval nuclei having eosinophillicfibrillary cytoplasm suggestive of plexiform NF.

DISCUSSION

Neurofibromatosis type I (NFI) was first described by Frederick von Recklinghausen in 1882 and for that reason has also been known as von Recklinghausen's neurofibromatosis.[1] The diagnosis of NF-1 is made on the basis of a group of clinical manifestations following the established NIH criteria proposed in 1988 (11). It includes cutaneous neurofibromas, café-au-lait spots (five or more of 1.5 cm size and larger in adults and 0.5 cm or larger in puberty and under), axillary freckling (Crowe's sign) and Lisch nodules among many others. Café au late spots are the first manifestation present in 90% of patients; 50% of patients develops lesions during their first year of life. Cutaneous nodules also are common manifestation is present in 40% of patients.[2] The tumor arising from neural element is not confined to skin and subcutaneous tissue but it also involves some viscera. Plexiform NF can be of two types, nodular and diffuse. Diffuse type is also known as elephantiasis neurofibromatosa. The patient which we have described is a case of nodular plexiform NF. He developed swelling in adulthood and presented to us with the symptoms

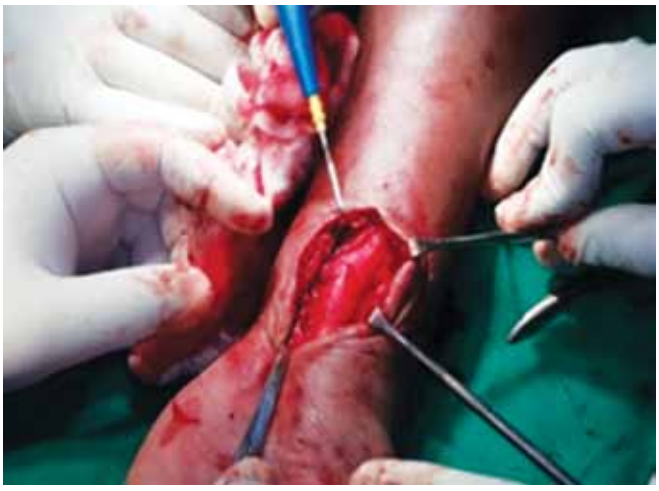

Fig. 1: Intraoperative picture showing swelling from palmaris longus tendon

Fig. 2: Swelling with palmaris longus tendon at its ends

resembling carpel tunnel syndrome. NCV confirmed the diagnosis of median nerve compression.

Although NF is a benign condition, it can undergo malignant transformation into a malignant peripheral nerve sheath tumor.[4-6] In some reports the incident rate has been up to 2 to 5%.[4] Only two forms of NF, plexiform and localized intraneural NF, are significant precursors of malignant peripheral nerve sheath tumors.[5]

The management of NF is not well-defined being a genetic etiology its management is aimed at mostly controlling symptoms. Excision of the tumor is the only available therapy. And to completely excise tumor from nerve there is possibility of partial or complete loss of function. According to Seddon, tumor resection is not necessary, unless the tumor causes pain, shows exuberant growth, or impairs function. Surgery was indicated, since patient was having symptoms of median nerve compression.[7] Swelling was localized to tendon of palmaris longus and was not from median nerve so complete removal was possible as we removed it with tendon. Excised swelling and tendon were resected successfully and the swelling was sent for histopathological reporting. Swelling was from nerve to palmaris longus branch of median nerve.

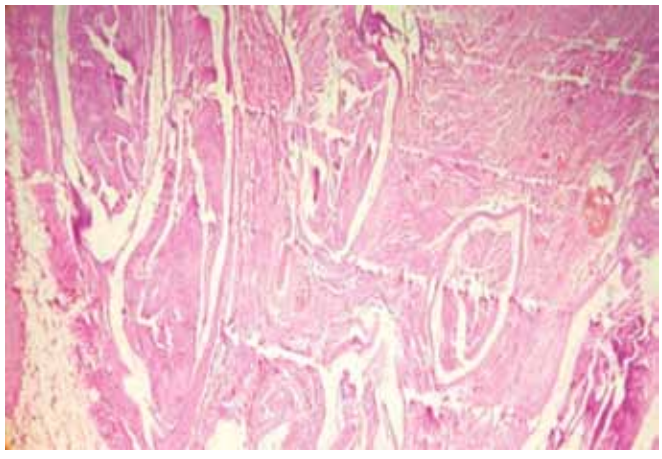

Fig. 3: Histopathological slide showing individual neural cells are elongated with oval nuclei having eosinophilic fibrillary cytoplasm suggestive of plexiform NF

CONCLUSION

Diagnosis of plexiform NF is difficult without associated lesions like café-au-late spot, irish nodule, axillary freckling, biopsy is must. As such no treatment is available but surgery is indicated when it causes functional impairment.

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10.5005/jp-journals-10036-1017

CASE REPORT

Long-term Survival in Tricuspid Atresia after Palliative Surgery

[1]Babita Ghodke, [2]Sanjeev Kumar Kalkekar, [3]Manish Radke

ABSTRACT

Here we report a rare case of tricuspid atresia. A 46 years old male treated palliatively by pulmonary artery banding. Patient is still surviving and is almost asymptomatic with limited exertion for so many years in spite of chronic hypoxia.

Keywords: Tricuspid atresia, Pulmonary artery, Hypoxia.

How to cite this article: Ghodke B, Kalkekar SK, Radke M. Long-term Survival in Tricuspid Atresia after Palliative Surgery. MGM J Med Sci 2014;1(2):101-104.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Tricuspid atresia (Figs 1A and B) is a type of congenital heart disease in which the tricuspid heart valve is missing or abnormally developed. It was first described in 1817. Frequency is equal in males and females.

The defect blocks blood flow from the right atrium to the ventricle. Incidence is 0.06 per 1000 live births with prevalence in clinical series of congenital heart disease of 1 to 2.4%.[1]

This defect is contracted during prenatal development, when the heart does not finish developing. In usual variety, there is agenesis of morphologic tricuspid valve so that no communication exists between morphologic right atrium and ventricle. An atrial septal defect (ASD) must be present to maintain blood flow. Systemic venous blood is received by the anatomic right atrium and passes through an interatrial communication to converge with pulmonary venous blood in the morphologic left ventricle.

Thus, the physiologic consequences of tricuspid atresia are:

- Obligatory right to left shunt at atrial level.
- The left atrium receives the entire systemic venous return via interatrial communication and receives the pulmonary venous blood directly.
- Mixture flows directly into the left ventricle.
- If the great vessels are normally related to pulmonary arterial flow is usually reduced, because a restrictive VSD constitutes a zone of subpulmonic stenosis. Left ventricular volume overload is curtailed but at the cost of cyanosis.
- This anatomic condition accounts for about 90% of cases. Approximately, 6% of infants born with tricuspid atresia are premature. The lifespan is shortest less than 6 months. One patient lived 21 years.

In tricuspid atresia with normally related great arteries presence of VSD is desirable when pulmonary blood flow is appropriately regulated but this balance is exceptional rarely favorable balance is achieved permitting survival from 2nd to 5th decade. Excessive pulmonary arterial flow results in volume overload of left ventricle and CCF. Death in these patients is due to Hypoxia and CCF.

Tricuspid atresia is the third most common cyanotic congenital cardiac lesion, with a mortality rate of 90% before the age of 10 years.[2] The Fontan operation is the usual goal of therapy for children with tricuspid atresia. According to one retrospective study, 204 patients (86%) were judged suitable for a future Fontan procedure at presentation. However, 99 (48%) of these are known to have died before a Fontan operation or became unsuitable for such surgery during follow-up, mostly because of death after palliative surgery (23 patients, 11%), sudden death (18 patients, 9%), and new adverse features (32 patients, 16%), such as sub aortic stenosis, pulmonary arterial distortion and ventricular dysfunction.[3]

CASE REPORT

A 46 years old male patient (Fig. 2) was admitted in MGM Hospital, Kamothe and CBD Belapur, Navi Mumbai, Maharashtra, India for plasmodium vivax Malaria. Patient was diagnosed to have congenital heart disease in early childhood which was investigated at John Hapkin Hospital in United States. While performing cardiac catheterization in 1968, it was confirmed that the patient was suffering from tricuspid atresia, therefore, he was subjected to pulmonary artery banding. Later on, the patient was re-evaluated at Southern Railway Hospital, Perambur, Tamil Nadu, India, at

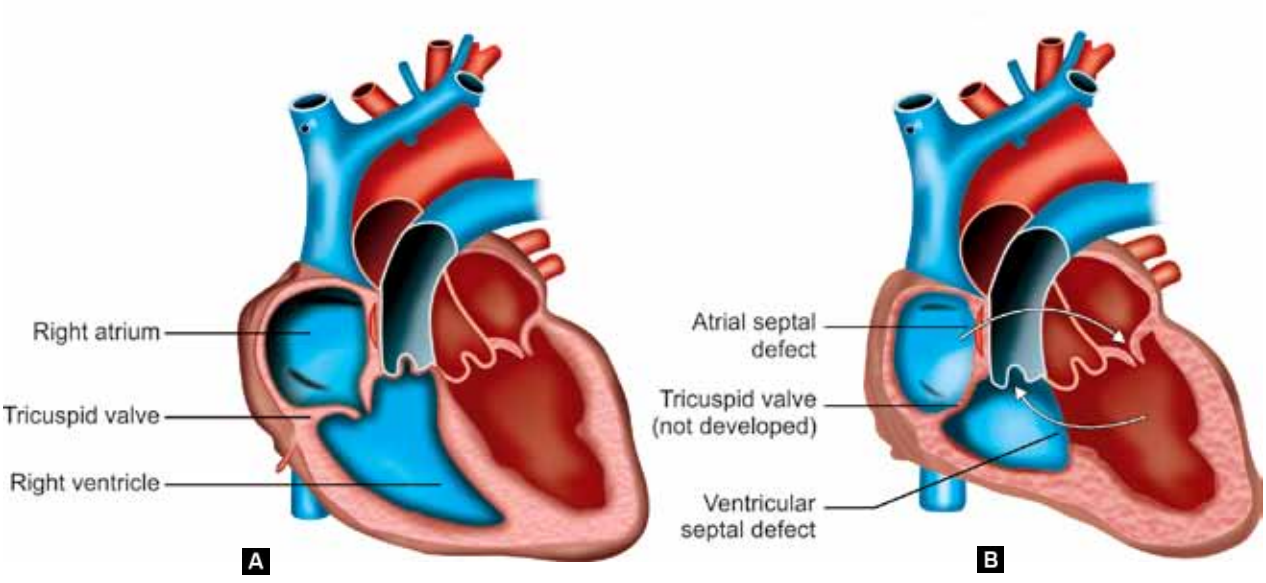
[1]Associate Professor, [2]Assistant Professor, [3]Physician

[1]Department of Medicine, MGM Hospital, Navi Mumbai Maharashtra, India

[2]Department of Cardiology, MGM Hospital, Navi Mumbai Maharashtra, India

[3]Intensive Care Unit ((ICU), MGM Hospital, Navi Mumbai Maharashtra, India

Corresponding Author: Babita Ghodke, Associate Professor Department of Medicine, MGM Hospital, Kamothe and CBD Belapur, Navi Mumbai, Maharashtra, India, e-mail: ghodke.babita@gmail.com



Figs 1A and B: (A) Normal heart and (B) Tricuspid atresia (*Courtesy*: Adam)

Fig. 2: Patient's photograph

Fig. 3: Central cyanosis

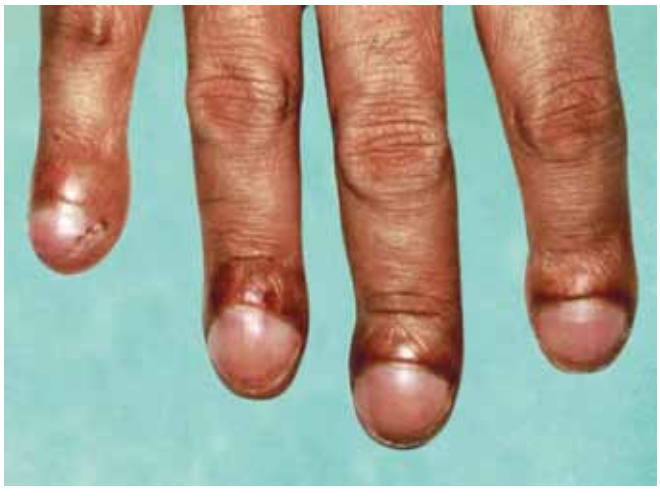


Fig. 4: Clubbing

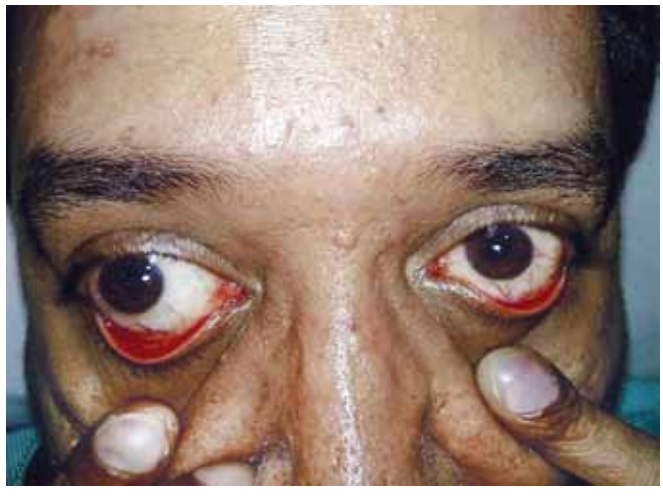


Fig. 5: Polycythemia

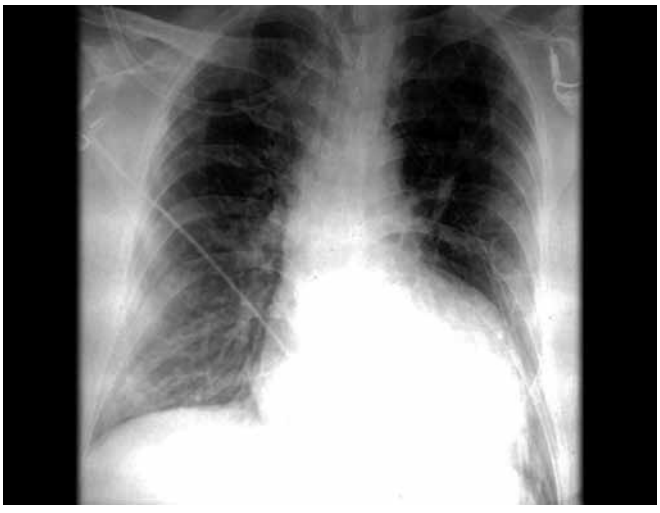


Fig. 6: Chest X-ray

the age of 16, in 1980. Findings after cardiac catheterization were as follows:

- Tricuspid atresia with post pulmonary artery banding.
- Large left ventricle with small hypoplastic right ventricle.
- High flow in pulmonary artery, (Large pulmonary artery with banding).

The patient was advised not to undergo any further procedure, since he was not found suitable for Fontan procedure.

Since, the patient was having high fever, he was admitted at MGM Hospital, CBD Belapur, Navi Mumbai, Maharashtra, India and was diagnosed that he was suffering from plasmodium vivax positive malaria.

His clinical evaluation reveals Central Cyanosis (Fig. 3), Grade 3 Clubbing (Fig. 4) and Hypoxia with SpO_2 84 to 85%.

His hemoglobin was 23 gm% and he was having polycythemia (Fig. 5) with PCV of 75% without any evidence of iron deficiency.

His uric acid level which was 11 mg% has come down to normal with tablet Zyloric. Other blood reports including LFT, RFT, sugar, lipid profile were normal except serum triglycerides 195 mg%.

X-ray (Fig. 6) chest shows CTR of 55% with near normal vascularity.

PFT showed minimal obstructive lung defect with an additional restrictive lung defect.

The cardiovascular examination revealed grade 4/6 systolic murmur with thrill.

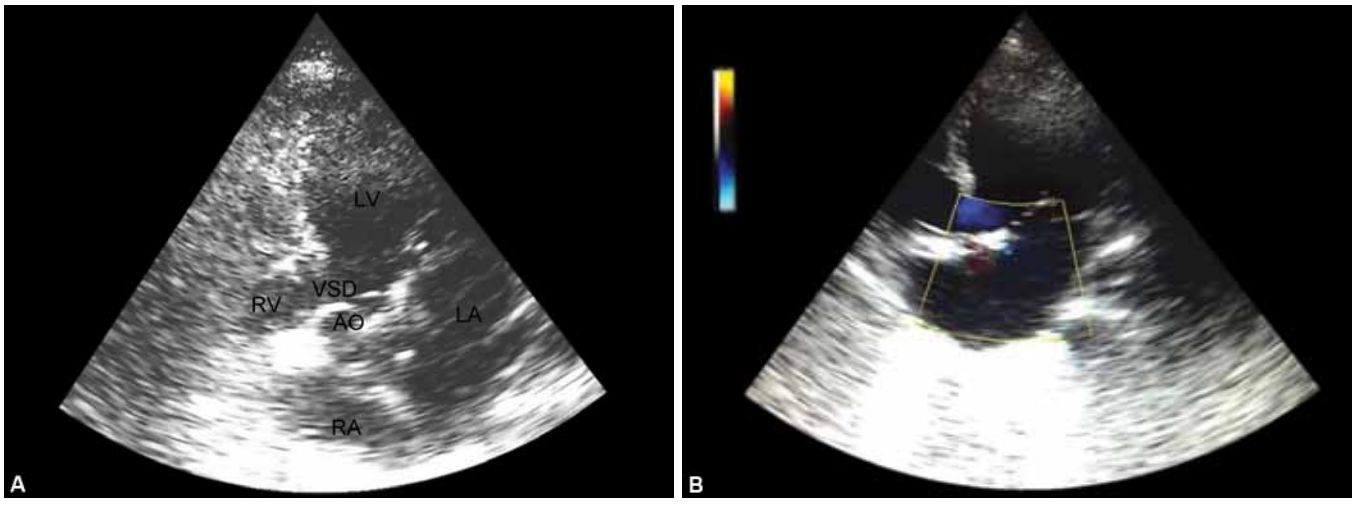
Echocardiography (Figs 7A and B) revealed

- S/P pulmonary banding.
- Tricuspid atresia.
- Large ASD with right to left shunt.
- Large muscular VSD with left to right shunt.
- Significant subvolvular RVOT obstruction (Gradient 95 mm Hg).
- Dilated hypokinetic LV with EF 40%. Dilated LA.
- Good size pulmonary artery and branches.

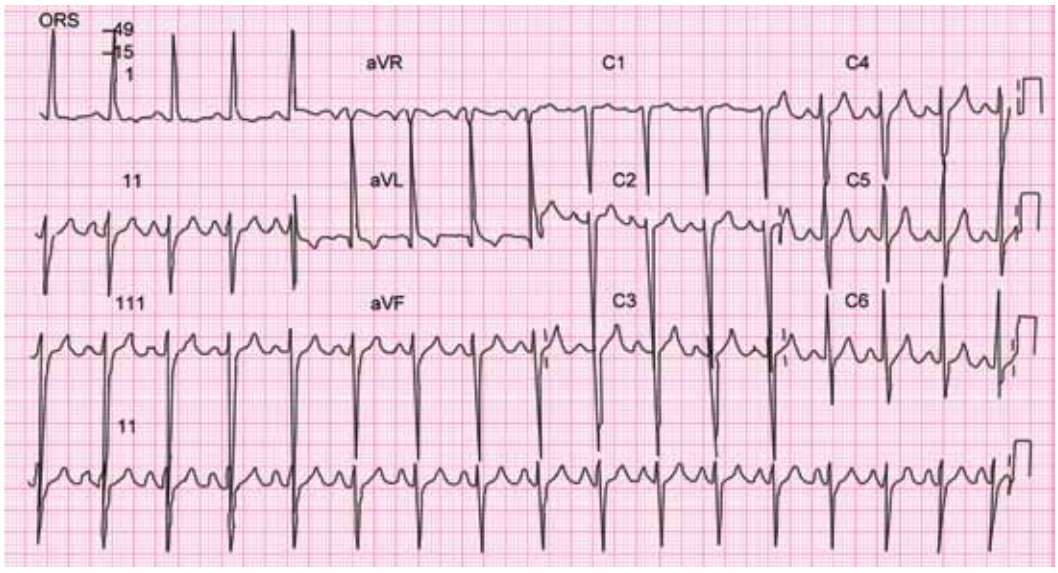
Electrocardiogram (ECG) (Graph 1)

SUMMARY

Thus in summary, patient is a middle aged gentleman, who was diagnosed to have tricuspid atresia with high flow in pulmonary arteries, subjected to pulmonary artery banding at the age of 4 years, still surviving where mortality rate is more than 90% without definitive surgery, now developed significant subpulmonary obstruction and is being considered for TCPC or Bidirectional Glen or BT shunt. Though patient is having chronic hypoxia (SpO_2 84-85%), he can do his routine activities without feeling breathless or fatigued.



Figs 7A and B: Echocardiography



Graph 1: Electrocardiogram (ECG)

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INSTRUCTIONS TO AUTHORS

INTRODUCTION

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The newly launched peer-reviewed quarterly journal would cover full spectrum of the specialties in biomedical research. Its second issue would be released in July 2014. The journal aims to publish articles arising out of original research, specialized topics, review articles, editorials and description of new diagnostic and therapeutic techniques and technologies. In addition, the journal includes pictorial reviews, letters to the editor, book reviews, and notices of meetings and courses. In this way, the journal hopes to provide a forum for the stimulation of new developments, clinical practices and research in the field of health and allied sciences. The salient feature of the journal would be to bring out from time to time special editions focusing on specific themes of national relevance, including the outcome of scientific meetings, etc. A section would be devoted exclusively to young researchers and students in order to encourage them for publishing their innovative ideas and research findings. In fact, it will be a 'student friendly' journal.

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