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MGM Journal of Medical Sciences



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From the Editors' Desk

We are pleased to place second issue of the fourth volume of MGM Journal of Medical Sciences (MGMJMS) before our esteemed readers. The journal is in 4th year of its publication. Looking at the positive feedback of many of our readers in India and abroad, we feel that our efforts in nurturing the journal and putting it on the right track are bearing fruit. Right from the time of its inception, our sole aim and effort has been to keep maintaining the quality of the journal at a decent level and keep on improving it. Every single manuscript that is accepted for publication is scrutinized thoroughly by us, by experts in respective disciplines and by peer-reviewers. Great emphasis is laid upon assessing scientific appropriateness of the papers; accuracy of data presented and correct statistical analysis. A number of medical colleges and health sciences institutes have started subscribing to MGMJMS. Eighteen international indexing agencies have already indexed it. It has been uploaded on University Grants Commission Journal Database website. Our proposal for getting it indexed in PubMed has been accepted in principle by concerned authorities in National Library of Medicine, Bethesda, MD, USA.

We gratefully acknowledge support of our esteemed contributors (clinicians, medical and biomedical scientists and other health & allied sciences professionals) for not only sending their papers for publication in MGMJMS, but also ensuring that the submitted papers stand scientific scrutiny as per international standards and meet all the quality benchmarks. Obsession with quality forces us many a time to return the articles to authors for corrections, re-corrections and re-writing. Even after that, if a paper is found unsuitable, it does not get published. We do hope that our esteemed contributors bear with us for this obsession, because we are determined to work for securing a coveted place for MGMJMS among prestigious research and scientific journals in Health sciences globally at the earliest. We cannot achieve that unless we, the members of editorial board, scrupulously and strictly adhere to the quality standards.

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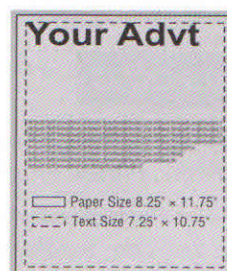
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Goitrous Hypothyroidism: Changing Clinical Profile

¹Alaka Deshpande, ²Abhijit Pancholi, ³Mayur Jain

ABSTRACT

Introduction: On availability of sensitive techniques and better understanding of pathogenesis, hypothyroidism is being detected in early stages in milder forms. The clinical picture is changing in the third millennium compared with what was described 50 years ago.

Materials and Methods: This is a comparative study of goitrous and nongoitrous cases referred for functional evaluation of the thyroid.

Results: One hundred and five cases of goitrous hypothyroidism are studied with hormonal and immunological parameters along with cytology; 80% of the cases were asymptomatic/had protean manifestations. The etiology was autoimmune thyroiditis as evident from raised levels of thyroperoxidase antibodies as well as histopathology.

Conclusion: Autoimmune thyroiditis is the commonest cause of goitrous hypothyroidism, i.e., being increasingly detected in the early stages with milder form. Clinicians need to be aware of the changing profile of goitrous hypothyroidism.

Keywords: Goitrous, Granulomatous thyroiditis, Hypothyroid, Thyromegaly.

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INTRODUCTION

Thyroid disorders are the commonest endocrine problems in India.¹ Forty years ago, majority of our hypothyroid patients used to be perimenopausal women presenting in severe forms, making a picture of a spot diagnosis (Fig. 1).

Severe hypothyroidism presented with characteristic features of myxedema facies, slow mentation/response, thick hoarse voice, dry skin, and menorrhagia. The only investigation then available at tertiary care centers was radioactive iodine uptake. Over the years, with better understanding of the pathogenesis and availability of ultrasensitive diagnostic tools, the cases are detected



Fig. 1: Atrophic idiopathic hypothyroidism, hypothyroid facies – puffiness, sallow expression, thick lips and tongue, pallor

much earlier. As a result, there is a change in the profile of hypothyroidism.

In early stages, it may be detected by functional evaluation of a goiter or incidentally in an asymptomatic patient with protean manifestations like hair fall, weight gain, etc.

The cases are referred to our thyroid clinic by various clinical disciplines for evaluation and management of thyroid disorders. In addition, a large number of cases alarmed with the presence of goiter walk in themselves for management. It was observed that a large number of these goitrous cases were clinically asymptomatic; however, they turned out to be hypothyroid on investigations. Therefore, a prospective study was undertaken.

MATERIALS AND METHODS

- A study group comprised males and females above the age of 18 years presenting with goiter.
- A control group comprised age-/sex-matched cases without goiter. All these cases in the control group were referred for thyroid hormone estimations for various indications like obesity, infertility, menstrual irregularities, bad obstetric history, and preoperative evaluation of the thyroid functions.

The study spanned over a period of 18 months. Consecutive cases with goiter and nongoiter were included after informed consent. A detailed clinical history was taken. Duration of thyromegaly was noted. Clinical examination including local examination of the thyroid was carried out. All the cases of control as

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well as study group were subjected to thyroid hormone estimation.

Cases with hormone profile revealed overt hypothyroidism (OH) with thyroid-stimulating hormone-sensitive (s-TSH) $>15 \mu\text{Iu/mL}$ or subclinical hypothyroidism (SCH) with normal T4 and S. The TSH varying between 5.1 and $14.9 \mu\text{Iu/mL}$ was once again probed with direct questions to find out symptoms suggestive of thyroid hypofunction.

Cases of OH and SCH were further subjected to antithyroperoxidase antibodies (TPO Abs) also known as antimicrosomal antibodies estimation. Fine-needle aspiration cytology was carried out in all cases with goiter.

Overt hypothyroid cases were then treated with thyroid hormone replacement as per the guidelines of American Thyroid Association with a dose of $1.6 \mu\text{g/kg/day}$ of the ideal body weight.²

The serum triiodothyronine (T3), thyroxine (T4), and TSH were estimated using enzyme-linked fluorescence assay on mini VIDAS from bioMerieux. Fine-needle aspiration cytology was carried out as an office procedure under strict aseptic precautions. The aspirate was fixed with methyl alcohol and stained with hematoxylin–eosin as well as Giemsa stain. The pathologist was blinded to the clinical, hormonal details.

All the hypothyroid cases were further investigated with electrocardiogram, echo cardiography, and serum lipid profile.

OBSERVATIONS

During a study period of 18 months, 150 cases with goiter formed the study group with a control group of nongoitrous 100 cases.

Control Group

There were 76 females and 24 males. The mean age of this group was 26.8 years; obviously none had thyromegaly. Only 4/100 cases had s-TSH varying between 5.6 and $9.7 \mu\text{Iu/mL}$; however, their free T4 and TPO antibodies were within normal limits. These cases were advised 6 monthly follow-up with s-TSH estimation.

Study Group

This group had 150 consecutive cases of thyromegaly. There were 140 females and 10 males, confirming the female preponderance in thyroid disorders; 45/150 cases were functionally euthyroid as shown by their hormone profile. Remaining 105 cases were diagnosed as goitrous hypothyroidism and studied in detail. There were 98 females and 7 males. The mean age of the study group was 27.6 years. All these cases were again probed for symptomatology, suggestive of hypofunction of the thyroid.

Symptoms like lethargy, depression, change in voice, constipation, and menorrhagia raised the index of suspicion for hypothyroidism. The present study had only 12 cases having one or two of these symptoms along with goiter. Moreover, all these patients were not menopausal but were in their thirties. The main indication for evaluation of thyroid functions was presence of goiter.

The remaining 93 cases did not volunteer any symptoms, suggestive of hypofunction. In other words, they were asymptomatic. They came to the health care facility for reasons shown in Table 1. These reasons were revealed only on direct questioning.

Slow relaxation of the ankle jerk was noted only in six cases.

Cases of infertility, bad obstetric history, irregular/scanty periods, sec. amenorrhea were referred for thyroid studies firstly because of the presence of the goiter and secondly because of the increasing awareness among the clinicians about the changing clinical profile of the thyroid dysfunction.

There were 27 young females with obesity/weight gain. Weight gain in hypothyroidism is due to myxedema, but these 27 cases had no evidence of puffiness, edema-pitting/nonpitting. More than clinicians, the weight loss programmers are increasingly referring obese females for thyroid hormone estimation because the hypothyroidism has protean manifestations.

Five cases with menstrual disorders had galactorrhea. The serum prolactin (PRL) levels in them ranged from 33 to 47 ng/mL .

Zulewski's clinical scoring³ system was used for the study group, and the results are shown in Table 2.

As can be seen, only 12 cases had a hypothyroid score, 53/105 cases of OH were clinically asymptomatic despite

Table 1: Clinical profile (n = 93)

<i>Clinical profile</i>	<i>No. of cases</i>
Apparently asymptomatic	93
Goiter	93
Weight gain	27
Lethargy	16
Constipation	03
Menorrhagia	02
Irregular/scanty menses	14
Sec. amenorrhea	02
Infertility	04
Bad obstetric history	04
Galactorrhea	05

Table 2: Zulewski's score

<i>Score</i>	<i>No. of cases</i>	<i>Diagnosis</i>
>5	12	Hypothyroid
3–5	40	Intermediate
<3	53	Euthyroid

Table 3: Grades of thyromegaly

Grades	Thyromegaly	No. of cases
I	Goiter visible with extended neck	40
II	Goiter visible with neck in normal position	46
III	Goiter extending up to sternomastoid	14
IV	Goiter extending beyond sternomastoid	04

Table 5: Thyroid cytology

Cytology	No. of cases
Lymphocytic thyroiditis	72
Granulomatous thyroiditis	06
Colloid goiter	27

probing history. The clinical scoring system of Zulewski lacks sensitivity and specificity (Table 3).³

One case had a multinodular goiter.

Hormone Profile

Table 4 shows the hormone profile of the study group. Serum T3 levels ranged from 0.4 to 2.46 nmol/L. Similarly, the serum T4 levels ranged from 9.85 to 77.7 nmol/L. Very low T3 and T4 levels were characteristically noted in 12 symptomatic cases. The 93 asymptomatic cases had normal T3, which is a metabolically active hormone. Serum T4 being low in these cases, the TSH was elevated by biofeedback mechanism confirming primary hypothyroidism. Serum TSH varied from 18 to 292 μ Iu/mL.

IMMUNOLOGICAL PARAMETERS

The mean anti-TPO antibody level was 836.94 ± 302.3 . Attempt to correlate TPO Abs with severity of the hypothyroidism based on serum TSH levels showed nonlinearity (Table 5).

Infiltration of thyroid parenchyma by inflammatory infiltrates containing small lymphocytes, plasma cells, and well-developed germinal centers is the cytological

Table 4: Hormonal profile

Type	Results	Reference range
Serum T3	1.18 ± 0.28 nmol/L	0.92–2.33 nmol/L
Serum T4	42.06 ± 22.74 nmol/L	60–120 nmol/L
Serum TSH	103 ± 72.56 μ Iu/mL	0.25–5.0 μ Iu/mL

picture of thyroiditis which was seen in all the cases. In addition, many thyroid follicles showed atrophic changes. The hallmark of Hashimoto's⁴ thyroiditis was Askanazy/Hürthle cells (Fig. 2). These are epithelial cells characterized by abundant eosinophilic, granular cytoplasm. It is a metaplastic response to inflammatory injury.⁵

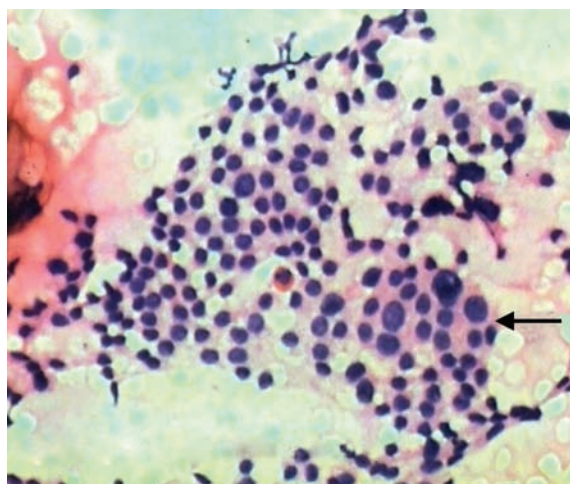
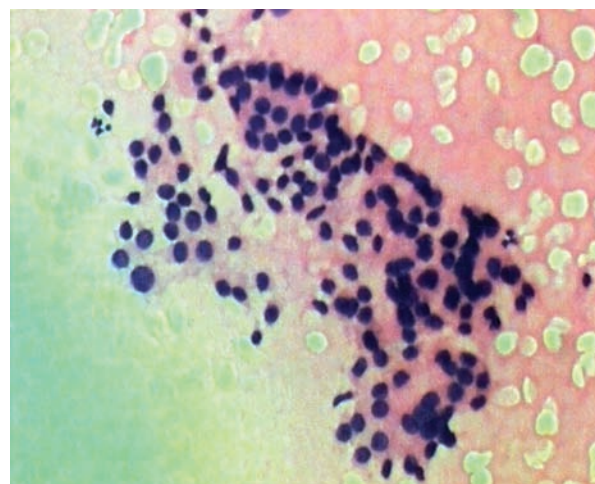
Six cases revealed clusters of lymphocytes, histiocytes with few giant cells lining the follicles diagnosed as granulomatous thyroiditis (Fig. 3).

Twenty-seven cases revealed abundance of colloid within the follicles with normal follicular epithelial cells, hence, reported as colloid goiter (Fig. 4), although hormonally and immunologically these cases had autoimmune thyroiditis.

DISCUSSION

Hypothyroidism results from inadequate production or inadequate action of thyroid hormone in target organs. Primary hypothyroidism is the commonest disorder, while secondary and tertiary hypothyroidisms are rare. Low levels of circulating T4 with increased levels of serum TSH are the diagnostic criteria of primary hypothyroidism.

It had been more prevalent in elderly women, commonly presenting at menopause. However, the mean age of the study group in this series is only 27.8 years. Hypothyroidism is being detected at a much earlier age simply because of the presence of the goiter and availability of sensitive diagnostic techniques, although these patients had no symptom or sign of hypothyroidism.

**Fig. 2:** Lymphocytic thyroiditis with Askanazy cell (arrow)**Fig. 3:** Colloid goiter

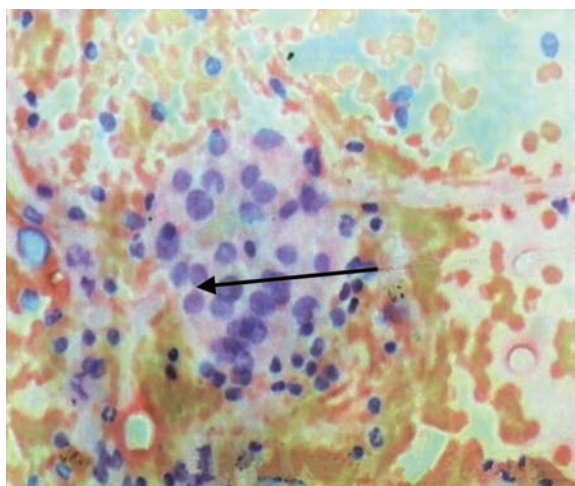


Fig. 4: Granulomatous thyroiditis

Female preponderance in thyroid disorders continues to remain the same.

The clinical profile of menopausal hypothyroid women had been described for all these years. These patients had symptoms like lethargy, depression, menorrhagia, constipation, hoarseness of voice. However, goiter was absent (atrophic thyroid). Over the years, it has been realized that there is a great symptom overlap⁶ between hypothyroids and normal population. The attempts to clinical scoring system have also turned out to be unsuccessful.³

Functional (overt) hypothyroidism was detected in 105/150 (70%) of young asymptomatic goitrous patients. Overt hypothyroidism was detected on functional evaluation of the goiter. Only 12 cases presented with symptoms suggestive of hypothyroidism. More than 80% of the hypothyroid cases are asymptomatic, thus emphasizing the need for high index of suspicion with increased awareness of the changing profile of the hypofunction.

Thyromegaly was mild, grade I to II, in 82.5% of the cases. As the thyroid starts failing, the inadequate production of T4 results in increased TSH secretion leading to thyromegaly in early stages of the disease process. But over the years, the gland goes on diminishing as a result of immunological destruction.

The hormone profile showed low T4 with high TSH. The paucity of symptoms may be explained based on the normal serum T3 levels seen in these cases. The presence of goiter also indicates early stage of autoimmune thyroiditis.

Hyperprolactinemia, serum PRL levels not exceeding 60 ng/mL, have been reported in about 20% of the hypothyroid^{7,8} patients, and it normalizes with thyroid replacement therapy. This series had five cases with galactorrhea, with serum PRL varying from 33 to 47 ng/mL. The exact cause of hyperprolactinemia is not understood;

probably, it depicts the hypersensitivity of the lactotrophs to the raised levels of thyrotropin-releasing hormone.

Autoimmune thyroiditis has now been recognized as the commonest etiology of primary hypothyroidism. Detection of serum anti-TPO Abs (antimicrosomal antibodies) and antithyroglobulin antibodies is a vital component of diagnosing autoimmune thyroiditis. Antimicrosomal antibodies (TPO antibodies) are more sensitive than anti-Tg Abs. Antibodies are known to be involved in thyroid cell destruction through cytotoxic mechanisms mediated by the complement and killer cells. The autoimmune process appears to be due to an inherited defect in immune surveillance, which leads to dysregulation, chronicity, and destruction of the gland.^{9,10}

Autoimmune mechanism is evident in this study by increased levels of TPO antibodies varying from 50 to more than 1,000. However, there was no linearity between levels of elevated serum TSH and antibodies.

Although thyroid cytology is not necessary for diagnostic and therapy purposes, it gives the confirmation of the etiology. The hallmark of the autoimmunity is extensive infiltration of inflammatory cells, including small lymphocytes, plasma cells, follicular atrophy, and fibrosis.

Hashimoto's thyroiditis is caused by a breakdown in self-tolerance to thyroid autoantigens, which is evident by the circulating autoantibodies against TPO and thyroglobulin. The autoimmunity has a strong genetic predisposition. Approximately 50% of the siblings show raised levels of thyroid antibodies.

In the early stages of autoimmune thyroiditis, the lesions are focal. Twenty-seven cases in this series were diagnosed as colloid goiter because the aspiration needle missed the focal lesion. It is the pitfall of the technique.

Six cases had granulomatous thyroiditis, but there was no history of pain. The granulomatous thyroiditis (de Quervain's) is less common. It usually occurs in the fifth decade. It is supposed to be triggered by the presence of viral infection. Clinically, the patient complains of pain in the thyroid region.

The clinician may also look for other autoimmune disorders like systemic lupus erythematosus, Sjögren's syndrome, type II diabetes mellitus, rheumatoid arthritis, and Grave's disease.

A rare cause of goitrous hypothyroidism is Pendred¹¹ syndrome, which is a genetic disorder with organification defect presenting in family members with sensorineural deafness, goiter, and hypothyroidism. Radioactive iodine uptake with perchlorate washout test clinches the diagnosis of organification defect.

CONCLUSION

A study of 105 cases of goitrous hypothyroidism revealed that: (1) The age of presentation was second and third

decade. (2) More than 80% of cases were asymptomatic/ had protean manifestations. (3) Patients with goiter, menstrual irregularities, bad obstetric history should be subjected to serum TSH estimation as a screening test. In addition, serum TSH estimation should be a parameter of preoperative evaluation. (4) Anti-TPO Abs were high in all of them. (5) Fine-needle aspiration cytology confirmed lymphocytic thyroiditis.

Clinicians of various disciplines need to be aware of the changing profile of hypothyroidism.

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Morbidity Profile of People Living in the Vicinity of Mobile Towers, Jaipur City, Rajasthan, India

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ABSTRACT

Introduction: In 2011, the International Agency for Research on Cancer classified mobile phone radiation as group 2B (possibly carcinogenic). Studies showed association with ailments like drying of the skin and fluid in the eyes, sleep disorder, lack of concentration/memory loss, tumors/cancers. Yet another study showed no significant association. According to data from the International Telecommunication Union, there are over 800 million mobile phone subscribers in India. The approximate estimate of cell towers in Jaipur city is 5,678. Hence, this study was done with the objective to find out morbidity profile of people living in the vicinity of mobile towers in Jaipur; secondary objective was to compare morbidity profile among people exposed to low vs high to moderate (HTM) level of mobile radiation.

Materials and methods: Observational cross-sectional analytical study was planned in four areas of Jaipur city having mobile tower for >10 years: Jawahar Nagar, Sanganer, Vidyadhar Nagar, and Vaishali Nagar. "Detex 189" was used to assess the radiation level, and SF-36 questionnaire was used to assess physical and mental morbidity.

Sample size: The sample size was 720 people, assuming 10% prevalence of radiation-related mental morbidity among people living in the vicinity of mobile tower, at 95% confidence interval with 2.5% absolute allowable error and keeping nonresponse as 25%, which will cover all morbidities.

Results and conclusion: Except for sleep disturbances (p -value = 0.002), there was no significant difference in presenting common health problems and diseases as per level of radiation. Status of physical functioning, bodily pain, vitality, mental health, overall physical component score, and mental component score was found to be significantly low among the people who are exposed to HTM level of radiation (with p -value = 0.000, <0.001, <0.001, <0.001, 0.028, 0.002 respectively), but it did not limit their day-to-day work performance (p = 0.848), social functioning (0.420), and feeling of general health (p = 0.176). Since people in HTM radiation were significantly older (p = 0.002), these differences need further verification.

Keywords: Mobile tower, Morbidity, Radiation.

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INTRODUCTION

People all over the world have been debating about associated health risks due to electromagnetic radiation from cell phones and cell towers. According to the data from International Telecommunication Union, there are over 800 million mobile phone subscribers in India.¹ The approximate estimate of cell towers in Jaipur city is 5,678.² In 2011, the International Agency for Research on Cancer classified mobile phone radiation as group 2B – possibly carcinogenic.³

An epidemiological study (2004) stated that regular use of a mobile phone over a decade or more was associated with an increased risk of acoustic neuroma, a benign brain tumor, not for less than 10 years.⁴ A pan-European study REFLEX [Risk Evaluation of Potential Environmental Hazards from Low Energy Electromagnetic Field (EMF) Exposure] in 2004 showed some compelling evidence of deoxyribonucleic acid damage of cells in *in vitro* cultures, when exposed between 0.3 and 2 W/kg, whole-sample average.⁵

Statistically significant electrocardiogram changes were found in 12 to 30% of study participants in 2006.⁶ In 2006, a large Danish group study followed mobile phone use over 420,000 Danish citizens for 20 years and showed no increased risk of cancer.⁷

Hardell et al⁸ found that cell phone users had an increased risk of malignant gliomas, link between cell phone use and a higher rate of acoustic neuromas, tumors more likely to occur on the side of the head that the cell handset is used, 1 hour of cell phone use per day significantly increases tumor risk after 10 years or more. A study in 2009 on the effects of exposure to radiofrequency radiation (RFR) emitted by standard GSM cell phones confirmed longer (slower) response times to a spatial working memory task when a standard GSM cellular phone was placed next to the head of male subjects. Right-handed subjects exposed to RFR on the left side of their head, on average, had significantly longer response

times when compared with exposure to the right side and sham exposure.⁹

Largest study of its kind ever; the 13 nation inter-phone project in 2012, claimed that for an average user (cell phone use for 2 hours a month), increase in cancer cases is not significant.¹⁰ Reevaluation of the Interphone study by a group of eminent scientists has found that even for average users, increase in brain tumor is significant for greater than 10 years of use, indicating some risk of carcinogenicity.³ Also, overuse of cell phones has been reported to cause drying of the skin and fluid in the eyes, sleep disorder, lack of concentration, and memory loss in various people. Children are usually considered at higher risk than adults due to thinner skulls.¹¹

In the past few years, health activists and “resident organizations” in Jaipur have repeatedly opposed establishment of telecom towers in densely populated areas, claiming radiation caused serious health risks. It is of great importance to know about the health effects of mobile radiation so as to guide people on prudent use of this wonderful technology for the benefit of health and development of our people without getting hurt; hence, we planned this study.

AIMS AND OBJECTIVES

- To find out morbidity profile of people living in the vicinity of mobile towers in Jaipur.
- Secondary objective was to compare morbidity profile among people exposed to different levels of mobile radiation observed.

MATERIALS AND METHODS

Study area: Four areas in Jaipur city having mobile tower for more than 10 years – Jawahar Nagar, Sanganer, Vidyadhar Nagar, and Vaishali Nagar – were selected randomly.

Study type: Community-based observational descriptive (cross-sectional analytical) study.

Study duration: Six months including 2-month survey period.

Study population: People of Jaipur city who have been living in the vicinity of mobile towers for at least 10 years and above.

Sample size: The sample size was 720 people, assuming 10% prevalence of radiation-related mental morbidity among people living in vicinity of mobile tower, at 95% confidence interval with 2.5% absolute allowable error and keeping nonresponse as 25%, which will cover all morbidities.

Plan of study: There were 10 mobile towers in four randomly selected areas. People living in the vicinity, i.e., within 100 m radius, of mobile towers and exposed to the electromagnetic (EM) radiations for at least a period of 10 years, were interviewed and checked for radiation

levels by using Detex 189 for the study. Based on the observed radiation level, the study population was categorized into two categories: (1) with “high to moderate (HTM) radiation” and (2) with “low level of radiation.” For comparing morbidity as per radiation level, 360 persons were selected from low- and high-radiation areas each, but no matching on any variable was done.

Eligibility criteria: People living in vicinity of mobile towers and exposed to mobile tower radiations for at least a period of 10 years and aged ≥ 18 years were selected.

Exclusion criteria: People already having any chronic medical illness for more than 10 years refused to participate.

Statistical Analysis

Qualitative data were analyzed as proportions, and any association was tested using chi-square test. Quantitative data were analyzed as mean and standard deviation, and any association was assessed using Student’s t-test.

DEFINITIONS

- Vicinity within 100 mg of range.
- *Detex 189:* It is broadband instrument and accurately detects the cumulative radiation in the range of 800 MHz to 4 GHz.
- *Low levels:* Less than -30 dBm.
- *Moderate level:* -30 to -15 dBm.
- *High level:* More than -15 dBm.

MATERIALS REQUIRED

- *Tool (Detex 189):* To assess radiation level. It is a broadband instrument and accurately detects the cumulative radiation in the range of 800 MHz to 4 GHz, which covers frequencies used by most modern communication systems that are encountered in our day-to-day life (CDMA, GSM900, GSM1800, 3G, and Wi-Fi/WLAN/Bluetooth frequency bands). It complies with the Bio-Initiative Report (2007) Recommendations and is IIT Bombay lab tested. The radiation levels are indicated by three light-emitting diodes (LEDs) – green, yellow, and red.
 - If only green LED lights up, it implies low level of radiation.
 - If yellow LED and green LED light up, it implies moderate level of radiation. Also, buzzer will start beeping intermittently.
 - If all the three LEDs light up, i.e., red, yellow, and green LEDs, it implies high level of radiation. Also, buzzer will start beeping continuously.
- *SF-36 Questionnaires (to assess physical and mental morbidity):* The SF-36 (short form 36 questions) is a survey questionnaire on health-related quality of life impersonalizing overall health (Tables 1 and 2).

Questions to find out whether person has one or more of: (1) cold; (2) asthma; (3) headache; (4) migraine; and (5) sleep disturbances and whether taking drugs for: (1) heart problems; (2) cancer or tumor; (3) diabetes; (4) thyroid disorder; or (5) any other problem were added.

- *Study Questionnaire:* To get sociodemographic details of the participants. Participation in the study was ensured after getting informed consent in due form.

Implication: Morbidity profile of people living in the vicinity of mobile towers and exposed to EM radiations

for at least 10 years would indicate the long-term effects of low, moderate, and high levels of EM radiations on the health of the community residing near mobile towers, if any, in this study.

OBSERVATIONS

Those who had HTM level of radiation belonged to higher age group ($p = 0.002$). Sex has no difference in level of radiation (Table 3).

It was observed that the status of physical functioning, vitality, emotional, and mental health was significantly

Table 1: Information on the eight scales in SF-36

Scales (dimensions)	No. of items contributing in the scale	No. of levels possible	Definition of lowest possible score (=0)	Definition of highest possible score (=100)
Physical functioning (PF)	10	21	Very limited in performing all physical activities including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role-physical (RP)	4	5	Problems with work or other daily activities as a result of physical health	No problems with work other daily activities
Bodily pain (BP)	2	11	Very severe and extremely limiting pain	No pain or limitations due to pain
General health (GH)	5	21	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality (VT)	4	21	Feels tired and worn out all of the times	Feels full of pep and energy
Social functioning (SF)	2	9	Extreme and frequent interference with normal social activities due to physical and emotional or problems	Performs normal social activities without emotional problems
Role-emotional (RE)	3	4	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities
Mental health (MH)	5	26	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time

Table 2: Summary information on the physical and mental component

Scales	No. of items	No. of levels	Definition of lowest possible score	Definition of highest possible score
Physical component summary	35	567 (a)	Limitations in self-care, physical, social, and role disabilities, severe bodily pain, frequent tiredness, health rated "poor"	No physical limitations, or decrements in activities, well-being, high energy level, health rated "excellent"
Mental component summary	35	493 (a)	Frequent psychological distress, social and role disability due to emotional problems, health rated "poor"	Frequent positive affect absence of psychological distress and limitations in usual social/ role activities due to emotional problems, health rated "excellent"

Table 3: Age- and sex-wise distribution of study participants as per radiation levels

Profile	Radiation level		Level of significance
	High and medium level of radiation, $n = 360$ (%)	Low level of radiation $n = 360$ (%)	
Mean age \pm SD	39.29 \pm 17.1	35.48 \pm 15.75	$p = 0.002$ (t test)
18–25	106 (29.44)	148 (41.11)	$p < 0.001$ (Chi-square)
25–35	69 (19.17)	43 (11.95)	
35–45	54 (15.00)	48 (13.33)	
45–55	64 (17.78)	89 (24.72)	
55–65	44 (12.22)	18 (5.00)	
> 65	23 (6.39)	14 (3.89)	
Sex			
Male ($n = 376$)	195 (54.17)	181 (50.28)	Chi-square $p = 0.267$
Female ($n = 344$)	165 (45.83)	179 (49.72)	

SD: Standard deviation

Table 4: Spectrums of health of participants as per SF-36, and level of radiation

Health status SF-36	Radiation		Level of significance
Mean score \pm SD	High and medium level of radiation (n = 360)	Low medium of radiation (n = 360)	Student's t-test p-value
PF score	76.792 \pm 15.0782	82.958 \pm 18.8953	0
RP score	81.875000 \pm 28.9009149	81.458333 \pm 27.2003490	0.848
BP score	93.9583 \pm 13.39842	95.9028 \pm 9.80579	<0.001
GH score	57.4722 \pm 26.39953	60.0278 \pm 24.04440	0.176
VT score	65.9167 \pm 12.92764	71.6389 \pm 12.19994	<0.001
SF score	92.0490 \pm 12.7811	92.847 \pm 13.7458	0.420
RE score	89.9077 \pm 21.68947	93.4261 \pm 18.19770	0.017
MH score	72.3222 \pm 11.32683	83.8778 \pm 12.92906	<0.001
PCS score	77.5243 \pm 16.00813	80.0868 \pm 15.15110	0.028
MCS score	81.4794 \pm 11.13367	84.0169 \pm 10.98258	0.002

PF: Physical functioning; RP: Role physical; BP: Bodily pain; GH: General health; VT: Vitality; SF: Social functioning; RE: Role emotional; MH: Mental health; PCS: Physical component summary; MCS: Mental component summary; SD: Standard deviation

Table 5: Common health problems as per level of radiation

Common health problem	High and medium levels of radiation	Low level of radiation	Level of significance (p-value for chi-square test)
Cold	31	31	1.000
Asthma/allergy	20	10	0.093
Headache	39	31	0.379
Migraine	13	9	0.516
Sleep disturbances	30	13	0.012

Table 6: Associated disease pattern in persons living in different levels of radiation

Associated disease	High and medium levels of radiation	Low level of radiation	Level of significance chi-square test (p-value)
Heart problems	25	15	0.143
Cancer or tumor	3	0	0.247
Diabetes	14	15	1.000
Thyroid-associated problems	11	6	0.326

low in persons living in areas of high to medium level of radiation as compared with low level of radiation ($p = 0.000$, <0.001 , 0.017 , and <0.001), as shown in Table 4. The mental component summary score and physical component summary score of people living in high and medium radiation range were significantly lower than that of people living in low level of radiations ($p = 0.002$, 0.028) as in Table 4. Also, the bodily pain status of people living in high and moderate level of radiations was poor as compared with people living in low level of radiations ($p \leq 0.001$) (Table 4).

It was observed that persons living in high and medium or low level of radiations had almost similar presentation of common health problems ($p \geq 0.05$) except for sleep disturbances ($p = 0.012$) as shown in Table 5. The investigator could not establish any difference in chronic disease patterns between high and medium or low level of radiation (Table 6).

DISCUSSION

Luria et al⁹ observed significantly higher response time among radiation-exposed group than nonexposed. Similarly, we also observed that vitality, emotional, and mental health status are significantly lower in persons exposed to high and medium level of radiations as compared with people exposed to low level of radiation. The

mental health summary score of people in high and moderate level of radiations is significantly lower as compared with people living in low level of radiations ($p = 0.002$).

Röösli¹² revealed that some users of mobile handsets have reported feeling several unspecific symptoms during and after its use. A cross-sectional study in Egypt observed that neuropsychiatric complaints, such as headache, memory changes, dizziness, tremors, depressive symptoms, and sleep disturbances were significantly higher among exposed inhabitants than controls. The present study observation of higher sleep disturbances among exposed is consistent with other studies.¹³

Our study found no association between mobile radiation exposure and diseases like diabetes, heart problems, cancer, tumors, or thyroid problems, similar to findings of Volkow et al.¹⁴ There is little scientific evidence to support the idea of EM hypersensitivity. We could not find any significant relationship between asthma or any other allergic disorder and radiations; this might be explained by the fact that individuals do not show consistent reactions under EMF exposure, nor is there any accepted biological mechanism to explain hypersensitivity.¹⁵

The study showed no significant relation between radiation level and risk of cancer, i.e., consistent with the 13 nation INTERPHONE project.¹⁶ But Swedish

scientific team's epidemiological study in 2004 suggested that regular use of a mobile phone over a decade or more was associated with an increased risk of acoustic neuroma, a type of benign brain tumor. The increase was not noted in those who had used phones for fewer than 10 years.¹⁷

CONCLUSION

Current study did not show any significant difference in the incidence of chronic diseases between people subjected to High to Moderate (HTM) radiation and those to low level radiation. However, Physical and Mental Component Scores (PCS & MCS) were significantly lower in areas of HTM radiation than in areas of low level radiation.

Further larger epidemiological studies of long term effects of HTM radiation on population at multiple centers are required for better understanding of the subject.

PAPER PRESENTATION

This article was presented by Dr Priyanka Kapoor in Rajasthan Conclave-3 organized from 13 to 14 December 2015 at Desert Medical Research Centre, Jodhpur. This project was done under ICMR student's project.

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Assessment of Medication Adherence in Type II Diabetic Patients: A Cross-sectional Study

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ABSTRACT

Introduction: Diabetes is a chronic disorder and requires long-term therapy. Lack of adherence to antidiabetic medication causes suboptimal glycemic control and can lead to treatment failures, development of complications, and increased mortality.

Aim: To study the medication adherence among type II diabetic patients at a tertiary care hospital in Navi Mumbai, Maharashtra, India.

Materials and methods: A cross-sectional, observational study was conducted for a period of 1 year in the Diabetology Clinic in a tertiary care hospital. A total of 100 type II diabetic patients, who were on antidiabetic drug therapy for at least 6 months, were enrolled. Blood glucose was measured and details of drug therapy were noted. Medication adherence was assessed using Morisky Medication Adherence Scale and adherence scores were calculated.

Results: Only 1% had high medication adherence, while 34% had moderate and 65% had low medication adherence. Medication adherence issues identified in type II diabetics were that they forgot to take/bring their medication when traveling, stoppage of medication once glycemic control is achieved, and difficulty in adhering to medication plan. Only 19% were having optimally controlled glycemic levels, whereas 81% were having uncontrolled glycemic levels. Medication adherence scores were lower (reflecting lower adherence) in type II patients with uncontrolled glycemic levels than those having optimally controlled glycemic levels, but this difference was not statistically significant.

Conclusion: Overall, the medication adherence was low in type II diabetic patients. The study shows that to improve medication adherence, better counseling and health education of patients are required.

Keywords: Medication adherence, Morisky Medication Adherence Scale, Type II diabetes.

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INTRODUCTION

Diabetes mellitus is one of the most common chronic diseases across the world, and the number of diabetic patient is on the rise. In 2011, there were 366 million people with diabetes globally, and this is expected to rise to 552 million by 2030.¹ It has been shown unequivocally that good glycemic control helps to prevent diabetic complications.^{2,3} In recent years, newer antidiabetic drugs have been introduced to optimally control diabetes, which have increased the complexity of diabetes treatment algorithms leading to multiple second-line and third-line options.⁴⁻⁷ Nonadherence to medication declines the efficacy of the medication and, in turn, the glycemic control.⁸

Adherence is referred as active, voluntary, and collaborative involvement of the patient in a mutually acceptable course of behavior to produce a therapeutic result.⁹⁻¹² Adherence to antidiabetic medications has been shown to improve glycemic control, and predicts good long-term prognosis of the disease.^{13,14} Medication adherence to antidiabetic agents has also been shown to be more cost-effective, as it may reduce hospitalization frequency and costs associated with complications.^{15,16} Worldwide, studies on medication adherence among diabetic patients have shown a wide variation.¹⁷⁻²⁴ In India, as per the Indian Council of Medical Research – INdia DIABetes national study report, there are 62.4 million people with type II diabetes and 77 million people with prediabetes. It is expected that these projected figures will increase to 101 million by the year 2030.^{1,25} Studies have documented that more than 50% of people with diabetes have poor glycemic control.²⁵⁻²⁷

Limited studies from Southern and Northern regions of India have documented wide variation in the medication adherence and have addressed the issues of non-adherence in diabetic patients.^{21,28-33}

AIM

Therefore, this study was conducted to assess the medication adherence among type II diabetic patients attending a tertiary care hospital in Navi Mumbai, India.

MATERIALS AND METHODS

A cross-sectional, observational study was conducted in the Outpatient Diabetology Clinic, MGM Hospital, Navi Mumbai, Maharashtra, India, from October 2014

to September 2015. Ethical clearance was obtained from the Institutional Ethics Committee.

Adult patients diagnosed with type II diabetes taking antidiabetic drug therapy for more than 6 months attending Diabetology Clinic were included and interviewed. After taking informed consent, patients were interviewed in the adjacent room. Their demographic data along with details of duration of treatment, current antidiabetic drug therapy, and medication adherence were recorded. Fasting and postprandial blood glucose was measured by Accu-Chek Active Glucometer. The study excluded type I diabetics, newly diagnosed type II diabetic patients on antidiabetic drug treatment for less than 6 months, and diabetics not willing for informed consent and/or blood glucose measurement. Participants were further categorized as having optimal controlled glycemic level based on the blood glucose level (fasting <130 mg/dL and/or postprandial <180 mg/dL).

To assess the medication adherence, 8-item Morisky Medication Adherence Scale (MMAS-8) was used after seeking permission from the concerned authorities in UCLA School of Public Health, Los Angeles, USA. (Use of the MMASc is protected by US copyright laws. Permission for use is required. A license agreement is available from: Donald E. Morisky, ScD, ScM, MSPH, Professor, Department of Community Health Sciences, UCLA School of Public Health, 650 Charles E. Young Drive South, Los Angeles, CA 90095-1772). The scale is designed to facilitate identification of barriers to and behaviors associated with adherence to medication. It is a self-report questionnaire with eight questions (items) having good validity and internal reliability. Response categories are yes/no for each item with a dichotomous response and a 5-point Likert response for the last item. Based upon the responses, each item is scored and a total score is calculated. Scores on the MMAS were categorized as: 0 to 6 = low, 6 = medium, and 7 to 8 = high.³⁴⁻³⁶

Statistical Analysis

Data recorded were entered in Microsoft Excel version 2007. Statistical analysis was done using Statistical Package for the Social Sciences version 20. Data were expressed in actual number, mean \pm standard deviation (SD), and percentage; t-test was used to compare the mean between the two groups. Probability p-value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 100 type II diabetic patients were included and analyzed. The mean age of the sample was 54 (± 10.3) years and male:female ratio was 65:35 (Table 1). Responses of the study participants to individual items of MMAS-8 are summarized in Table 2.

Table 1: Characteristics of type II diabetic patients enrolled in the study

Patient characteristics		Value
Patients with type II diabetics		100
Age in years (mean)		54 \pm 10.3
Gender	Male	65 (65%)
	Female	35 (35%)
Duration of treatment in years (mean)		6.9 \pm 4.4
Number of medications (mean)		2.05 \pm 0.7
Mean blood glucose (mg/dL)	Fasting	176 \pm 35
	Postprandial	214 \pm 46
Glycemic status	Controlled level	19 (19%)
	Uncontrolled level	81 (81%)

Table 2: Responses of the participants to individual items of MMAS-8

Questions	Yes (%)	No (%)
1 Do you sometimes forget to take your antidiabetic pills?	50	50
2 People sometimes miss taking their medications for reasons other than forgetting. Thinking over the past 2 weeks, were there any days when you did not take your antidiabetic medicine?	32	68
3 Have you ever cut back or stopped taking your antidiabetic medication without telling your doctor, because you felt worse when you took it?	21	79
4 When you travel or leave home, do you sometimes forget to bring along your antidiabetic medication?	83	17
5 Did you take your antidiabetic medicine yesterday?	51	49
6 When you feel like your diabetes is under control, do you sometimes stop taking your medicine?	61	39
7 Taking antidiabetic medication every day is a real inconvenience for some people. Do you ever feel hassled about sticking to your antidiabetic treatment plan?	69	31
8 How often do you have difficulty remembering to take all your antidiabetic medications?		
Never/rarely	35%	
Once in a while	21%	
Sometimes	30%	
Usually	14%	
All the time	0%	

Responses of patients were analyzed; 83% said they forgot to take medicines when away from home and/or traveling; 69% complained of inconvenience and difficulty in adhering to medication plan; 50% said they just forgot to take medicines. In this study, based upon the total MMAS score, only 1% had perfect/high medication adherence, while 34% had moderate and 65% had low medication adherence (Table 3). Type II diabetic patients were further analyzed based upon glycemic status.

Table 3: Level of medication adherence among type II diabetic patients

Medication adherence level (as per MMAS)	Percentage
Low adherence (score <6)	65
Moderate adherence (score 6 to <8)	34
Perfect adherence (score 8)	1

Table 4: Comparison of medication adherence score between diabetic patients with controlled and uncontrolled glycemic levels

Variable	Glycemic status		p-value*
	Controlled	Uncontrolled	
MMAS total score (mean \pm SD)	5.07 \pm 2.1	4.37 \pm 2.05	0.49

*p-value between group comparisons by independent t-test

We found that only 19% were having controlled blood glucose, whereas 81% were having uncontrolled blood glucose despite being on drug therapy. On subgroup analysis, MMAS score was higher in controlled group in comparison with uncontrolled group, but this difference was not statistically significant (Table 4).

DISCUSSION

The findings of the study suggest that the medication adherence was low and addresses the issue of nonadherence among type II diabetic patients. Worldwide studies using various research assessment instruments and systematic reviews have addressed issues of poor medication adherence among diabetes patients.^{17-22,37}

In this study, medication adherence was assessed using MMAS-8. It is a reliable and validated scale. The scale is designed to facilitate identification of barriers to and behaviors associated with adherence to medication.³⁴⁻³⁶ Only 1% had high while 34% had moderate and 65% had low medication adherence. It was observed that many patients forgot to take medicines with them while traveling. Some of them stopped taking medicines on their own because they believed that their diabetes was under control. Others felt it was difficult to stick to a prescribed treatment plan and so stopped medication.

The findings are comparable to several Indian studies documenting poor medication adherence in diabetic patients.^{21,28,29,38} Sharma et al²¹ documented that only 16.6% of the patients were adhering to the prescribed antidiabetic drugs, and majority often forgot to take antidiabetic medications. Nonadherence was high and significantly ($p < 0.001$) associated with frequent dosing and multiple drugs in the prescription, especially attributed to the "forgetfulness" in the older/occupationally retired age groups. Patients would deliberately take drug holidays without the knowledge of their physician. More than half of the patients desired a decrease in the number and the frequency of medications. More than 50% of patients were not aware of the consequences of missing the drugs; 13.3% of patients experienced a number of side effects contributing to medication nonadherence ($p < 0.05$). Study conducted by Shaimol et al²⁸ (Kerala) reported that only 21.8% of patients showed high adherence, 43.3% moderate adherence, and 35.3% low adherence toward the therapy. The study concluded that among educated patients, medication adherence is higher. Study described

that low-income patients were less adherent to the prescribed therapy than high-income patients. The patients with onset of diabetes at younger age showed more adherence to treatment than older patients. Study conducted by Khan et al²⁹ also documented that only 9.8% diabetic had high adherence. Majority of the diabetic patients were on three-drug combination and showed poor glycemic control with poor compliance to drug therapy.

However, some studies have documented better medication adherence than our study.³⁰⁻³³ Priyanka et al³⁰ documented that majority (60%) had high medication adherence, and this high medication adherence rates were regardless of number of medicines prescribed. Majority of diabetics had positive beliefs about the necessity of their medication and this may have resulted in high adherence. Similarly Baishnab et al³¹ recorded that the adherence levels were 64.90% (high adherence), 29.80% (medium adherence), and 5.29% (poor adherence). The most common reasons for nonadherence were the patient feeling better, cost of medications being expensive, and high quantity of medications. Similarly, the study undertaken by Sajith et al³² (in Maharashtra) found that the adherence levels were high (40.95%), medium (37.14%), and poor (21.90%) among diabetic patients. Arulmozhi and Mahalakshmy³³ chronicled that 49.8% were high, 24.7% moderate, and 26% low adherent. This better medication adherence probably could be explained by increased awareness about diabetes mellitus and its complications among the population. They substantiated that poor family support was a significant factor associated with low medication adherence and emphasized to assess patients regularly for medication adherence and also include their families in counseling sessions.

Secondary analysis revealed that only 19% type II diabetics were having glycemic level optimally controlled, whereas 81% were having uncontrolled glycemic levels. Indian studies have shown that more than 50% of people with diabetes have poor glycemic control, and this is a growing concern. In this study, the medication adherence scores were comparatively lower in type II patients with uncontrolled glycemic levels than those having optimally controlled glycemic levels, reflecting lower medication adherence in type II diabetics with uncontrolled levels, but this difference was not statistically significant. Glycemic control can be influenced by multiple factors, namely dietary adherence, regular

physical activity, and appropriate drug therapy, of which antidiabetic drug therapy plays an important role. As adherence to medication declines, efficacy and glycemic control also decrease.⁸ Therefore, adherence to medication is an essential component in diabetic care management.

Adherence could be affected by patient-centric, physician-dependent, or health care establishment factors. Physicians can play a major role in improving medication adherence by increasing interaction with patients. The physician–patient relationship plays a major role in keeping the patient well informed about the medications they consume. Patients' adherence, when the treatment regimen is simple, seems effective. If they believe the benefits exceed the costs and that their environment supports regimen-related behaviors, their medication adherence improves.³⁹ Diabetes is a chronic disorder which requires lifelong compliance with treatment regime. Efforts should be made by the physicians to identify the reasons for nonadherence and initiate steps to improve it. They need to educate and counsel the patients on the importance of medication adherence and self-care activities in order to achieve optimal glycemic control.

LIMITATIONS

The study sample size was limited. As it was conducted at a single tertiary care hospital, the findings cannot be generalized to the community. Glycosylated hemoglobin is the gold standard but due to financial restraint, only blood glucose measurements by glucometer were used. Dietary, lifestyle modifications, and physical activity-related factors were not addressed. Further multicentric hospital and community-based studies with larger sample size are warranted. Medication adherence was assessed using MMAS-8, a self-reported scale likely to be affected by recall bias and error in self-observation.

CONCLUSION

Overall, the medication adherence was low in type II diabetic patients. There is a need to address the issue of nonadherence to medication. Efforts should be made by physicians to identify the reasons for nonadherence and initiate steps to improve it. Counseling and health education of the patients related to medication adherence need to be improved.

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Laparoscopic Ventral Hernia Repair: Our Experience in 75 Patients

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ABSTRACT

Introduction and aim: Laparoscopic ventral hernia repair has become a method of choice for treatment of ventral hernias. It has benefits of shorter hospital stay, less pain, and better cosmetic results, although it continues to remain a challenging procedure, more so in reoperative abdomen and in patients with serious comorbidities. The aim of this study is to evaluate our experience of laparoscopic ventral hernia repair carried out by a single surgical team.

Materials and methods: Ventral hernia, both primary and incisional hernia, was repaired by laparoscopic intraperitoneal onlay mesh (IPOM) repair in 75 patients at a single center within 3 years between January 2013 and December 2016. This was done at a tertiary care center by a single operating team standardizing the procedure and evaluating the learning curve.

Results: Seventy-five patients underwent laparoscopic IPOM repair of which 45 were females and 30 males. The average age was 52 years (35–72) and size of defect ranged from 4 to 12 cm. Dual mesh with expanded polytetrafluoroethylene was used in all patients. Sixty-two cases were incisional hernias, 10 paraumbilical hernias, and 3 umbilical hernias. Of these, 14 were recurrent incisional hernias after open mesh hernioplasty out of which two cases recurred after laparoscopic IPOM. Mean operative time was 60 to 130 minutes. There were no conversions to open technique. The average hospital stay was 2 to 3 days. One patient had postoperative Richter's hernia which was managed by relaparoscopic reduction and transfascial closure of the defect. Three patients had postoperative ileus, three developed minor wound infection, and one patient had seroma. The average follow-up period was around 12 months.

Conclusion: Laparoscopic IPOM ventral hernia repair is a safe procedure in most cases with benefits of rapid recovery and better patient outcomes, more so in large recurrent incisional hernias and in patients with serious comorbidities.

Keywords: Incisional hernia, Intraperitoneal onlay mesh, Ventral hernia.

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INTRODUCTION

Laparoscopic intraperitoneal onlay mesh (IPOM) has become a method of choice for treatment of ventral and incisional hernias. It provides benefits of shorter hospital stay, less postoperative pain, and good cosmetic benefit. The procedure remains challenging as there is significant learning curve, more so in reoperative abdomen and malignancy. Additionally, it is expensive as the mesh used is costly along with its fixation devices. Laparoscopic incisional and ventral hernia repair was first reported in 1993.¹ It has since evolved with availability of better mesh and fixation devices along with improved laparoscopic vision. Laparoscopic IPOM surgery is not without problems. When the hernia is repaired by open technique without mesh, the chances of hernia recurrence is about 50%, whereas recurrence rate after mesh insertion is 20%. The recurrence rate is usually higher initially when surgeons are gaining experience and is related to learning curve.²

AIM

The aim of this study was to evaluate our experience of laparoscopic repair of various types of ventral hernias with IPOM and to study various aspects of this procedure, namely postoperative pain, period of hospital stay, rate of recovery, ease in placing a larger mesh, and overall outcome.

MATERIALS AND METHODS

A total of 75 patients with ventral hernia underwent laparoscopic IPOM repair between January 2013 and December 2016 in the Department of Surgical Gastroenterology at Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow, India. Operations were done by a single surgical team who used a standardized procedure. It also afforded us an opportunity to evaluate the learning experience objectively. A total of 45 female and 30 male patients with a mean age of 52 (35–72) years underwent surgery. Sixty-two cases had incisional hernia, 10 cases paraumbilical, and 3 cases umbilical hernia. Of these, 14 patients had recurrent incisional hernia after



open mesh hernioplasty out of whom two cases were postlaparoscopic IPOM repair (Table 1). The mean body mass index (BMI) was 35 (25–45). Single hernia defect was found in 66 patients and multiple in 9 (14.1%) cases. The maximum diameter of defect ranges from 4 to 12 cm. We used 20 × 15 cm for small and 30 × 20 cm for large defects. All cases were repaired by dual mesh (Parietex, Covidien, Germany) and tackers were used to fix it after transfascial sutures (Absorbatack, Covidien, Germany). Most patients had comorbidities like diabetes mellitus, hypertension, obesity, and pulmonary disease. The learning curve was assessed on the following parameters: (a) Ease of placement and fixation of the large sized mesh; (b) time taken. The time was divided into time for initial dissection and time for the mesh placement and fixation.

Inclusion Criteria

Any patient with ventral hernia who was fit for general anesthesia.

Exclusion Criteria

Patients unfit for general anesthesia, presence of incarcerated bowel loops, evidence of vascular compromise on imaging and pregnancy.

Preoperative Preparation

All patients had documented detailed medical history. They underwent thorough physical examination with estimation of the hernia defect. All routine blood parameters including complete blood counts, renal and



Fig. 1: Port position with transilluminated hernia sac as seen externally

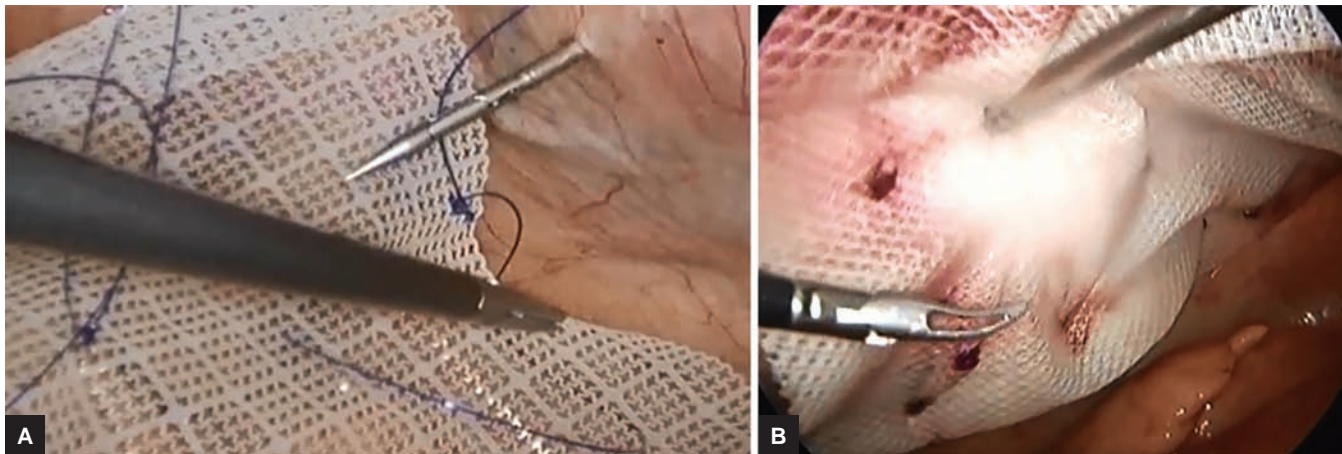
hepatic function tests, coagulation profile were evaluated. Patients with medical comorbidities like diabetes, hypertension, underlying malignancy, etc., were evaluated by respective specialists and optimized for surgery. Contrast-enhanced computed tomography abdomen was done in every patient to confirm the size of defect and its contents, and to look for other associated hernias that may have been missed on physical examination (Fig. 1).

Surgical Technique

The patient was placed supine with arm adducted. After induction of general anesthesia single dose of Injection Augmentin 1.2 gm intravenously was given as routine after sensitivity testing. Pneumoperitoneum was created with Veress needle which was introduced at a point away from hernia. Umbilicus or a point 2 cm below left costal margin in the midclavicular line (Palmer's point) was utilized for initial access.³ Ports were introduced in previously nonoperated area. In case the defect was in lower abdomen, the operative surgeon stood at head-end and when defect site was in upper abdomen, surgeon's position was in between the legs. Usually we used three ports. One was a 5 mm visual port for 30° telescope which was usually converted later to 12 mm port for the placement of large size of mesh. Another two 5 mm ports for working were utilized depending on site and size of ventral hernia (Fig. 2). Preoperatively, the margins of hernia defect were marked. Gentle reduction of contents and adhesiolysis was done with harmonic scalpel or electrocautery with a combination of blunt and sharp dissection. The margins and periphery of the defect were evaluated by direct vision and palpation after complete reduction of contents (Fig. 3). After complete reduction of herniating contents, the abdomen was deflated and the margins were reconfirmed. Suitable sized mesh was prepared by placing preplaced nonabsorbable sutures for

Table 1: Patient demography and hernia characteristics

Sex (male/female)	30/45
Age, mean (years)	52 (35–72)
<i>Type of hernia</i>	
Incisional: 62	
Midline	12
Right paramedian	0
Appendectomy	0
Right subcostal	0
<i>Paraumbilical hernia: 10</i>	
Primary with divarication recti	3
Recurrent	14
Postlap IPOM	3
Umbilical hernia: 3	2
Epigastric: 0	0
BMI, mean	35 (25–45)
Comorbidity	20
Defect size (cm)	4–12
Operating time (min)	60–130
Hospital stay (days)	2–3
Average follow-up (months)	12
Total no. of cases	75 (100%)



Figs 2A and B: Trans fascial preplaced suture fixation and tacker fixation of dual mesh

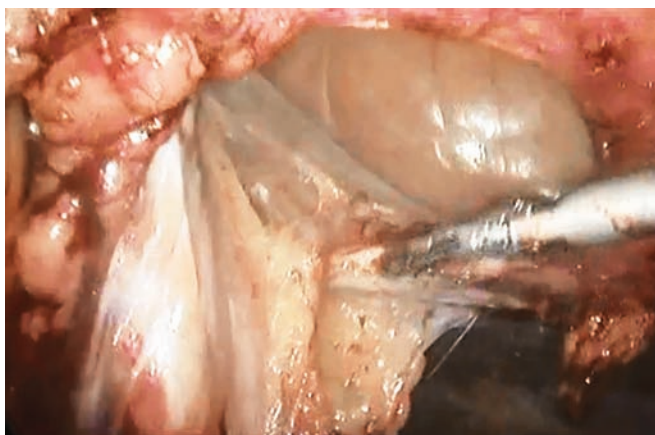


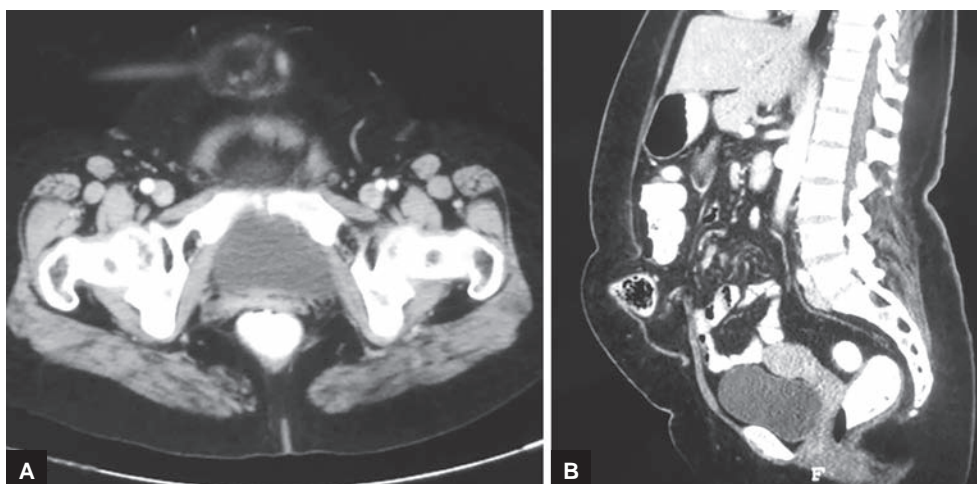
Fig. 3: Adhesiolysis from hernia sac

trans fascial fixation. We routinely used one central and four peripheral sutures of Prolene or Nylon. The largest mesh was 30×20 cm in size and smallest 20×15 cm. In all patients, we used Parietex dual mesh (polyester with collagen-polyethylene glycol-glycerol coating, manufactured by Covidien, Germany). Prepared mesh was rolled and introduced into abdomen through 12 mm port. This was usually the optic port although any port could be

exchanged with 12 mm based on the surgeons' preference. The time was recorded starting from placement of mesh in the abdomen and its final fixation. Initially we used 10 mm scope to pass the rolled mesh but over a period of time 12 mm was found to be less cumbersome to introduce even the biggest mesh easily. The mesh was unrolled inside the abdomen, taking care of the orientation before fixation. Oxidized cellulose side was kept on visceral surface. The preplaced sutures at the periphery and center were pulled out using trans fascial fixation needle (Aesculap, Germany) after very small skin incision. We usually pick the central fixation first as it helps in orientation of a larger sized mesh. These sutures are ligated subcutaneously and require no skin sutures. Mesh is then duly fixed with 5 mm absorbable tackers in two layers (Fig. 4).

RESULTS

In this study, intraoperative blood loss was not significant and there were no conversions to open method. Operative time ranged from 60 to 130 minutes which decreased with time. Mesh fixation after placement required



Figs 4A and B: Axial and sagittal image of infraumbilical incisional hernia

Table 2: Surgical complications

Complications	Number (%)
<i>Intraoperative complications</i>	
Bowel injury	0
Bleeding	0
Difficult dissection	30 (40%)
Conversion to open	0
<i>Postoperative complications</i>	
Hematoma	0
Seroma	2 (2.6%)
Wound infection	1 (1.3%)
Chest infection	1 (1.3%)
Early recurrence	0
Ileus	3 (4%)
Port site Richter's hernia	1 (1.3)
Total cases	75 (100%)

around 30 minutes and variable time was required for adhesiolysis depending upon previous surgeries and adhesions. Umbilical and paraumbilical ventral hernia with minimal adhesions only required 60 minutes of operative time. There were no iatrogenic bowel injuries during procedure. One patient had feeding jejunostomy following a gastrojejunostomy for a benign gastric outlet obstruction. The Weitzel loop of bowel had to be brought down for placement of mesh, which was done successfully after incising a bit of parietal wall. Postoperative heaviness in abdomen and mild pain was the most common complaint. Postoperative ileus developed in three patients which resolved by conservative treatment. Minor wound infection occurred in three patients and one had a seroma (Table 2). One patient developed Richter's hernia through the 12 mm port. She was an obese lady with diabetes, hypertension, and had treatment for non-Hodgkin's lymphoma with multiple abdominal surgeries earlier with failed open mesh repair. This was diagnosed on day 4 and was managed by relaparoscopy and reduction of bowel loop. The defect was fixed transfascially under vision. This rare complication has been published.⁴ The postoperative hospital stay ranged 2 to 3 days. The average follow-up period was 12 months during which no recurrence was observed.

DISCUSSION

Ventral and incisional hernias are common long-term postoperative complications of abdominal surgery and have an incidence of 3 to 20%.⁵ It is more common in females. Early studies to describe laparoscopic repair of incisional hernia was published in 1993 by LeBlanc and Booth.¹ It offers early recovery, decreased hospital stay, minimal morbidity, and very low recurrence. It allows clear identification of multiple hernia defects which could be missed during open hernia repair.⁶ Mesh overlap should be 4 to

5 cm from the edge of defect. Minimal acceptable overlap is 3 cm if transfascial sutures are used.⁷ Adequate overlap promotes tension-free repair and proper closure of the defect. We used minimum mesh overlap of 4 to 5 cm on all sides. This is fixed with transfascial preplaced sutures and absorbable tackers in two layers. This allows proper mesh placement and reduces early folding or dislodgement of the mesh, which may be a cause of recurrence. In principle, laparoscopic repair of ventral hernia utilizes the same concept as open repair popularized by Stoppa,⁸ Rives and Pire,⁹ and Wantz.¹⁰ These include using large mesh prostheses, adequate overlap of hernia defect with tension-free repair. Operating time of laparoscopic ventral repair is longer than open ventral hernia repair, although some authors have reported no difference. Laparoscopic ventral hernia repair may be a challenging procedure with long-standing defects, incarcerated small bowel, morbid obesity, multiple previous repairs, and need for placement of prosthetic mesh but offers significant benefits of less postoperative pain, shorter hospital stay, early return to work, and placement of a large-sized mesh which have been confirmed in various studies. In this study, patients required analgesia on need basis up to 12 hours. Thereafter, only oral nonsteroidal anti-inflammatory drugs were used if needed. They all were mobilized early and tolerated the surgery well. Six patients had minor complications like wound infection, seroma, and ileus. Only one patient had significant problem as postoperative Richter's hernia through the 12 mm defect which was diagnosed and early redo laparoscopy with repair of defect was done successfully.⁴ Mesh shrinkage is greater in the tack group as compared with suture group when used individually. Recurrence of hernia following repair is a problem and is reported variably with the usage of different mesh fixation techniques¹¹⁻¹³ Carbajo et al¹² mentioned a recurrence rate of 4.4% during follow-up period of 44 months, although another study has reported a recurrence rate of 1% during mean follow-up of 27 months.¹³ In our study, there was no major morbidity and no operative mortality. Significantly, in our early experience, there were no major complications except Richter's hernia at port site in one case in immediate postoperative period. We used standardized protocol and similar technique in each case and documented the operative time after adhesiolysis and mesh fixation. Time taken for adhesiolysis was dependent on presence of adhesions of previous surgery or mesh placements. In case of simple umbilical hernias, the operative time was around 60 minutes for the entire procedure. The placement of large-sized prepared mesh was easier through 12 mm port as compared with 10 mm port and we shifted to 12 mm after initial four cases. The mesh handling was better and preserved the collagen layer from being torn,

etc. Parietex dual mesh (Covidien) was used in each case. In our scenario, the cost is important and laparoscopic ventral hernia repair is expensive using costly mesh and fixation device. But the procedure was more patient friendly, with less morbidity, shorter length of hospital stay, limited need of drains, less chance of infection, and overall similar operative time as compared with open surgery. More so, obese patients with medical comorbidities and recurrent hernias did quite well. There was no early recurrence in the average follow-up of 1 year. We routinely applied abdominal binder for 6 weeks following surgery. One patient had excision of redundant skin excision under local anesthesia after umbilical hernia repair. Therefore, laparoscopic repair may be termed as better than open repair.¹⁴ Pooled data analysis of 45 published series, representing 5,340 patients (4,582 laparoscopic, 758 open), demonstrates a significantly lower recurrence rate with laparoscopic ventral hernia repair compared with open ventral hernia repair series.¹⁵ Although recurrence still remains an important problem after laparoscopic ventral hernia repair, it does not exceed 5 to 10% in most of the published reports.^{16,17}

CONCLUSION

In this study, our early experience in 75 patients was that the laparoscopic ventral hernia (laparoscopic IPOM) repair is a safe procedure in most cases with benefits of rapid recovery, less pain, reduced hospital stay, and fewer complications, even in patients with medical comorbidities, and with very low early recurrence.

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Anorectal Surgeries under Local Anesthesia: A Single Center Experience

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ABSTRACT

Introduction: Surgeries done under local anesthesia are associated with fewer perioperative risks and postoperative complications compared to general or spinal anesthesia. This study was contemplated to test the feasibility and efficacy of local anesthesia in anorectal surgeries.

Materials and methods: This study was done in the Department of Surgery, Dayanand Medical College & Hospital, Ludhiana, Punjab, India. A total of 50 patients presenting with anorectal problems, aged more than 16 years and qualifying for grades I and II of American Society of Anesthesia classification, were selected for the study, after informed consent. A cocktail of bupivacaine hydrochloride 0.5%, lidocaine 2%, sodium bicarbonate and adrenaline, was injected around the perianal skin. Intraoperative parameters, such as blood pressure, pulse, respiratory rate, and intensity of pain were recorded in all the patients. Each patient was closely monitored postoperatively for timing and frequency of analgesic dose, need for bladder catheterization, immediate and delayed complications, time needed for patient to be ambulant and length of hospital stay.

Results: The duration of procedures was 19 ± 6 (mean \pm standard deviation) minutes. Patients required analgesic dose after 4.25 ± 1.14 hours, with almost half (48%) requiring it after 6 hours. Majority of patients (82%) were ambulatory within the 1st hour with a meantime of 50 ± 13 minutes. Three cases had complicated postoperative course, with perianal infection and fissure formation.

Conclusion: Local anesthesia is effective and safe for anorectal surgeries, reducing recuperating time and allowing early ambulation. Such day care procedures, requiring lesser monitoring, can emerge as a preferred technique in low-resource settings, considering their cost-effectiveness.

Key words: Anorectal surgeries, Early ambulation, Local anesthesia, Perioperative complications.

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INTRODUCTION

Day care surgery has emerged as an accepted modality for various surgical interventions. The current trend of minimal access surgery should be supplemented by means to decrease cost and to provide early ambulation and timely discharge of the patients.¹ Day care surgery is popular because of its, 4 'A's, i.e., alertness, alimentation, ambulation, and analgesia.² Around 5% of adult population have anorectal diseases.³ Local anesthesia for surgeries of anal canal can provide full relaxation associated with fewer risks and complications compared with general and spinal anesthesia.^{4,5}

MATERIALS AND METHODS

A total of 50 patients presenting with anorectal problems to the Department of Surgery, Dayanand Medical College and Hospital, Ludhiana, Punjab, India, were selected for experiment under local anesthesia. After taking informed consent, patients were assessed and worked up as per protocol for general anesthesia for safety reasons. Patients were counselled about the procedure, the type of anesthesia, amount of pain expected, and the postoperative benefits. This ensured cooperation from these well-motivated patients. Inclusion criteria were patients aged more than 16 years, requiring surgeries for anorectal problems, such as hemorrhoids, anal fissures, fistula, perianal abscess, perianal hematoma, hypertrophied papilla, perianal sinus, rectal polyp, etc., who were American Society of Anesthesia grades I and II and gave consent for surgery under local anesthesia.

Exclusion criteria were patients aged less than 16 years, over-apprehensive, mentally unsound, suffering from highly infectious diseases, morbidly obese or having complications of anal diseases, e.g., obstruction or strangulation of hemorrhoids. Preoperative preparation included keeping patients on clear liquid diet 1 night prior to surgery and nil per oral for 6 hours. All patients were given three tablets of dulcolex orally,

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1 night prior to the surgery. One hour before surgery, an applicator containing 5% lignocaine base ointment was inserted into anal canal, and about 5 gm was squirted inside and the ointment was spread along the anal walls manually. Patient was placed in a jack-knife position, and the buttocks taped apart. For sedation, 2 mg to 3 mg of midazolam hydrochloride (5 mg in a 5 mL solution) was given intravenously. An additional 5 gm dose of lignocaine (5%) ointment was squirted into anal canal and was spread on rectal walls with gloved finger.

During surgery, a cocktail of local anesthesia composed of 10 mL bupivacaine hydrochloride (0.5%) and 10 mL xylocaine (2%), 1 mL soda bicarbonate and 1 mL adrenaline (1:2,00,000) was slowly injected around the perianal skin using a 24-G needle. This was to block the sensation of the anoderm. Right angle retractor was inserted. Wherever necessary, additional 2 mL of local anesthesia was injected directly in the submucosal space on the right and left sides of anal canal to obtain full relaxation of the internal sphincter. This was especially necessary in anal fissure cases in which the extreme internal sphincter spasm had to be overcome. This made the operative field ready for any type of anal surgery. Intraoperative parameters like blood pressure, pulse and respiratory rate, intensity of pain, i.e., mild, moderate, or severe, were closely monitored. Postoperative parameters recorded were: Timing and frequency of analgesic dose requirement, need for bladder catheterization, nausea, vomiting, headache, respiratory complication, time needed for the patient to be ambulant and hospital stay. Intravenous paracetamol was kept for rescue analgesia. Delayed complications like wound infection and hematoma formation were documented.

RESULTS

Among the 50 patients of anorectal diseases selected for surgery under local anesthesia, 44% (22 patients) had anal fistula, 26% (13 patients) had anal fissure, 12% (6 patients) had hemorrhoids, 6% (3 patients) had perianal hematoma, 4% (2 patients) from perianal abscess and 2% (1 patient) each from perianal sinus, hypertrophied papilla and rectal polyp. In 2% (1 patient) cases, anal biopsy was taken for carcinoma anal canal under local anesthesia (Table 1). Approximately 84% (42 patients) experienced no pain and tolerated the procedure very well and 12% (6 patients) complained of mild pain during the procedure. The first prick on the anal verge was painful in these cases. Only 4% (2 patients) who were operated for hemorrhoids had moderate pain, as surgery got prolonged in them (Table 2). The average duration of procedure was 19 ± 6 (mean \pm SD) minutes. Surgery was completed within 20 minutes in 78% (39 patients). In rest of the

Table 1: Number of cases of each anorectal diseases

Diseases	Number of cases	Percentage
Hemorrhoids	6	12.0
Anal fissure	13	26.0
Fistula	22	44.0
Perianal abscess	2	4.0
Perianal hematoma	3	6.0
Hypertrophied papilla	1	2.0
Perianal sinus	1	2.0
Rectal polyp	1	2.0
Biopsy	1	2.0

Table 2: Intensity of pain at the time of surgery

Intensity	Number of cases	Percentage
No pain	42	84
Mild	6	12.0
Moderate	2	4.0
Severe	0	0
Total	50	100.0

Table 3: Duration of procedure

Duration (in minutes)	Number of cases	Percentage
10–20	39	78.0
21–30	11	22.0
31–40	0	0
Total	50	100.0

patients (22%, $n = 11$), the duration of procedure lasted from 21 to 30 minutes (Table 3). The patients required analgesic dose after 4.25 ± 1.14 hours of completion of the procedure. About 46% patients required first dose of analgesic after 2 to 4 hours, 48% after 4 to 6 hours, 4% after 7 to 8 hours. Merely 1 patient required analgesia within 1 to 2 hours after operation (Table 4). Average time required for ambulation after the procedure was 50 ± 13 minutes. Nearly 82% (41 patients) were ambulant within 31 to 60 minutes of completion of procedure, 4% (2 patients) within first 30 minutes, and 14% (7 patients) needed rest of 1 to 1½ hour before mobilization (Table 5). Around 6% (3 patients) had a complicated postoperative course. 4% (2 patients) had postoperative wound infection (Table 6). One of them was a known case of diabetes mellitus with uncontrolled glycemic status, operated for hemorrhoids.

Table 4: Time after completion of procedure when patient required analgesic dose

Time (in hours)	Number of cases	Percentage
<1	0	0
1–2	1	2.0
2–4	23	46.0
4–6	24	48.0
6–8	2	4.0
>8	0	0

Table 5: Time required for ambulation

Time (in minutes)	Number of cases	Percentage
1–30	2	4.0
31–60	41	82.0
61–90	7	14.0
91–120	0	0
120–150	0	0
Total	50	100.0

Table 6: Incidence of postoperative complications

Complication	Number of cases	Percentage
Catheterization	0	0
Nausea/vomiting	0	0
Wound infection/ abscess formation	2 (4%)	4.0 (8%)
Hematoma formation	0	0
Respiratory complications	0	0
Others	0	0

The infection was controlled with good glycemic control and antibiotics. Another case with anal fissure, in which left lateral internal sphincterotomy was done, had abscess formation, for which incision and drainage had to be done. The duration of hospital stay varied from 1 day to 4 days (56% up to 1 day, 22% for 2 days, 20% for 3 days).

DISCUSSION

Ambulatory surgeries account for over 60% of all elective operative procedures performed. Patients benefit from day care surgery as it minimizes cost, decreases separation from their home and family environment, reduces surgery waiting time, decreases their likelihood of hospital acquired infections, and appears to reduce postoperative complications.^{6,7} The conventional spinal or general anesthesia impose restrictions on perioperative oral intake and movement in addition to need for recovery room stay.⁸ This study highlights the benefits of local anesthesia in anorectal surgeries. Local anesthesia proved to be a satisfactory and safe alternative for the surgeon by providing adequate level of anesthesia and relaxation at the operative site, with minimum systemic risks. It was as good for the patient in terms of lesser need for postoperative analgesia and its dosages. It has been demonstrated by experimental studies that local infiltration inhibits build-up of local nociceptive molecules and therefore, there is better pain control in postoperative period. The pain incidence in the present study (No pain -84%, mild -12%, moderate -4%, severe -0%) was slightly more as compared to study by Henriques et al⁹ where 96.7% patients experienced no pain at all. The results of the present study were better than those reported by Sobrado et al.¹⁰ who have reported severe pain in 16.1% cases out of 351 patients studied, and Selvasekar et al,¹¹ who reported pain

in 47% cases operated for grades II and III symptomatic hemorrhoids, under local anesthesia. Spinal and general anesthesia is known to have complications like hypotension, headache, backache, meningitis, sore throat, nausea, vomiting, urinary retention etc. Local anesthesia is safe as it has minimal systemic effects. It is slowly absorbed and whatever is absorbed into the systemic circulation is metabolized. With the dose of xylocaine and bupivacaine used in this study, they are unlikely to reach the toxic levels in the systemic circulation. Vital signs of all the study patients, i.e., pulse rate, blood pressure, and respiratory rate did not show any remarkable change in the perioperative period. No hypersensitivity or systemic adverse effects occurred in any of the patients and no one had complications like nausea, vomiting, headache, urinary retention etc. Local anesthesia could be comfortably given to patients who were poor risk cases for general or spinal anesthesia and it proved to be a safe alternative in patients with cardiorespiratory disease. Five patients, in the present study, who had cardiovascular comorbidities, were safely and successfully operated under local anesthesia without any complications. The technique of administration of local anesthesia is easy to learn and can be mastered easily as compared to spinal anesthesia. There was no intraoperative excessive bleed or postoperative hematoma formation suggesting no increased bleeding tendencies during procedures under local anesthesia. Average time required for ambulation after the procedure was 50 ± 13 minutes. Majority of the patients (86%) were ambulatory within 60 minutes and all within 90 minutes with very little discomfort while walking, mainly due to anal packing, however few of them required support while walking. Almost all patients were initiated on oral diet within 1 hour of the surgery as there was no postoperative nausea or vomiting. In a study by Read et al,¹² recovery time for patients undergoing anorectal surgery under local anesthesia with intravenous sedation was 79 ± 34 minutes. The incidence of complication was 4%, which consisted of nausea, vomiting, transient hypotension, bradycardia or arrhythmia, hypoxia or hypoventilation, urinary retention or severe patient discomfort.¹² No such complication were observed in the present study, the recovery time was 50 ± 13 minutes and 56% patients were discharged on the same day. The wound infection seen in some patients could be due to the inherent diseases (diabetes) and inadvertent fecal contamination, the risk of which remains in all perianal surgical.

This study, however, is not without limitations. The study group could not be compared head-on to a contemporary (spinal/general) anesthesia group. The parameters, such as pain are subjective and can lead to reporting bias. For doing anorectal surgery under local anesthesia, it is not only the technique of administration

of anesthesia which matters, but also the ability of surgeon to operate gently.

Local anesthesia eliminates the need for prolonged hospitalization, thus minimizing lifestyle disturbances and giving the patient a psychological benefit. If the patient can be discharged from the hospital early, it helps to reduce the load on the packed surgical wards. It decreases the surgeons' dependence on the anesthesiologists, making it possible for them to do such procedures in peripheral hospital where the services of trained anesthesiologists are not always available. The procedures are also comparatively economical with feasibility even in poor infrastructure settings. Thus, local anesthesia for anorectal surgery is effective and useful alternative to contemporary modes of anesthesia for doctors and patients and it should be included in surgical training of residents.

CONCLUSION

Local anesthesia is effective and safe in anorectal surgeries. The benefit of early alimentation and ambulation enhances patients' satisfaction. This technique can prove to be a boon for developing countries, like ours, minimizing the cost and infrastructural burden.

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Role of Y Chromosome Microdeletions in the Clinical Evaluation of Infertile Males

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ABSTRACT

Infertility is a multifaceted condition, which is on the rise in the last few decades. A stage of great importance in the development of human male gametes is spermatogenesis, which is governed by a set of genes located on the q arm of the Y chromosome. Loss of these genes can cause disruptions in spermatogenesis and, thus, lead to male infertility. Studies have identified several deletions on the long arm of the Y chromosome, called Yq microdeletions, which occur in three distinct loci termed AZFa, AZFb, and AZFc. In addition to these, there exist small subdeletions in the AZFc locus, called gr/gr, b1/b2, or b2/b3 subdeletions. Such deletions can lead to azoospermia or oligozoospermia by causing Sertoli cell-only syndrome, impairment in spermatogenesis, or maturation arrest. Testing for Y chromosome microdeletions is clinically significant for several reasons, since these deletions are exclusively associated with male infertility and their detection can help identify the cause of infertility. Knowing the presence or absence of Y chromosome microdeletion also aids in predicting the prognosis of oligozoospermic males, who are usually known to progress to azoospermia over time. The occurrence and type of Yq microdeletion are correlated with testicular phenotype in infertile males and, thus, serve as a good predictor of sperm retrieval. Vertical transmission of Y chromosome microdeletions from father to the male offspring is common in pregnancies achieved via assisted reproductive technologies; hence, the diagnosis of these deletions becomes imperative in such couples to prevent perpetuation of infertility in the next generation. Screening for Yq microdeletions is, thus, clinically significant and must be offered to all infertile males.

Keywords: Azoospermia, Male infertility, Microdeletions, Sperm count, Y chromosome.

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INTRODUCTION

The term infertility can be defined as the inability to bear offspring which brings a sense of failure to many

couples. The World Health Organization defines infertility as “the inability of a couple to conceive within two years of exposure to the risk of pregnancy.” About 48 million couples worldwide suffer from infertility,¹ while reports from India suggest that approximately 33 million couples of reproductive age face infertility.² Clinical analysis of infertile couples show that in nearly 40% of cases, the defects occur in the male partner, in another 40%, the defects occur in the female partner, while in the remaining 20% cases, the cause of infertility is unknown.³ These observations have given rise to a clinical condition known as male infertility.

Male Infertility

Male infertility refers to the inability of the male partner to cause pregnancy in a clinically normal female. However, the incidence of male infertility is not well reported, especially in countries where cultural differences and patriarchal societies preclude accurate statistics from being assembled. A recent literature survey suggests that almost 30 million males worldwide are infertile, with the largest niches of male infertility occurring in Central and Eastern Europe (8–12%) and Australia (8–9%).⁴ Male infertility can be clinically addressed as the following conditions:

- Azoospermia – Absence of sperm in the ejaculate
- Oligozoospermia – Less than 15×10^6 spermatozoa in the ejaculate
- Severe oligozoospermia – Less than 5×10^6 spermatozoa in the ejaculate
- Normozoospermia – Normal values of sperms in the ejaculate
- Asthenozoospermia – Low levels of motility observed in less than 50% of sperms
- Teratozoospermia – Less than 30% of sperms have normal morphology
- Aspermia – Failure in ejaculating semen^{5,6}

Male infertility can be classified as non-idiopathic (cause of infertility is known) or idiopathic (cause of infertility is unknown) in nature. Some known causes of male infertility include cryptorchidism (absence of one or both testes in the scrotum), varicocele (abnormal enlargement of the pampiniform venous plexus in the scrotum), hormonal imbalances, alcohol consumption, and chemotherapy.⁷ However, in most cases, the cause of male infertility remains unknown and, in such cases,

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genetic causes are believed to be potential candidates responsible for the infertility. Some of the genetic defects observed in infertile males are karyotypic abnormalities, gene copy number variations, single gene mutations, and polymorphisms or deletions on the long arm of the Y chromosome (Y chromosome microdeletions or Yq microdeletions).⁶ All these genetic defects interfere with the development of the male gonads, the urogenital tract, arrest of germ cell production and maturation, or lead to the production of nonfunctional spermatozoa.⁸ Among the various genetic factors, karyotypic abnormalities and Yq microdeletions are the leading causes of male infertility. The Yq microdeletions are submicroscopic deletions of the Y chromosome that are undetectable on routine karyotype analysis. These microdeletions have been recognized as a cause of male infertility, and their presence has been noted in azoospermic males, while males with a normal spermiogram have shown absence of these microdeletions. In this review, we shall focus on the Yq microdeletions and how they cause male infertility.

In order to comprehend how Y chromosome microdeletions cause male infertility, it is essential to understand the structure of the human Y chromosome and the different genes that are found on it.

Y Chromosome Structure

The human Y chromosome is found only in males, haploid in nature, and does not undergo meiotic recombination. As compared with the other chromosomes, the Y chromosome is one of the smallest chromosomes [~ 60 million base pairs (Mb)], representing around 2 to 3% of a haploid genome. This chromosome is gene sparse with more than 50% of its sequence comprising of repeat elements.⁹ However, the human Y chromosome plays a focal role in testicular development and male infertility. Cytogenetically, there are three distinct regions of the Y chromosome (Fig. 1), which include:

1. Two pseudoautosomal regions (PAR1 and PAR2),
2. Heterochromatic region, and
3. Euchromatic region.

The PAR1 is located at the terminal region of the short arm (Yp) and the PAR2 at the tip of the long arm (Yq). These regions are called PARs because they behave like autosomes during meiosis. The PARs are regions where the Y chromosome pairs and exchanges genetic material with the PAR of the X chromosome. The genes present within the PAR are inherited in the same manner as autosomal genes. The PAR1 and PAR2 represent only 5% of the entire Y chromosome. The remaining 95% of the Y chromosome comprises the so-called "non-recombining Y" (NRY), which includes the euchromatic and heterochromatic regions of the chromosome.¹⁰ The heterochromatic region comprises the distal Yq, a region assumed to be genetically inactive and polymorphic in length in different male populations. It is composed primarily of two highly repetitive sequences families, DYZ1 and DYZ2, containing about 5,000 and 2,000 copies of each respectively.¹⁰

The euchromatic region lies distal to the PAR1, and consists of the short-arm paracentromeric region, the centromere, and the long arm paracentromeric region (Fig. 1). The euchromatic NRY region does not recombine with the X chromosome, and, hence, it is called the non-recombining region. The NRY sequences contain 8 Mb of Yp and 14.5 Mb of Yq. These sequences are subdivided into three discrete classes: X-transposed, X-degenerate, and ampliconic. The ampliconic sequences are characterized by eight massive palindromes, six of which contain testis-specific protein-coding genes.¹¹ Compared with the autosomes, the NRY has a limited number of genes. Approximately 115 genes have been mapped to the Y chromosome, of which 43 genes have been identified on the short p arm of the Y chromosome. Some of the genes on this arm include *SRY* (sex-determining region Y), *ZFY* (zinc-finger Y), and *AMELY* (amelogenin Y).

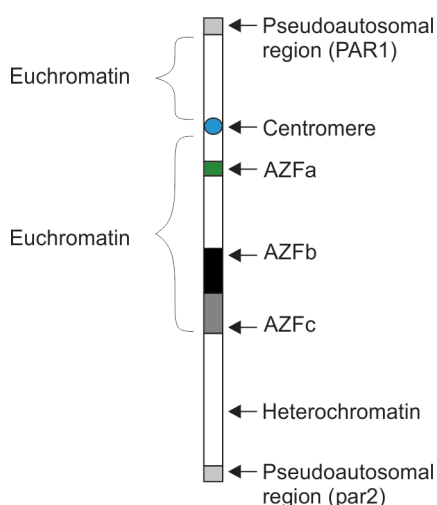


Fig. 1: Gene regions on the Y chromosome

Genes on the Short Arm of the Y Chromosome (Yp)

The *SRY*, the mammalian Y chromosomal testis-determining gene, is located adjacent to PAR1, and is composed of a single exon, which encodes a protein of 204 amino acids. This gene is essential for initiating testis development and differentiation of the bipotential gonad into the testicular pathway. The *SRY* has been proposed to be the master gene regulating the cascade of testis determination.¹² The *ZFY* encodes a zinc finger-containing protein that functions as a transcription factor. The binding of *ZFY* to deoxyribonucleic acid (DNA) is mediated by the interaction of the GGCC core base pairs with zinc fingers 12 and 13. A significant paralog of this gene is *ZFX* and

amplification of this gene is often used to determine the sex of DNA samples.¹⁰ The *AMELY* encodes a member of the amelogenin family of extracellular matrix proteins. Amelogenins are involved in biomineralization during tooth enamel development. This gene also has a paralog on the X chromosome, *AMELX*.¹³

Genes on the Long Arm of the Y Chromosome (Yq)

The long arm of the Y chromosome (q arm) contains several genes implicated in spermatogenesis. Some of these genes include *USP9Y* (ubiquitin-specific protease, Y), *DBY* (DEAD box, Y), *UTY* (ubiquitously transcribed tetratricopeptide repeat gene, Y-linked), *CDY* (chromodomain, Y), *RBMV* (ribonucleic acid [RNA]-binding motif, Y), *EIF1AY* (translation initiation factor1A, Y), and *DAZ* (deleted in azoospermia). Many studies have demonstrated that deletions in these genes often lead to male infertility.

The first correlation between spermatogenic failure and an underlying genetic cause was demonstrated by Tiepolo and Zuffardi.¹⁴ These Italian researchers studied the Y chromosome of several azoospermic males and observed microscopically detectable deletions at the distal section of band q11 of the Y chromosome in six males. Based on this observation, the authors for the very first time suggested the role of the Y chromosome in spermatogenesis. The authors also proposed the existence of a spermatogenesis factor, called the "azoospermia factor" (AZF) encoded by a gene on distal Yq. Following this report, a map of the Y chromosome was created by Vergnaud et al¹⁵ in 1986, using 23 Y-specific restriction fragments. Later studies confirmed the location of AZF in Yq11.¹⁶⁻¹⁸

With the advent of molecular biology tools, Vollrath et al¹⁹ created a deletion map of the human Y chromosome by testing 96 individuals with partial Y chromosomes for the presence or absence of many DNA loci. Their studies resolved the euchromatic region (short arm, centromere, and proximal long arm) of the Y chromosome into 43 ordered intervals, defined by naturally occurring chromosomal breakpoints and averaging less than 800 kilo base pairs (kb) in length. A later study by Vogt et al²⁰ proposed the presence of not one, but three spermatogenesis loci in Yq11, with each locus being active during a different phase of male germ cell development. This group observed that Y chromosome microdeletions occurring in infertile males followed a certain deletion pattern, with three recurrently deleted nonoverlapping subregions in proximal, middle, and distal Yq11. The three loci were designated "AZFa," "AZFb," and "AZFc" respectively.

AZFa Locus and its Genes

The AZFa subregion spans about 800 kb and encodes single-copy genes, which are essential for normal

spermatogenesis. Candidate genes of spermatogenesis in the AZFa locus include *USP9Y* (ubiquitin-specific peptidase 9, Y-linked), *DBY*, and *UTY*.¹³ The *USP9Y* was the first gene to be identified in the AZFa region. This gene was previously known as *DDFRY* (*Drosophila* fat facets-related Y). It consists of 46 exons and spans 159 kb of genomic DNA. It encodes an ubiquitin-specific protease and belongs to the peptidase C19 family.²¹ The *USP9Y* is not a testis-specific gene, but is expressed in multiple tissues because its homologous gene on the X-chromosome can escape X-inactivation.²²

The *UTY* encodes a protein-containing tetra-tricopeptide repeats, which are thought to be involved in protein-protein interactions. The encoded protein is also a minor histocompatibility antigen, which may prompt graft rejection of male stem cell grafts. This gene encodes a large number of alternatively spliced transcripts; however, the full-length nature of some of these variants has not been determined.¹³ The *DBY* is made up of 17 exons, which encode a putative ATP-dependent RNA helicase belonging to the DEAD box proteins. Deletion of AZFa is known to be a major cause for the occurrence of a severe testicular pathology, the Sertoli cell-only syndrome (SCOS).¹⁰

AZFb Locus and its Genes

The AZFb locus is located in the central region of Yq11 and overlaps with the AZFc region by 1.5 Mb. The AZFb region contains several single-copy genes as well as multicopy gene families. Single-copy protein-coding genes found within the AZFb include *KDM5D* (lysine-specific demethylase 5D), *EIF1AY*, and *CYORF15* (chromosome Y open reading frame 15A and 15B). The AZFb region also contains a set of seven multicopy gene families: *XKRY* (XK, Kell blood group complex subunit-related, Y-linked), *HSFY* (heat shock transcription factor, Y-linked), *RBMV*, *PRY* (PTPN13-like, Y-linked), *CDY*, *BPY2* (basic protein Y2, Y-linked), and *DAZ*. Twenty members from these gene families are located in AZFb, but several genes also occur on the AZFc region.²³

The *RBMV* proteins are characterized as having an auxiliary C-terminal domain containing four 37 amino acid repeats and a single RNA-binding domain.¹³ The *RBMV* is a multicopy gene, but its role in human spermatogenesis is challenging to prove because no damaging mutations have been identified in it. In the testis, *RBMV* is expressed in spermatogonia, spermatocytes, pachytene cells, and spermatids.^{24,25} Beyond the germ cells, *RBMV* has also been detected in the tail of human spermatozoa. Furthermore, an antibody against human *RBMV* has been found to block sperm motility, implying that this protein may be involved in motility.²⁵ The *EIF1AY* encodes an abundantly expressed translation initiation factor, Y isoform of eIF-1A. The *EIF1AY* is involved in translation initiation.¹³

AZFc Locus and its Genes

The AZFc locus codes for 21 candidate genes and 11 families of transcription units that are exclusively expressed in the testis.²³ This locus is palindromic and repetitive in nature, and, hence, highly susceptible to intrachromosomal rearrangements during meiotic recombination. This is why the AZFc locus is prone to deletions, duplications, and copy number variations of the eight gene families that are harbored within it.²⁶ Some of the genes belonging to the AZFc locus include *DAZ* (deleted in Azoospermia), *GOLGA2LY* (Golgi autoantigen, golgin subfamily A, 2-like, Y-linked), *TTY4* (testis-specific transcript, Y-linked 4), *CSPG4LY* (chondroitin sulfate proteoglycan 4 pseudogene, Y-linked) *CDY1* (chromodomain protein, Y-linked, 1), *BPY2* (basic charge, Y-linked, 2), and *TTY3* (testis-specific transcript, Y-linked 3).²⁶

Among these genes, the *DAZ* gene is thought to be decisive in determining male infertility by playing an important role in spermatogenesis.²⁶ The *DAZ* gene is vital in stimulating germ cell progression to meiosis and has four functional copies in the AZFc locus (*DAZ1*, *DAZ2*, *DAZ3*, and *DAZ4*) that encode for a RNA-binding protein. Each of the four copies is highly polymorphic and expressed in the testis. The human *DAZ* proteins carry out transportation, translational activation of developmentally regulated transcripts and their storage.²⁷ Infertile males showing a loss of individual copies of *DAZ* genes are highly predisposed to azoospermia or severe oligozoospermia.²⁸⁻³⁰

The *GOLGA2LY* gene is present in two copies (*GOLGA2P2Y* and *GOLGA2P3Y*) on the AZFc locus. This gene is believed to encode a protein consisting of 108 amino acids, which is transcribed in the testis. No function has been attributed to *GOLGA2LY*; however, males harboring *GOLGA2P3Y* deletion display decreased sperm concentration and motility compared with males without deletion or with deletion of *GOLGA2P2Y*, thus suggesting the role of this gene in spermatogenesis.³¹

The *BPY2* gene, which lies in the AZFc region, encodes for a highly charged protein, which is testis specific and is involved in cytoskeletal regulation in spermatogenesis. The *BPY2A*, *BPY2B*, and *BPY2C* are the three copies of *BPY2*. The *BPY2* is present in the nuclei of spermatocytes, round spermatids, and spermatogonia. The function of *BPY2* is yet to be established, but reports indicate it interacts with *UBE3A*, a ubiquitin protein ligase E3A.³² As *UBE3A* is expressed in the testis, it can be said that *BPY2* is involved in modulating target specificity of *UBE3A*.¹³ The *TTY4* gene has three copies, *TTY4A*, *TTY4B*, and *TTY4C*. This gene has not been studied in detail, and is considered to be RNA that does not encode any protein. The *TTY3* is also a nonprotein coding RNA and has two

copies. The *CSPG4LY* gene also has two copies and is regarded as a pseudogene.³²

The *CDY1* gene exists in two copies (*CDY1a* and *CDY1b*) in the AZFc locus and encodes for chromodomain protein 1. The *CDY* proteins have two functional motifs namely a C-terminal domain that has CoA-dependent acetyl transferase activity and N terminal chromatin-binding domain (chromo domain), which aid in regulation of gene expression and chromatin remodeling. Deletions of *CDY1* gene copies are also linked to infertility.³⁰

Yq Microdeletions

Studies involving molecular analysis and sequencing of the Y chromosome long arm have revealed eight large palindromic regions containing an array of different ampliconic sequences.^{9,26} Homologous recombination between any of these eight palindromic sequences leads to occurrence of Y chromosome microdeletions.³³ The Yq microdeletions are defined as chromosomal deletions that span several genes, but are not large enough to be detected using conventional cytogenetic methods. They can be visualized only by sequence-tagged site (STS)-polymerase chain reaction (PCR) or Southern hybridization. Each of the three AZF regions located within the long arm of the Y chromosome contains several genes that play a role in different stages of spermatogenesis. It is known that only the AZFa and AZFb regions are needed to initiate spermatogenesis, but that without the AZFc region, spermatogenesis will not be completely normal. Deletions of AZFa lead to the complete depletion of germ cells and that of AZFb result in spermatogenic arrest, but both these deletions are less frequent. Deletions in the AZFc region are more frequent accounting for up to 90% of all Yq deletions with phenotypes varying from azoospermia to severe oligospermia. Complete deletions of the AZFc region may occur in two different ways: either as a result of a previous deletion within the AZFc or spontaneously from a normal AZFc region. Thus, microdeletions in the AZF regions of the Y chromosome are recognized to play an important role in determining male fertility, although the exact genotype-phenotype relationship of microdeletions and infertility in the AZF locus have not been fully explored.

gr/gr Subdeletions

The AZFc region is particularly susceptible to deletions because its structure is majorly composed of amplicons.²⁶ Studies using DNA sequence alignments within the AZFc region of the Y chromosome have revealed the presence of smaller deletions called subdeletions in this region brought about by intrachromosomal recombination in

this AZF region. Detailed analysis of the AZFc region using molecular markers has confirmed the existence of three such subdeletions termed as gr/gr, b1/b3, and b2/b3.^{21,34} These subdeletions lead to loss of one or more copies of genes within the AZFc and produce a plethora of phenotypes, ranging from mild oligozoospermia to azoospermia.

The most prevalent subdeletion, gr/gr, is caused by recombination, resulting in the loss of two of the four copies of the *DAZ* gene and one of three copies of the *BPY2* gene.²¹ The outcome of b2/b3 and b1/b3 deletions is similar, leading to the retention of two *DAZ* gene copies and one or two *BPY2* gene copies. Several studies have associated this deletion as a risk factor for the loss of spermatogenesis,^{30,35,36} while others have failed to find a correlation.³⁷ A study in the Han population in China reported that duplication of the gr/gr region is detrimental to fertility, further contributing to uncertainty about the role that this region plays in determining a male's fertility status.³⁸

Prevalence of Y Chromosome Microdeletions

According to the present knowledge, the following recurrent microdeletions of the Y chromosome are clinically relevant, and are found in men with severe oligo or azoospermia: AZFa, AZFb (P5/proximal P1), AZFbc (P5/distal P1 or P4/distal P1), and AZFc (b2/b4). The most-frequent deletion type is the AZFc region deletion (~80%) followed by AZFa (0.5–4%), AZFb (1–5%), and AZFbc (1–3%) deletion. Deletions, which are detected as AZFabc are most likely related to abnormal karyotype, such as 46,XX male or iso(Y).¹¹

Approximately 25 to 55% of males with severe testicular pathologies, such as hypospermatogenesis, sperm maturation arrest, and SCOS and 5 to 25% males with severe oligozoospermia or azoospermia harbor Y chromosome microdeletions, making them the most common known genetic cause of spermatogenic failure.³⁶

There is wide variation in the prevalence of Y chromosome microdeletions world over. A report from the Middle East indicates a high prevalence of Y chromosome microdeletions (7.5%),³⁹ and a study from Iran in azoospermic infertile males has reported a prevalence of 12%.⁴⁰ A South American study has identified classical AZF microdeletions in 5.75% of Chilean patients with spermatogenic failure.⁴¹ Similarly, Pina-Neto et al⁴² have reported a prevalence rate of 7.5% in Brazilian infertile males, who seek assisted reproduction aid. A recent meta-analysis by Filho et al⁴³ from Brazil revealed that 10.8% of infertile males showed presence of Y chromosome microdeletions. The overall prevalence of Y chromosome microdeletions in Korean infertile males was found to

be 7.7%.⁴⁴ While the frequency of AZF microdeletions was found to be significantly higher (11.75%) in a group of Chinese azoospermic males compared with severe oligospermic males (8.51%) in a study by Fu et al.⁴⁵ Y chromosome microdeletions have also been identified in almost 15.6% infertile Serbian males,⁴⁶ while a group from Italy found that the prevalence of microdeletions was 3.2% in unselected infertile males, 8.3% in males with nonobstructive azoospermia, and 5.5% in males with severe oligozoospermia.⁴⁷

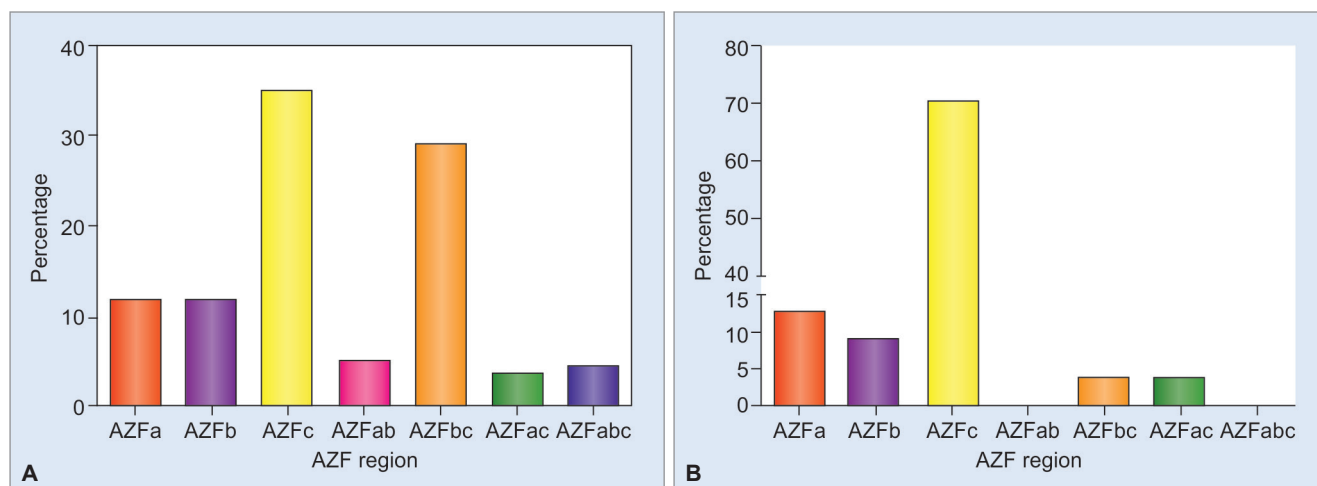
Prevalence of Yq Microdeletions in India

Studies from India have also reported a wide variation in the prevalence of Yq microdeletions in infertile males. A study by Abid et al⁴⁸ in 200 males found a low prevalence of Y chromosome microdeletions (3%), while a study by Suganthi et al⁴⁹ reported a higher microdeletion frequency of 36% when they examined South Indian infertile males. A more recent study by Mascarenhas et al¹ noted that 8.3% of azoospermic males and 2.3% oligozoospermic males showed the presence of Y chromosome microdeletions. An extensive meta-analysis of the data available on the prevalence of Yq microdeletions in the Indian population by Sen et al⁶ revealed a prevalence rate of 5.8%). On segregating these data based on the type of AZF deletion and sperm count, it was observed that the AZFc microdeletion frequency is about 35% in azoospermic males (Graph 1A) and 70% in oligozoospermic males (Graph 1B).

It has been noted that the prevalence of Y chromosome microdeletions varies with geographical locations, the highest occurring among South Indian males and the lowest among Northern and Western parts of India. This suggests that ethnicity might also influence the prevalence of Y chromosome microdeletions.⁶ Sen et al⁶ have reported that the occurrence of Y chromosome microdeletions in Indian males with Klinefelter's syndrome, varicocele, and cryptorchidism is not a rare phenomenon. These findings suggest that in the Indian population, clinically, it is necessary to offer Y chromosome microdeletion testing to all the classes of infertile males. As such, no clinical prediction regarding microdeletions is obtained from phenotypical parameters, such as testicular volume, mal-descended testis, hormone levels, infections, and varicocele, hence, making screening for Y chromosome microdeletions imperative for diagnosis of the right cause of male infertility in India.

Prevalence of gr/gr Subdeletions

Studies by Repping et al²¹ have shown that the gr/gr deletions do not completely abolish any testis-specific gene family, but decrease the copy number of gene



Graphs 1A and B: Variation of AZF deletion type in (A) azoospermia; and (B) oligozoospermia

families on the Y-chromosome. They also noted that the dosage of one or more of these families affected the quality of sperm produced. Hence, the semen picture in gr/gr deletions may vary from azoospermia to normozoospermia with differences depending on ethnicity and geography. Several studies have reported different frequencies of gr/gr deletions. A number of studies have reported a significant association between the gr/gr deletions and spermatogenic failure;^{50,51} however, other studies suggest the absence of such an association.^{52,53} The Y haplotype is one of the factors contributing to such discrepancies. Other partial deletions (b2/b3 and b1/b3) in the AZFc region are rare and, hence, have been studied less often. A study by Rozen et al³⁵ has established that the b1/b3 deletion increased the risk of severe spermatogenic failure, while the b2/b3 deletions did not appear to be a risk factor for severe spermatogenic failure. They also found that the b2/b4 deletions increased the risk of severe spermatogenic failure 145 times. The gr/gr deletions have been found to be extremely common in Japanese males.⁵⁴

Although the gr/gr subdeletions are more common in infertile males, they have also been detected in fertile individuals. Extensive molecular analysis of males with AZFc subdeletions suggests that copy number variations or loss of copies of the *DAZ* gene, *CDY1* gene, or the *GOLGA* genes increases the susceptibility for gr/gr deletions toward infertility.^{30,31}

Prevalence of gr/gr Subdeletions in the Indian Population

Till date, three studies have been reported regarding the presence of gr/gr deletions in the Indian population. In a case-control study, Shahid et al²⁹ identified the presence of gr/gr, b1/b3, and b2/b3 subdeletions in azoospermic males as well as in oligospermic males (7.17%). Interestingly, they also identified presence of

gr/gr deletions in normozoospermic males (2.9%). This group noted that deletions of *DAZ* genes could contribute differently toward the impairment of the spermatogenic process resulting in spermatogenic arrest, oligospermia, or SCOS.²⁹ A study from our laboratory has found that the frequency of gr/gr is higher in oligozoospermic (10.5%) and azoospermic (11.6%) males as compared with controls (5.1%).³⁰ Another Indian study found the frequency of gr/gr deletions was the highest (5.84%) and were significantly associated with male infertility ($p = 0.0004$).³⁶

Diagnosis of Y Chromosome Microdeletions

Initially, deletions on the Y chromosomes of infertile men were detected using karyotype analysis.¹⁴ However, Y chromosome microdeletions were found to be strenuous to be detected by standard karyotype evaluation and here the PCR using STS markers technique was found to be a more feasible approach. The Y chromosome has been reported to contain around 300 STS that occur in the different AZF regions. These STS can be exploited for easier characterization of microdeletions. Many studies have demonstrated the utility of adopting this strategy by developing a targeted multiplex PCR using STS specific to their populations.⁵⁵⁻⁵⁷ Multiplex PCR offers the advantage of detecting numerous STS sites in one reaction. Presently, the STS PCR-based technique is widely accepted for detection of Y chromosome microdeletions. The European Molecular Genetics Quality Network recommends the use of six STS markers (sY84 and sY86 for AZFa, sY127 and sY134 for AZFb, and sY254 and sY255 for AZFc microdeletions) that are considered most robust, nonpolymorphic, and specific, that correctly identify the infertility causing microdeletions in more than 99% of cases with no false negativity. These six STS markers have been extensively utilized internationally for Yq microdeletion testing in various clinical settings. However, there

have been growing concerns regarding the clinical use of only these six recommended markers considering the heterogeneity in the Yq sequences in different populations. Sen et al⁶ have shown that in the Indian setting, the six European Molecular Genetics Quality Network markers are not adequate to detect Y chromosome microdeletions, and have proposed a 13-marker panel for the same. This panel may be used for detection of the Y chromosome microdeletions in Indian males.

Clinical Implications of Yq Microdeletions

Although there is universal agreement on the need for chromosome analysis by karyotyping in the workup of male infertility, there is still a lack of consensus regarding the clinical utility of testing for Y chromosome microdeletions in azoospermic and oligozoospermic males. While the American Society of Reproductive Medicine recommends the use of both, karyotyping and Y chromosome microdeletion studies, in males preparing to undergo intracytoplasmic sperm injection (ICSI), the National Institute for Health and Care Excellence recommends only karyotyping for this group of patients.¹ There is no such consensus in India for the same.

Screening for Y chromosome microdeletions has several clinical implications:

- *Identifying the main cause of infertility:* The Y chromosome contains several genes required for spermatogenesis and the loss of one or more of such genes can cause impairment of spermatogenesis. By investigating Y chromosome microdeletions in the male partner, we can determine the underlying genetic etiology of male factor infertility. It will also help clinicians to provide more effective solutions for problems faced by infertile couples. For example, low sperm count and motility can be treated with hormones, antioxidants, and lifestyle changes to improve the seminogram.⁵⁸ However, these strategies of treatment will fail if the cause of infertility is genetic. Therefore, if the male partner is detected with a deletion, the couple can directly be offered assisted reproductive techniques (ARTs) and not be subjected to medical treatments to improve sperm count and motility.
- *Predicting the prognosis of infertile males:* It is known that oligozoospermic individuals harboring Y chromosome microdeletions progress to azoospermia over time. These males require being clinically followed up for their possible progression to azoospermia, genetically counseled, and updated regarding sperm cryopreservation for fertility options using ART in the future.
- *Predicting outcome of testicular sperm aspiration (TESA):* Most males with Y chromosome microdeletions would be infertile and have absence of or very few sperms in ejaculate. To achieve pregnancy, sperm can be retrieved directly from the testes using techniques like testicular sperm extraction (TESE) or TESA. These sperms can be used for ICSI, thus circumventing underlying spermatogenetic defects. The occurrence and type of Yq microdeletion have been found to correlate with testicular phenotype. Studies by Dada et al⁵⁹ have identified infertile males showing AZFa and AZFb deletions with a corresponding testicular cytopathology of presence of Sertoli cells and the complete absence of germ cells. Other infertile males investigated in this study showed the presence of AZFc microdeletions with a phenotype of hypospermatogenesis and secondary spermatocyte maturation arrest, indicating that sperm may still be successfully retrieved using such procedures. Hence, screening for Y chromosome microdeletions before undertaking invasive procedures, such as TESE/TESA can be used as a good predictor of sperm retrieval using such techniques.
- *Predicting the success of ART:* Since most males harboring Y chromosome microdeletions would be infertile, they would be offered ART for achieving biological parenthood. Technologies, such as ART-ICSI allow males with suboptimal sperm quality to overcome natural selection mechanisms and produce a viable zygote. However, it is clinically relevant to know what possible outcomes the couples might express post-ART. Several studies reporting about ICSI performed in couples with male partners carrying AZFc deletions describe lower fertilization rate, poor embryo quality, a significantly impaired blastocyst rate,⁶⁰ and lower overall success of the procedure.⁵² Hence, Yq microdeletion screening would aid in counseling couples regarding the probability of success rates after taking up ART.
- *Prevention of vertical transmission of the genetic defects:* The ART, like *in vitro* fertilization and ICSI, bypasses all the natural mechanisms and checkpoints related to normal fertilization. Thus, males carrying Y chromosome microdeletions perpetuate infertility in the next generation owing to 100% transmission of the genetic defect to the male offspring from the fathers. A study by Kleiman et al⁶¹ reported how an AZFc microdeletion was transmitted in three generations of males, some of whom were born after ICSI. Although other reports indicate that most children conceived through ART seem normal, a slight increase in the prevalence of aneuploidy in the sex chromosomes of children born via ICSI (from 0.2 to 0.6%) and an increase in autosomal chromosome abnormalities (from 0.07 to 0.4%) have been reported.⁶² However,

these data are difficult to interpret because patients who use ICSI or other ARTs have a higher incidence of abnormalities due to their infertile status. Due to these reasons, Y chromosome microdeletion testing is highly recommended for all infertile males who opt for ICSI for biological parenthood. The patients can then be appropriately counseled and well informed before offering ART.

CONCLUSION

Infertility attributable to male factors is on the rise and constitutes 30 to 40% of cases of infertility. Studies have shown that AZF microdeletions occurring on the Y chromosome are a common cause of male infertility and occur in males with azoospermia and severe oligozoospermia. Screening for these microdeletions has several advantages, such as identifying the root cause of infertility, managing its treatment, predicting the outcomes of ARTs and invasive techniques like TESE and TESA.

The AZF microdeletions are vertically transmitted to offspring born using ART-ICSI, thus perpetuating infertility among generations. This information emphasizes the need to offer elaborate genetic counseling to infertile couples who wish to undertake the procedure. In the Indian scenario, screening of Yq microdeletions should not be merely an academic exercise, but should be offered to all cases of infertile males in a clinical setup in order to prevent the transmission of these small interstitial deletions to the male progeny and predict the embryo quality. Further research should be carried out to investigate the long-term impact on the children born to fathers who have adopted ART. Using this knowledge, clinicians will be able to treat infertile patients optimally and make knowledgeable decisions about the use of ART.

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Photoplethysmography and Its Clinical Application

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ABSTRACT

Photoplethysmography (PPG), introduced in 1937, is routinely used for monitoring heart rate, blood perfusion and oxygen saturation of the blood in the intensive care units for the past several decades. It is also being used for the assessment of peripheral blood flow and venous filling time in noninvasive vascular laboratories. It works on the principle of light/infrared absorption in the body segment and detection and processing of transmitted light/infrared radiation.

In the past few decades, there has been more emphasis on the pulse morphology. Analysis of higher harmonic components and derivation of cardiovascular indices have emerged as powerful tools for the assessment of arterial aging, endothelial function, and vascular compliance. The ease of operating and extreme low cost of PPG system has made it ideal for objective assessment of autonomic nervous system (ANS). This technique is presently being explored for the personal monitoring of blood glucose noninvasively.

Keywords: Digital blood flow, Endothelial function, Heart rate variability, Photoplethysmography, Stiffness index, Venous filling time.

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INTRODUCTION

Literal meaning of plethysmography is the recording of instantaneous volume of an object. Due to irregular

shape of different body parts, it is routinely used for volume assessment in the field of medicine. There are several plethysmographic methods for recording volume changes in any part of the body, such as volume displacement plethysmography, strain gauge plethysmography, impedance plethysmography, and PPG. These methods have been employed selectively from time to time depending upon the application. For quick assessment of blood flow in the limbs, air displacement plethysmograph, commercially available as pulse volume recorder (PVR) has been in common use till late 1970s. Strain gauge plethysmography has been in common use for respiratory monitoring, nocturnal penile tumescence, and venous occlusion phlebogram. Volume displacement plethysmography and strain gauge plethysmography have a common limitation in accurate estimation of blood flow as they are unable to distinguish between change in the limb volume caused by flow of blood or that of any other fluid. Strain gauge plethysmography, however, is still a method of choice for monitoring of respiration and nocturnal penile tumescence.

Electrical impedance plethysmography is more direct than the above two methods, as it takes into cognizance the electrical resistivity of the blood. Since blood is a good conductor of electricity as compared with remaining constituents of the body, such as bone, muscle, fat, skin, etc., the amount of blood in any part of the body is inversely proportional to the electrical impedance offered by the body segment. Therefore, pulsatile blood volume changes in the limb segment caused by rhythmic contraction of the heart can be recorded as pulsatile impedance changes. Huge volume of work has been done on this technique by large number of researchers in India as well as abroad and it is still a method of choice for continuous monitoring of cardiac output noninvasively.¹⁻³ However, the method calls for placement of surface electrodes on the body surface of the subject, free environment from electrical noise, and stringent requirement on the specifications of the instrument from the consideration of patient safety. There is always a need for non-Ohmic method, which can estimate blood circulation quickly, easily and accurately.

Photoplethysmography,^{4,5} based on the optical properties of the blood, is an ideal choice for the measurement of blood flow for two reasons: (1) There is no electrical contact between the patient and instrument, and (2) it is specific for

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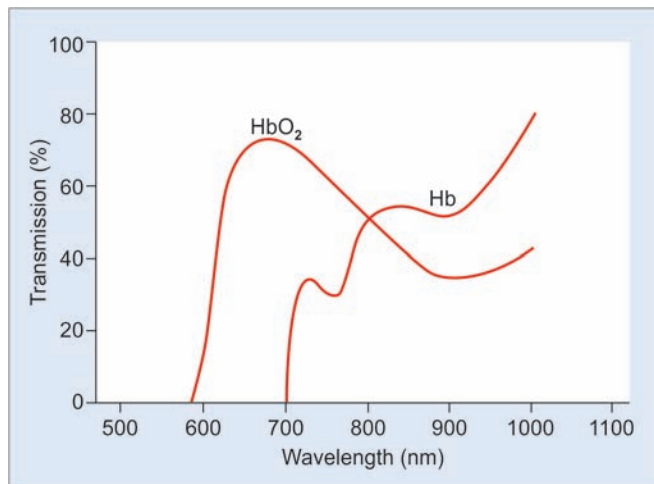
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the blood unlike PVR and strain gauge plethysmography. Graph 1 shows the spectral transmission characteristics of oxy-hemoglobin (HbO₂) and reduced hemoglobin (Hb) in the visible and infrared regions of the electromagnetic waves.⁶ As can be seen from the figure, transmission is highest for oxy-hemoglobin and reduced hemoglobin at wavelengths of 640 and 825 nm respectively, with common value at 805 nm. It increases for both beyond 900 nm. These characteristics are especially useful for monitoring oxygen saturation noninvasively in critically ill patients.

Graph 2 shows a typical PPG system in transmission mode. The light-emitting diode used as transmitter and photodiode used as receiver are mounted on the opposite side of the transducer cap or clip. It is energized with the help of square wave generator (100–500 Hz). Transmitted light received on the photodiode in the form of photocurrent is amplified and filtered with the help of 10 kHz low-pass filter. The output of filter is



Graph 1: Transmission characteristics of oxy-hemoglobin and reduced hemoglobin in the visible and infra red regions of electromagnetic waves

sampled and held with the logic input synchronized from square-wave generator. The output of sample and hold is amplified using differential amplifier. The direct current (DC) signal from the sample and hold is cancelled using a DC cancellation circuit as shown in the figure. The output of the differential amplifier (ΔP) can be recorded on a strip chart recorder or can be connected to an analog to digital converter (ADC) card for viewing it on personal computer (PC) monitor. For estimation of arterial blood flow, time derivative of ΔP signal is taken, known as dP/dt , and like ΔP it can be viewed on the monitor.

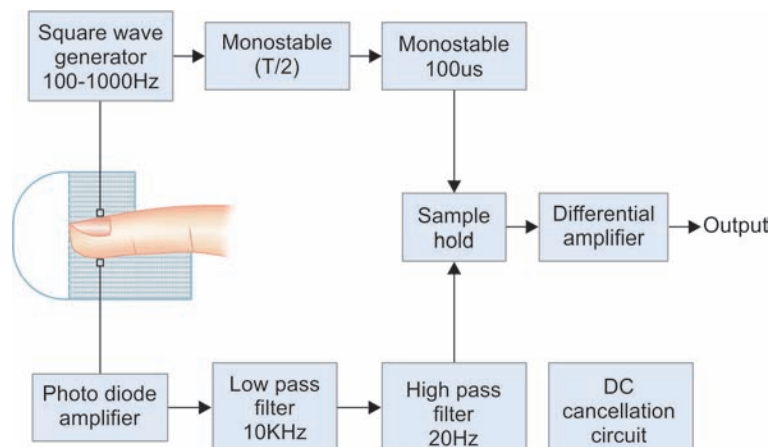
When the red light falls on finger/toe/earlobe, the light received on the other side through transmission depends on several factors, such as pulsatile blood volume in the arteries/arterioles (A), blood volume in the veins and tissues in the optical path (V), absorption in the skin and tissue pigments (T). “A” represents information on arterial blood, which is pulsatile and “V” and “T” represent the attenuation by venous blood and other tissue in the optical path, which are more or less constant.⁷

According to Beer–Lambert law, if the incident light intensity is I_0 , a is the absorption coefficient for the dissolved solute in a solution with its concentration c , and L is the thickness of the solution measured along direction of light, intensity (I) of emergent light is given as:

$$I = I_0 e^{-aLc}$$

Assuming that the Beer–Lambert’s law is valid for the whole blood, i.e., present in the finger/toe/earlobe, and that the attenuation of light by multiple scattering and reflection can be neglected, the intensity of transmitted light can be written as:

$$I = I_0 e^{-aLc - \alpha'd - \alpha''v}$$



Graph 2: Typical photo plethysmograph system. In transmission mode the light emitter and photo sensor are mounted on opposite side of the transducer cap or clip. The transmitted light produces proportional electric current in the sensor, which is amplified and processed to obtain change in blood volume as a function of time

where a_L represents absorbance by nonblood compartment, d is quantity of blood present at the end of systole, α' is the absorption coefficient of the blood at the end systole, v is the quantity of the arterial blood that flows into the finger/toe, and α is the absorption coefficient of the arterial blood.

This transmitted light, when falling on the photoelectrical element, produces electrical output with DC component corresponding to the venous blood and tissues in the optical path and an alternating current (AC) component corresponding to arterial flow. Thus

$$E_{DC+AC} = I_0 A e^{-\gamma a_L - \gamma \alpha' d - \gamma \alpha v}$$

where A and γ are constants specific to the photoelectrical element. On similar lines, the DC component of the photoelectric output can be written as:

$$E_{DC} = I_0 A e^{-\gamma a_L - \gamma \alpha' d}$$

Division of these equations leads to:

$$\frac{E_{DC+AC}}{E_{DC}} = e^{-\alpha v}$$

Taking natural logarithm on both sides leads to:

$$v = -1/\alpha \ln(E_{DC+AC}/E_{DC})$$

or $v = -Y/\alpha$

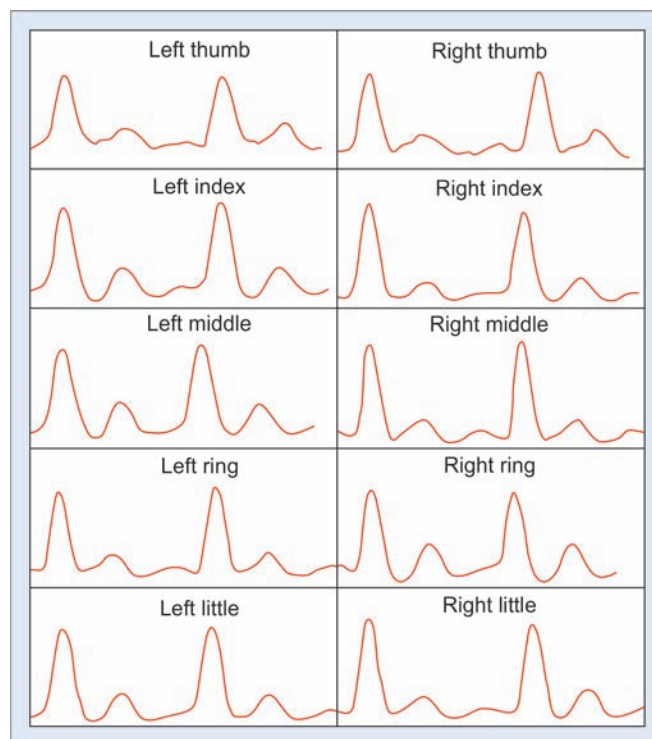
where Y is the logarithmic difference of E_{DC+AC} and E_{DC} .

This equation shows that the amount of blood entering the finger/toe during systole is directly proportional to the logarithmic difference of total photoelectric output and its DC component. This relation makes this technique far superior to air displacement and strain gauge plethysmography and can be used to assess the arterial blood flow in the extreme ends of the extremities.

CLINICAL APPLICATIONS

Estimation of Arterial Blood Flow in Toes/Fingers

As described above, it is possible to record the arterial blood flow in the fingers and toes of the subject and the PPG waveform can be analyzed to be normal or pathological depending upon the amplitude and morphology of the pulse. There are several conditions like Reynaud's phenomenon, radiation injury, etc., where assessment of arterial circulation in the digits is of prime importance. In such cases, PPG is performed in all the fingers in case of upper extremity disease and in all the toes in case of lower extremity disease. The data from fingers or toes can be compared to arrive at the diagnosis in the manner described by Iyer et al⁸ for impedance plethysmography. The advantage of PPG over impedance plethysmography



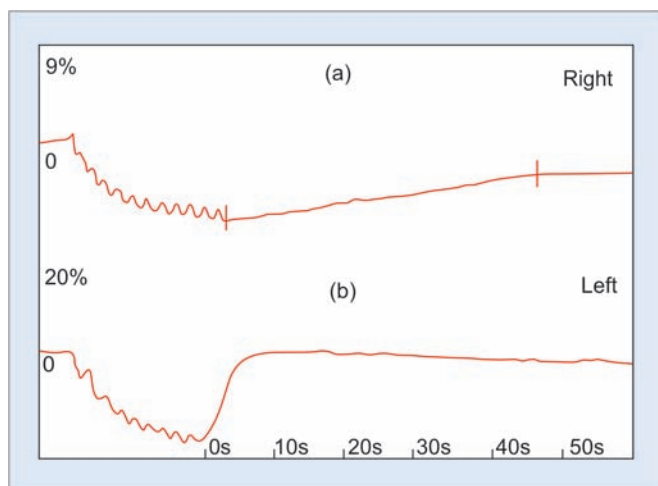
Graph 3: Photoplethysmography waveforms recorded from digits in a normal subject

is the ease of application of the probe in case of former and cumbersomeness of application of electrodes in the latter. Graph 3 shows arterial blood flow waveforms (time derivative of PPG signal) recorded from upper extremities in a control subject.⁹

Venous Reflux Test

The venous reflux test, also called the muscle pump test, is an exercise test to diagnose insufficiencies of the venous valves in the lower extremities.¹⁰ For this investigation, reflection mode PPG is used in place of the transmission type described hitherto. The patient is sitting on a height adjustable chair with knee extended to an angle of 110°. The reflectance PPG transducer is applied approximately 8 cm above the ankle between the inner and backside of the calf on a healthy skin. The patient then carries out dorsiflexion exercise to pump the blood out of the veins. For this, the patient must flex his foot upward above the heel and then relax. This exercise is repeated about 10 times. After finishing the exercise the patient must wait motionless for a period of 2 minutes to allow the refilling of the veins completely.

Graph 4 shows the venous reflux graph (a) in a normal leg and (b) in a diseased leg with incompetent venous valves. As can be seen from the figure, there are initial spikes in both the curves representing the motion artifact during exercise. The refilling takes about 50 seconds in a normal leg, whereas the same takes only 5 seconds in the leg with venous incompetence. This exercise test allows



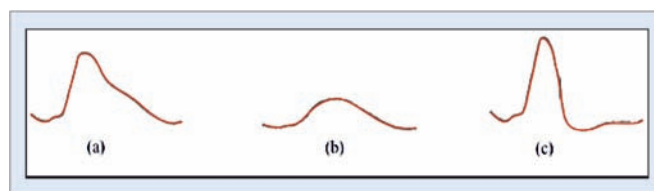
Graph 4: Photoplethysmography waveforms recorded from lower extremities in a patient with venous incompetence in the left leg. As can be seen, the refilling time is greater than 40 secs in the normal leg (a) and less than 10secs in the leg (b) with venous incompetence (courtesy Ralf Schöler, Medis GmbH)

a fast and noninvasive diagnosis and is the method of choice as a screening procedure.

Analysis of PPG Pulse Morphology

The shape of the PPG pulse depends on thickness of blood vessels, contractility of heart and vascular smooth muscle in the vessel wall. Therefore, condition of the blood vessel can be assessed from the morphology of the PPG pulse. For this examination, the patient lies on a couch usually in relaxed position. The probe is correctly applied on the tip of the finger or toe so as to cover the photometric sensor completely. The arterial pulse waves are recorded with the help of PPG equipment described above. Graph 5 shows three different types of arterial pulses recorded from the fingers or toes in various conditions. A physiologically normal pulse has fast slope, small crest, fast return to the baseline during systole, and slow return to the baseline during diastole as shown in Graph 5a. In case of an arterial occlusion, the crest is delayed and round, and the return to the baseline is also slow as shown in Graph 5b. In case of an insufficient arterial perfusion pressure, the pulse wave has a fast slope, small crest, and fast return to the baseline throughout as shown in Graph 5c.

Sherebrin and Sherebrin¹¹ have performed harmonic analysis of peripheral pulse in three age groups of 10 to 29, 30 to 59, and 60 to 89 years. They have selected these age groups since they have noted in their other experiments that there was a marked decrease in extensibility in human aortas above the age of 30 years and a further change beyond about 60 years. The power spectrum of 2nd to 6th harmonics has shown considerable decrease in the power of 2nd and 6th harmonics at $p < 0.05$. The



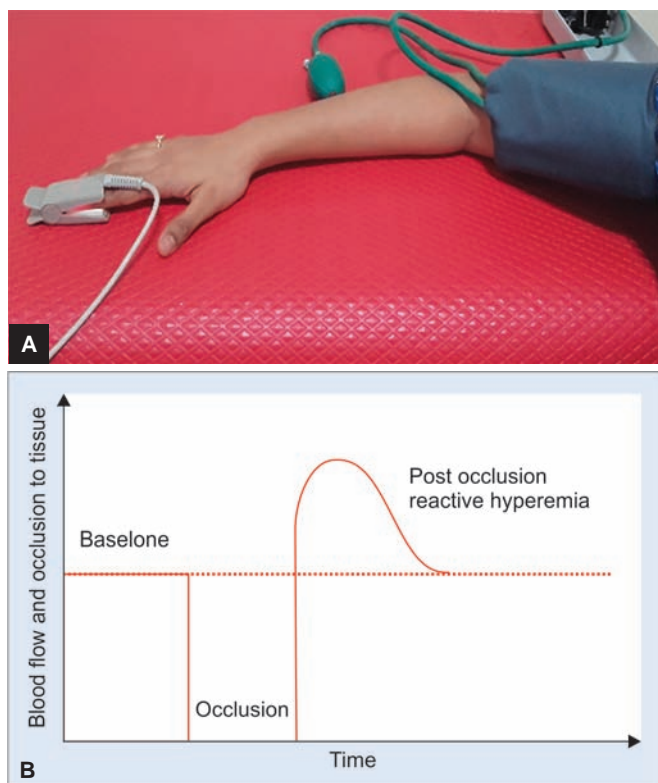
Graph 5A to C: Morphology of the PPG pulse (a) in a normal subject, (b) in a patient with arterial occlusion and (c) in a patient with generalized atherosclerosis. The normal pulse is characterized by fast rise, round crest and slow return to the base line with a discernible dicrotic notch as shown in (a). In case of an arterial occlusion, the rise is slow; the crest is round and broad with a slow return to the base line as shown in (b). In case of deficient arterial perfusion pressure, the rise of pulse is sharp, crest is rounded and small and a fast return to the base line as shown in (c).

2nd harmonic power was significantly different between the youngest and both the older age groups. The 6th harmonic was significantly different between the youngest and oldest group. Their most important observation has been marked decrease in the relative power of the 2nd harmonic with age.

Endothelium Function

Endothelium is single layer of cell lining forming the interior layer of blood vessels and serves as interface between the blood circulating in lumen and outer wall of the vessel. These cells line entire circulatory system from heart to smallest capillary. Endothelial cells are involved in many vascular aspects like vasoconstriction, vasodilation, blood clotting, atherosclerosis, angiogenesis, inflammation, and swelling. Endothelium synthesizes and releases several vasoactive factors like nitric oxide which play important role in maintaining normal function. Disorders like peripheral vascular disease may lead to endothelial dysfunction. These diseases can be diagnosed from pulse wave amplitude (PWA) using finger plethysmograph. Endothelium dysfunction can also detect cardiovascular disease in early stages and can be considered a precursor to coronary artery disease. Analysis of PWA during reactive hyperemia maybe used to study peripheral vascular endothelial dysfunction.

Reactive hyperemia is temporary increase of blood flow to an area as a result of ischemia, or an arterial blockage. Reactive hyperemia is measured by inducing temporary occlusion with the help of a tourniquet for a period of about 5 minutes that gives better results.^{12,13} Graph 6a shows the placement of tourniquet above elbow and PPG probe in the index finger. A trace of baseline PPG wave for 30 seconds is obtained with patient in sitting. Ischemic phase is induced by inflating tourniquet to 30 mm Hg higher than the systolic pressure. The cuff is deflated suddenly at the end of 3/5 minutes and postischemic PPG tracing is recorded for about 120 seconds. Amplitude of the systolic peak of the base-

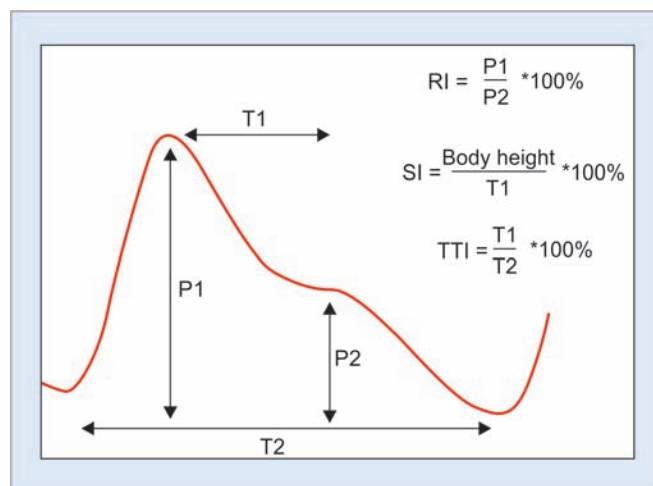


Graph 6A and B: Experiment setup for placement of tourniquet and PPG probe with the patient in supine (a). Plot of amplitude of systolic wave during baseline recording, during occlusion and post ischemia is shown in (b). The crest value divided by baseline around 1.3 is considered normal

line PPG as well as that postischemia is plotted as shown in Graph 6b. Endothelial dysfunction is considered to be present if the postischemic systolic amplitude did not increase by more than 30% in comparison to the baseline value.

Cardiovascular Indices

The hardening or stiffening of arteries is age related and can be accelerated by some medical conditions, like renal disease, diabetes mellitus, etc. Arterial stiffness is also associated with hypertension which is a risk factor for stroke and coronary artery disease. In stiffer arteries, pulse travel faster from the heart to the periphery, thus increasing the arterial pulse wave velocity.¹⁴ The forward pressure pulse augmented by a fast returning reflected wave indicates arterial stiffness. Stiffness index (SI), transit time index (TTI), and reflection index (RI) give information about arterial stiffness and vascular tone. The SI is calculated from the body height (in meters) divided by the time delay (in seconds) between the pulse systolic peak and the point of inflection on the reflection wave (units m/s), TTI is the normalized transit time with respect to the cardiac cycle time and the RI is obtained as the percentage ratio of the height of the diastolic notch to the systolic pulse height as shown in Graph 7.



Graph 7: Computation of reflection index, stiffness index and transit time index from the PPG signal. T2 represents one cardiac cycle. T1 is the time elapsed between the peak of the systolic wave (amplitude P1) and the point of inflection on the reflection wave (amplitude P2) and represents transit time of the pulse wave

Continuous Monitoring of Oxygen Saturation in the Blood

This is the most popular and most commonly used application of PPG. As far as intensive care monitoring is concerned, it is next to electrocardiography. Noninvasive blood gas monitoring is essential for the patient with cardiorespiratory complications. Transmittance plethysmography provides a very safe and simple solution to this problem.⁷ As described in preceding section, the oxy-hemoglobin has maximum transmission at 650 nm and has transmission equal to that of reduced hemoglobin at 805 nm. Therefore, transmitted light at 650 nm gives an estimate of oxy-hemoglobin and that at 805 nm gives an estimate of total hemoglobin. Thus oxygen saturation of the blood, abbreviated as spO_2 , is given as:

$$spO_2 = A - B \frac{\alpha^{650}}{\alpha^{805}}$$

where A and B are constants related to the absorption coefficient of hemoglobin and oxy-hemoglobin respectively.

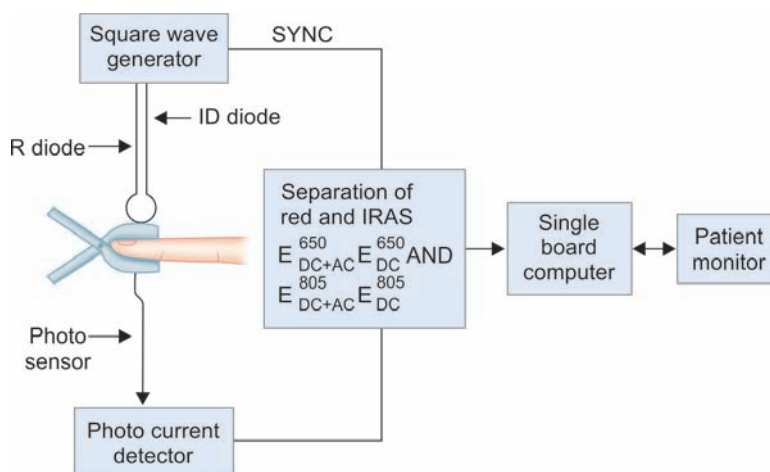
In terms of Y (defined as the logarithmic difference of E_{DC+AC} and E_{DC}), absorption coefficient is expressed as:

$$Y^{650} = -\alpha^{650} \gamma; \text{ and } Y^{805} = -\alpha^{805} \gamma$$

Therefore, spO_2 can be given as:

$$spO_2 = A - B \frac{Y^{650}}{Y^{805}}$$

Thus, it is possible to continuously monitor oxygen saturation of the blood noninvasively by photoplethysmographic method.



Graph 8: Schematic block diagram of a fingertip oxymeter. The red and infrared light emitting diodes are alternatively switched on with the help of square wave and corresponding photo current are sensed and amplified by the photo current detector. The output of the photo current detector is separated into DC and AC components of infrared and red lights and fed to single board computer

Graph 8 shows a typical spO_2 monitoring system. It comprises a clip type transducer on which red light emitter, infrared light emitter, and photosensor are mounted along with the cushions on the opposite sides in the inner surface as shown in the figure. The light emitters are sourced from a square-wave generator, which alternately puts-on the red and infrared light. Corresponding transmitted light is sensed by the photosensor and converted into electrical signal by photodetector. With the help of synchronization signal from square-wave generator, the red and infrared signals are separated to obtain, $E_{\text{DC+AC}}^{650}$, E_{DC}^{650} , $E_{\text{DC+AC}}^{805}$, E_{DC}^{805} . These signals are then given to the ADC inputs of a single board computer, which computes spO_2 as per above equation and displays the same along with any of the four voltage signals. Single board computer is linked to patient monitor through a serial link. The correlation between the oxygen saturation values measured by PPG method and conventional radiometric method has been observed to be 0.983, and it is observed to be within $\pm 5\%$ of that obtained by blood gas analysis. Thus, it is an ideal method for continuous monitoring for oxygen saturation noninvasively.

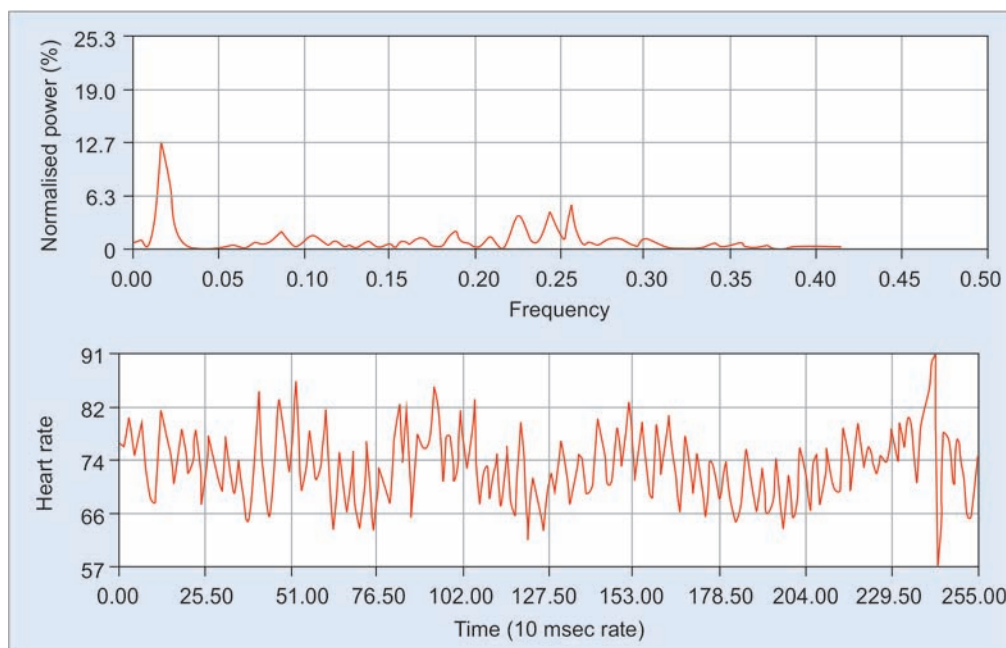
Objective Assessment of ANS

The ANS or the involuntary part of the nervous system tracks the requirement of different organ or systems of the body and keeps on modifying the physiological activity through parameters, such as heart rate; respiration rate; stroke output; peripheral blood flow; systolic, diastolic and mean blood pressures; body temperature; peristalsis; secretion of endocrinal and salivary glands; glucose-glycogen conversion; motility of large and small intestines; secretion of urine; and so on. Autonomic activity

is initiated at the levels below, cerebrum, implying that it does not get stimulated voluntarily. However, the body may perceive the effect of stimulation, such as increase in the heart rate; the rate and force of heart beat; the secretion of the glands and alimentary track; the contraction of involuntary muscles and the size of pupil of the eye. Since the ANS performs the task of increasing or decreasing the activity of any particular system, it is further divided into two parts: Sympathetic and parasympathetic nervous system. These two have opposite effects on a particular system, meaning, that if sympathetic system increases the activity of a particular organ, the parasympathetic decreases activity of the same and *vice versa*.

Sympathetic stimulation (SS) prepares the body to deal with excitement and with stressful situations, e.g., strengthening its defenses in danger and in extremes of environmental conditions. It is often said that SS mobilizes the body for fight or flight. On the contrary, parasympathetic stimulation (PS) has a tendency to slow down body processes except the digestion, urinary excretion, and sex organs. Its effect is similar to that of peacemaking, allowing restoration processes to occur quietly and peacefully. Due to the nature of functions described earlier, the rhythm of PS lies in the higher frequency band (0.1–0.4 Hz) than that of the SS (0.01–0.1 Hz). These rhythms are objectively estimated from heart rate variability (HRV) obtained from processing of electrocardiographic (ECG) signal or blood flow signal.¹⁵⁻¹⁸

Graph 9 shows HRV in time and frequency domain obtained from PPG, which is similar to that obtained from electrocardiography. Similarity between HRV obtained from PPG and ECG renders PPG as a simple, reliable, and quick method for the objective assessment of ANS.



Graph 9: Heart rate variability in time (lower) and frequency (upper) domain recorded from a control subject with the help of photoplethysmography. The variability spectrum appears more or less similar to that obtained from electrocardiography

Table 1: Photodetector output of transmitted radiation through finger/earlobe

Sl. no.	Blood glucose	Output of photodetector at different wavelengths of incident radiation				
		565 nm	650 nm	940 nm	1310 nm	1550 nm
1	91	0.12	0.70	2.00	0.80	1.20
2	164	0.10	1.10	2.50	0.60	0.52
3	122	0.20	0.70	2.00	0.90	0.76
4	108	0.16	0.70	2.00	0.80	1.40

Prospective Method for Blood Glucose Monitoring

Visible light and infrared spectroscopy is being explored for the past few decades for the noninvasive personal monitoring of blood glucose keeping in view of the fact that more than 600 million people in the world and 60 million people in India suffer from type II diabetes. 10% of these patients require strict vigilance and hence, multiple needle pricks every day. It has been observed that some wavelengths are more sensitive to blood glucose concentration. Table 1 gives the PPG output in volts for different incident radiations at different blood glucose levels in a human subject. Appreciable fall in photodetector output at wavelengths 1310 and 1550 nm, with increase in blood glucose, can be noted from the table. In contrast, output at 650 and 940 nm shows increase, and 565 nm give unpredictable output. Though the observations appear impressive, they have to be reproducible in large number and wide variety of subjects. The studies carried out to date suggest that PPG cannot be implemented as a noninvasive analytic method; however, it

can be used in a limited way for personal monitoring. Even to this extent it may give relief to some percentage of patients from multiple needle pricks.¹⁹

CONCLUSION

Photoplethysmography is used worldwide for the non-invasive monitoring of oxygen saturation of blood and is an essential instrument for every critical care unit and intensive care unit. As described earlier, this technique is very useful in monitoring digital blood flow in Reynaud's and similar diseases, where established methods like color Doppler are of little help. Morphology analysis of the PPG pulse has several parameters like power of higher harmonics, endothelial index, SI, TTI, and RI, which all have potential to reveal cardiovascular risk at early stages. These have not been sufficiently explored for their benefits and need more emphasis.²⁰ Its application in personal monitoring of blood glucose is worth further investigation. Simplicity of usage and extremely low cost of this modality makes it a method of choice for developing countries like India for host of applications described above.

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CASE REPORT

A Case of Fournier's Gangrene of Penis leading to Complete Loss of Penile Urethra

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ABSTRACT

Fournier's gangrene (FG) of penis is a rare but fulminant condition often associated with significant morbidity and mortality. Fournier's gangrene typically spares testis, urethra, and deep penile components in view of their deeper blood supply, which is independent of compromised fascial and subcutaneous circulation. An unusual case of a 55-year-old nondiabetic male who presented to the emergency department of MGM Medical College, Navi Mumbai, India, with acute urinary retention due to impacted urethral calculus is reported. Patient developed FG of penis with isolated involvement of corpus spongiosum, leading to loss of penile urethra. Emergency penile exploration and debridement was done followed by elective perineal urethrostomy at a later date.

Keywords: Corpus spongiosum, Fournier's gangrene of penis, Penile urethra.

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INTRODUCTION

Necrotizing fasciitis of the male genitalia and perineum is commonly referred to as FG. In approximately 95% of cases, a source of infection can be identified. Fournier's gangrene isolated to the penis is a rare occurrence due to highly vascular nature of the penis. It typically spares urethra and deep penile components in view of their deeper blood supply which is independent of compromised fascial and subcutaneous circulation. Fournier's gangrene of penis with involvement of corpus spongiosum leading to loss of penile urethra is an uncommon finding.

CASE REPORT

A fifty-five-year-old gentleman with no known comorbidities presented to the emergency department with acute urinary retention. On examination, there was palpable tender bladder with edematous penis and tight phimosis. Dorsal slit was given. Attempt of per-urethral catheterization was made which failed. So suprapubic catheter placement was done. On investigation, X-ray abdomen and pelvis showed impacted urethral calculus measuring 16 × 12 mm. Hemogram showed hemoglobin 11 gm/dL, platelet count 77,000/mm³, and total leukocyte count 8800/mm³. His other laboratory tests, such as renal function test, liver function test, and random blood sugar were within normal limits. Urine culture was sterile. On second day of admission, patient started having fever with chills with persistent thrombocytopenia with herpes labialis-like lesions around the lips. Common medical causes of fever with thrombocytopenia like dengue, malaria, leptospirosis were ruled out and conservative management in the form of hydration, intravenous antibiotics (ceftriaxone, amikacin), and antiviral drug (tablet acyclovir) were started. On fourth day of admission, there was 3 × 2 cm warm tender fluctuant swelling on ventrolateral aspect of penis with persistent penile edema. Ultrasound of local area showed 4.5 × 3.5 × 3.5 cm echogenic collection with moving internal echoes. Corporeal bodies of penis and scrotum were normal on ultrasound study. Incision and drainage of collection was done and fluid was sent for culture and sensitivity. Postdrainage, patient was afebrile but his total leukocyte counts started rising. There was foul-smelling brownish-colored discharge from drainage site (Fig. 1) with persistent edema and evolving erythema along the penile shaft. Patient was subjected to emergency penile exploration. On exploration of penis, there was necrosis of tissues below the skin on the ventral aspect involving penile dartos fascia up to corpus spongiosum and penile urethra, thus exposing the urethral plate (Fig. 2). Adequate debridement with excision of pregangrenous preputial skin was done.

Fluid sent for culture grew *Streptococcus*, *Klebsiella*, and *Acinetobacter*, which were sensitive to piperacillin and meropenem. Patient was started on culture-specific antibiotics and regular dressings were done. Patient improved dramatically. His total leukocyte count and platelet count became normal. Wound was granulating

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Fig. 1: Brownish discharge from incision site

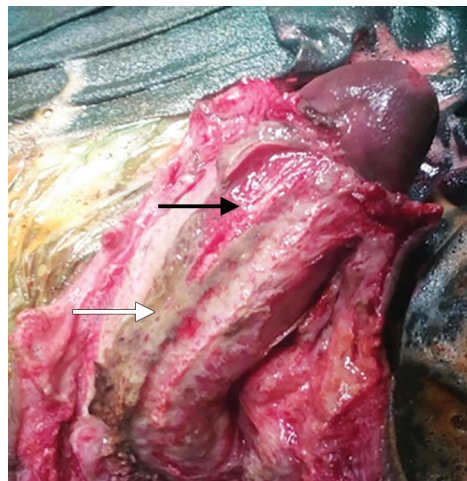


Fig. 2: Exposed urethral plate (black arrow) and necrosed corpus spongiosum and penile urethra (white arrow)

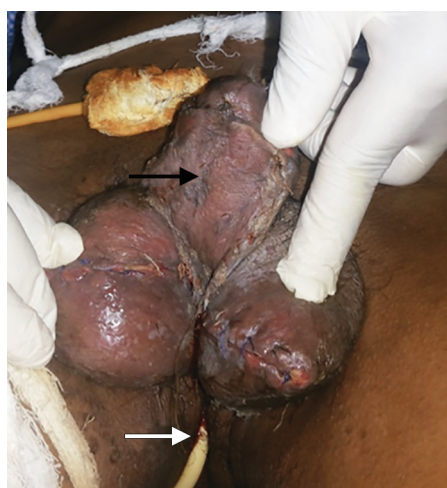


Fig. 3: Split skin graft with 100% take (black arrow) and perineal urethrostomy site with *in situ* Foley's catheter (white arrow)

and contracting. After repeated debridements and dressings the bed was finally healthy. Patient was taken up for elective perineal urethrostomy 3 weeks later as per his preference. Patient's penile urethra distal to bulb was completely destroyed and replaced by fibrocollagenous tissue. Perineal urethrostomy with bivalving of scrotum was done. Impacted urethral calculus was removed at the same time. An unexpanded, meshed, split-thickness skin graft was placed on the ventral surface of the penis. The graft dressing was changed on the 4th and 6th postoperative days, and it revealed a 100% take of the graft (Fig. 3). The postoperative period was uneventful. Patient had good urinary stream from healthy perineal urethrostomy.

DISCUSSION

Fournier's gangrene of penis is a rare entity with only a few cases reported till date.^{1,2} Our case was further unique in that there was selective destruction of corpus spongiosum and penile urethra, which in our knowledge is the first such case to be reported in the literature. A case

of elective gangrene of corpus spongiosum of idiopathic origin has been reported by Kharbach et al³ but that was dry gangrene of glans penis and corpus spongiosum which is a separate entity from FG.

Fournier's gangrene is a devastating disease with an estimated mortality of 10 to 20% depending on the severity of presentation.⁴ It is no longer considered idiopathic, as its etiology is usually an infective pathological process originating from overlying skin, urinary tract, or colorectal area. Fournier's gangrene is a polymicrobial infection, the usual organism isolated being anaerobic streptococcus synergistic with other organisms like enterobacteria, species, staphylococcal species, and bacteroides. Introduction of bacteria that initiates the infectious process leads to obliterative endarteritis causing cutaneous and subcutaneous vascular necrosis leading to localized ischemia and further bacterial proliferation, which spreads rapidly due to enzymatic digestion of fascial barriers.

Arterial vascularization of the penis is provided by three branches of the internal pudendal artery: dorsal artery, cavernous artery, and bulbourethral artery. Anatomical variations include an extrapenile alternative arterial system from the external obturator or iliac arteries. This important vasculature explains the rarity of ischemic gangrene of the penis.⁵ Penile urethra should have been spared in view of its deeper blood supply independent of compromised fascial and subcutaneous circulation. In addition, there was no prior history of trauma/hypospadias/perineal surgery which could have affected antegrade or retrograde blood supply of penile urethra.

Singam et al⁶ have reported a case wherein a patient with impacted urethral calculus with neglected symptoms progressed to development of FG of penoscrotum with subsequent gangrene of corporeal bodies and right testis, ultimately requiring total penectomy and right orchiectomy. Infected urine proximal to obstruction enters

into periurethral glands and the invading organism then spreads within corpus spongiosum.⁶ In our case, there was impacted urethral calculus, treatment of which was delayed due to persistent thrombocytopenia. Urinary extravasation of infected urine at the time of attempting per-urethral catheterization could have been the reason for this problem.

Singh et al⁵ in a review of penile gangrene cases over 10 years have reported five cases of FG of penis, out of which four required total/partial penectomy and only one patient survived. In our case, patient survived without significant physical loss because of early intervention. In FG early therapy is the key, including debridement of the entire affected shaft of the penis and other affected tissues, proximal urinary diversion, parenteral broad-spectrum antibiotics with anaerobic cover, and nutrition followed by elective definitive surgery for rehabilitation.

CONCLUSION

Fournier's gangrene of penis causing loss of penile urethra is a rare but life-threatening condition often

leading to devastating physical loss in the form of partial/total penectomy. Penis can be salvaged with early aggressive management.

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CASE REPORT

A Case of Postoperative Hypotension in a Patient of Sheehan's Syndrome

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ABSTRACT

Sheehan's syndrome is acute infarction and ischemic necrosis of the pituitary gland resulting from postpartum hemorrhage and hypovolumic hypotension. A 45-year-old female para 2 patient was admitted for total abdominal hysterectomy in view of pyometra. Patient was a known case of Sheehan's syndrome with hypothyroidism. On day 2 of her surgery, she suddenly went into hypotension and tachycardia with electrocardiogram (ECG) finding of T-wave inversion. Biological marker for myocardial infarction namely creatine phosphokinase-MB was normal. The patient was started on hydrocortisone 100 mg intravenous injection thrice a day. Immediately, after the first dose of injection, she became normotensive and the pulse rate settled down. The ECG, taken 24 hours later, was normal.

Keywords: Postoperative hypotension, Postpartum hemorrhage, Sheehan's syndrome.

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INTRODUCTION

Sheehan's syndrome is postpartum pituitary necrosis resulting from postpartum hemorrhage and or hypovolemic shock. During pregnancy complications, such as postpartum hemorrhage, hypovolemic shock may occur leading to decrease in blood supply to the pituitary gland mainly anterior lobe causing necrosis of anterior lobe. Enlarged pituitary gland is vulnerable to ischemia and does not have the ability to regenerate. Scar tissue substitutes the necrotic cells. The presence of 50% of pituitary gland is sufficient for the maintenance of normal functions. Partial or total hypopituitarism develops with necrosis of 70 to 90% of the gland. Growth hormone (GH) and prolactin (PRL) involvement are seen in 90 to 100% of the patients; whereas, involvement of gonadotrophs,

thyrotrophs and corticotrophs may be seen in 50 to 100% of the patients¹. Since adrenal insufficiency is the most life-threatening complication, adrenal function should be immediately assessed in any woman suspected of having Sheehan's syndrome.²

The prevalence of Sheehan's Syndrome in India is estimated to be 2.7 to 3.9% among parous women older than 20 years. Hence, in developing countries like India, where home deliveries are widely practised and obstetric care is poor, it is one of the leading causes of hypopituitarism.

CASE REPORT

A 45-year-old female para 2 patient came to Outpatient Department with complaints of foul smelling discharge per vaginam, abdominal pain since 2 months, fever since 2 weeks, and with the history of premature menopause at age of 30 years after second delivery. She had two vaginal deliveries. Second delivery was complicated with uterine inversion and postpartum hemorrhage 15 years back. Two years back, patient was admitted to our hospital with complaints of generalized weakness and pain in abdomen. She also gave history of failure to lactate and absence of pubic hair after second delivery. Hormonal study was suggestive of hypothyroidism, low follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and low cortisol levels. Magnetic resonance imaging (MRI) of brain was also done and was suggestive of empty sella. Based on the hormonal profile and MRI scan, the diagnosis of Sheehan's syndrome was made and the patient was started on thyroxine 50 gm and prednisolone 5 mg tablets once a day (OD). However, she discontinued prednisolone after 6 months. During present illness, the patient was admitted with complaints of fever, abdominal pain, and foul smelling vaginal discharge. The pelvic examination and sonographic findings were suggestive of atrophied uterus and cervix with pyometra.

Laboratory investigations showed deranged pituitary hormones—thyroid stimulating hormone (TSH)—50.10 mIU/L (normal 0.5/4.7 mIU/L), FSH—3.34 IU/L (Normal postmenopause 30.6-106.3 IU/L), LH—0.740 IU/L (Normal postmenopause 15.9-54 IU/L) and Papanicolaou smear suggestive of atypical squamous hyperplasia. The patient was posted for total abdominal hysterectomy. Day 1 after surgery was uneventful. On day 2, she suddenly went into hypotension and tachycardia.

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ECG showed T-wave inversion. Creatine phosphokinase-MB (CPK-MB) and 2D Echo were within normal limits. Serum cortisol was 0.56 µg/dL (morning normal 7-28 µg/dL). Next day, in view of past history of Sheehan's syndrome and hypotension refractory to intravenous (IV) fluids, it was decided to put the patient on hydrocortisone to compensate for possible low cortisol levels in the patient. Patient was started on hydrocortisone 100 mg IV injection every 8 hours. After first dose of hydrocortisone, patient became normotensive and pulse rate settled down. The ECG taken 24 hours later was normal without any T-wave inversion. The patient recovered completely and was shifted to ward on day 4 of surgery. Injection hydrocortisone was continued till day 5, after which, it was changed to prednisolone 5 mg tablet OD. Patient was discharged on day 7 with instruction to continue prednisolone tablet.

DISCUSSION

The patient described above had past history of significant blood loss after delivery requiring admission to the Intensive Care Unit. Only a small number of patients with Sheehan's syndrome develop acute postpartum hypopituitarism after postpartum hemorrhage. The most frequent scenario is a woman with amenorrhea occurring years later, with the diagnosis of Sheehan's syndrome being made retrospectively. However, it is important to emphasize that Sheehan's syndrome is a neurological and endocrinological emergency and is potentially lethal. In Sheehan's syndrome, inability to lactate after delivery due to PRL deficiency and the development of amenorrhea from gonadotropin deficiency are classical features. In addition, these patients become infertile; there is failure to regrow shaved pubic hair and signs of hypothyroidism and hypoadrenalism occur.

The aim of Sheehan's syndrome treatment is to replace the missing hormones and restore endocrine homeostasis.

The hormones adrenocorticotrophic hormone and TSH may be replaced in addition to glucocorticoids and thyroxine respectively. On the contrary, replacing mineralocorticoids is not necessary in most cases. It is important to replace a patient's sexual hormones as part of the treatment before menopause and replacing GH for giving better quality of life to the patient. The patient was advised thyroxine and prednisolone on diagnosis, which she had discontinued after 6 months on her own.

In terms of prognosis of Sheehan's Syndromes, it depends on how soon the diagnosis is made and how promptly proper treatment is initiated. If the syndrome is diagnosed early and adequate replacement therapy is initiated, the prognosis is excellent. On the contrary, if there is delay in identifying and managing these patients, they may present with severe and multiple problems, such as adrenal crisis, symptomatic hypoglycemia, symptomatic hyponatremia, and other endocrinal deficiency disorders.

CONCLUSION

Sheehan's syndrome is not an uncommon disorder in India. However, the diagnosis is often missed. In this case, though the diagnosis was made, the patient discontinued the treatment on her own. The patient had unexplained hypotension 24 hours after surgery. The cortisol deficiency was suspected and confirmed by cortisol levels. The cortisol replacement therapy in the form of hydrocortisone helped in recovery.

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CASE REPORT

A Case of Progressive Supranuclear Palsy/Steele–Richardson–Olszewski Syndrome

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ABSTRACT

Progressive supranuclear palsy (PSP) is an uncommon neurological disorder, the hallmark of which is supranuclear ophthalmoplegia involving vertical gaze. Other clinical features include pseudobulbar palsy (dysphagia and dysarthria), neck dystonia (retrocollis), bradykinesia, postural instability, and repeated falls occurring early in the course of the disease, personality changes, a staring unblinking facies, mild dementia, and cerebellar and corticospinal tract signs. Magnetic resonance imaging (MRI) of the brain on midsagittal images may reveal a characteristic atrophy of the midbrain in a shape that suggests a bird, particularly a hummingbird. The PSP may resemble Parkinson's disease (PD), but the pathophysiology is distinct from PD. Here, we report a rare case of a 72-year-old man who came with difficulty in naming objects and persons, dysphagia, dysarthria, difficulty in vertical gaze, and history of recurrent fall even while in sitting down position. He was diagnosed as PSP based on clinical examination and neuroimaging. The PSP has poor prognosis.

Keywords: Hummingbird sign, Mickey mouse ears sign, Progressive supranuclear palsy, Steele–Richardson–Olszewski syndrome.

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INTRODUCTION

Progressive supranuclear palsy^{1,2} is an uncommon brain disorder that affects movement, control of walking (gait) and balance, speech, swallowing, vision, mood, behavior, and thinking.

The PSP was first described as a distinct disorder in 1964, when three scientists published a paper that distinguished the condition from PD. It was referred to as the Steele–Richardson–Olszewski syndrome reflecting the combined names of the scientists who defined the disorder.³

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CASE REPORT

A 72-year-old male patient came with complaints of

- History of recurrent falls even while in sitting down position, progressed over 1 year
- Difficulty in downward gaze since 2 months
- Difficulty in naming objects and persons since 2 months
- Dysarthria since 1 month
- Dysphagia since 2 weeks

On examination, patient's vitals were stable.

Clinical examination revealed:

- Loss of vertical and downward gazes
- Loss of horizontal gaze to left
- Difficulties with convergence (convergence insufficiency),
- Narrow-based gait
- Sway while turning to walk
- Action tremors on outstretched hands
- Bilateral brisk knee jerks and equivocal plantars
- Bilateral palmomental reflex

His mini mental state examination score was 25/30 showing mild cognitive impairment.

INVESTIGATIONS

All the lab parameters were within normal limits. Magnetic resonance imaging of the brain showed the prominence of ventricular system, basal cisterns, and cortical sulci, suggestive of cerebral atrophy with age-related changes in periventricular white matter (Fig. 1). Midsagittal images showed characteristic atrophy of

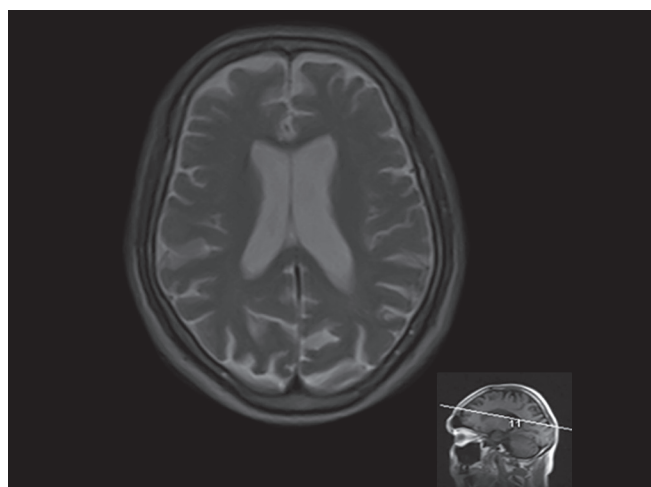


Fig. 1: Magnetic resonance imaging brain showing age-related ischemic changes and cerebral atrophy

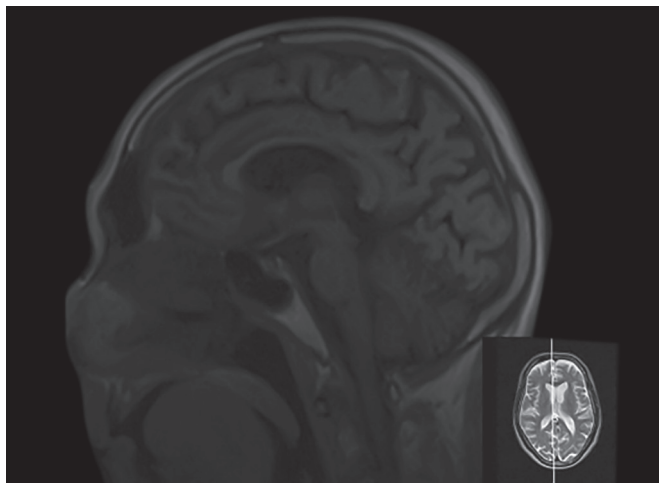


Fig. 2: Sagittal section of MRI brain showing “hummingbird sign” (atrophy of the midbrain with relative preservation of the pons resembling the head with narrow beak and body of a hummingbird)

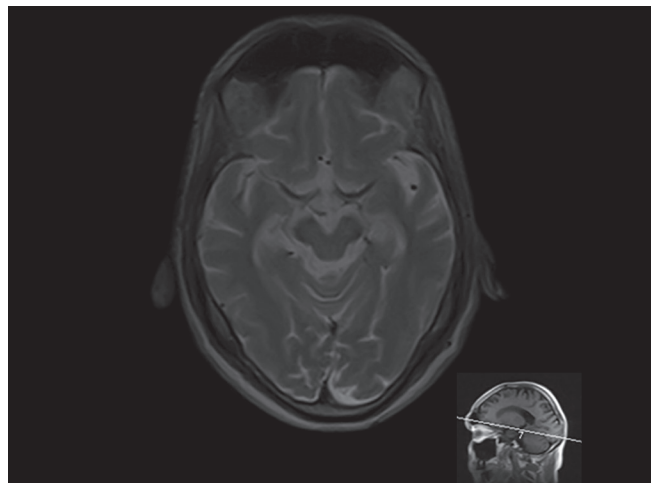


Fig. 3: The MRI brain axial image showing “Mickey mouse ears” sign

the midbrain with relative preservation of the pons, the “hummingbird sign”⁴ (Fig. 2). This is a typical pattern of MRI in PSP and relates to midbrain atrophy. Axial images showed “Mickey mouse ears” sign (Fig. 3), which reflects selective atrophy of the tegmentum, with relative preservation of the tectum and cerebral peduncles.

COURSE DURING HOSPITALIZATION

Based on clinical features and MRI findings, the patient was diagnosed as PSP. He was started on a combination of Levodopa (100 mg) with Carbidopa (25 mg) 8 hourly. He was also given balance and gait training. Ophthalmic evaluation was done and ortho-optic exercises were taught to avoid recurrent falls. His relatives were educated about the progression of the disease and the care to be provided to the patient in future. He was discharged with advice of follow-up after 3 months. On follow-up, he came with deterioration of upward and downward gaze palsy, which was persistent.

DISCUSSION

The PSP,⁵ also known as Steele–Richardson–Olszewski syndrome, is a neurodegenerative disease that affects cognition, eye movements, and posture. The classical diagnostic feature of PSP is paresis of conjugate gaze. Initially, there is a problem with looking up and down on command (saccade), and as the condition advances, there is difficulty in following objects up and down (pursuit). Although the disturbance with gaze is first apparent in the vertical plane, ultimately horizontal gaze also becomes affected as in the present case.

Interruption of the saccadic and pursuit pathways before they reach the eye-movement generators results in loss of voluntary eye movements. There is an overreaction of the frontalis muscles giving “astonished facial

expression” or “perpetual surprise” (as opposed to the lack of facial expression/hypomimia seen with PD) and extension of the neck to compensate for the weakness of upward conjugate eye movement. In PSP, the typical neck posture is one of extension rather than flexion, as in PD. Patients with supranuclear palsy usually have an akinetic syndrome involving all limbs, with prominent rigidity of the neck and impairment of righting reflexes. As the condition advances, there is intellectual impairment. The falling in PSP is more often backward, probably because of retrocollis (tendency to tilt the head backward). In PD, the patient tends to fall forward as if chasing center of gravity. Present case had history of recurrent falls as early symptom.

Two main clinical subtypes^{6,7} have been described:

1. Richardson’s syndrome (54%), which features early appearance of falls, absence of tremor, symmetry of signs, and poor response to Levodopa.
2. Progressive supranuclear palsy–parkinsonism (32%), characterized by delayed onset of falls, presence of tremor, asymmetry, and response to Levodopa.

The clinical picture of PSP often overlaps with that of PD and, hence, is usually referred as a form of atypical Parkinsonism. The PSP is the most common of the so-called Parkinson plus syndromes.

Several features, however, may alert the astute clinician to the possibility of PSP. These include early instability and falls, especially in the first year of symptom onset, speech and swallowing difficulties early in the disease course, florid frontal lobe symptomatology, such as apathy, impaired abstract thought, decreased verbal fluency or frontal release signs (bilateral palmomental reflex was evident in present case), and a predominantly axial pattern of Parkinsonism. Unique MRI features of midbrain atrophy, eye signs, and falling history clinch the diagnosis. Other degenerative conditions that can

manifest a supranuclear vertical gaze disorder are corticobasal–ganglionic degeneration, Lewy body disease, Parkinson disease, and Whipple disease, but never to the extent seen in PSP. The PSP is tauopathy, while PD is ubiquitinopathy.⁸ In PSP, abnormal tau is present in brain areas that are consistent with the clinical signs. The gross pathologic findings in PSP are substantia nigra and locus coeruleus pigmentation with midbrain atrophy. Variable atrophy of the palladium, thalamus, and subthalamic nucleus together with mild symmetric frontal volume loss may also be present.

The age of onset of this disease process is usually in the sixth and seventh decades (average age 63 years), and it advances more rapidly than Parkinson's disease. There is sometimes a family history suggesting autosomal dominant inheritance. Males and females are affected almost equally and there is no racial, geographical, or occupational predilection. The prevalence of PSP is age-dependent and estimated at 6 to 10% of that of PD, or 6 to 7 cases per 100,000.⁹ Nearly half of all patients are markedly disabled or wheelchair bound within 4 years of onset. Early onset, the presence of falls, slowness, and inability to move the eyes downward early in the development of the disease predict poor survival time.

No evidence-based therapies are available, although physical therapy with balance training and family education may be helpful.

In the early stages of clinical evolution, there may be some response to dopaminomimetic therapy, but none in later stages. Death, occurring in 2 to 12 years (the median survival is 9.5 years), is often due to the sequelae from falls or dysphagia (may cause aspiration pneumonia).⁷

CONCLUSION

The PSP is one of a number of diseases collectively referred to as Parkinson plus syndromes. Early falls are

characteristic, especially with Richardson syndrome. A case of a 72-year-old male patient with PSP is presented. Clinical presentation and brain MRI features are described.

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CASE REPORT

Cervical-pharyngeal-brachial Variant of Guillain-Barré Syndrome: A Sequel of Leptospirosis

¹Fernaz Sherdiwala, ²Jeetendra Gavhane, ³Ishani Nathwani, ⁴Ankita Patel, ⁵Natesan Rewathi, ⁶Shekhar Patil

ABSTRACT

Guillain-Barré syndrome (GBS) is a lower motor neuron disease due to postinflammatory immunological reaction leading to demyelination. Usual preceding etiologies are acute viral episodes caused by cytomegalovirus, Epstein-Barr, and Zika infections, among others. Bacterial organisms causing GBS are *Mycoplasma pneumonia*, *Campylobacter jejuni*, *Haemophilus influenzae*, and *Shigella*. It can also occur postimmunization against rabies, influenza, MMR (measles, mumps, rubella) and conjugated meningococcal vaccine. A rare case of GBS (acute inflammatory demyelinating polyneuropathy) occurring after an episode of leptospirosis infection is presented.

Keywords: Cervical-pharyngeal-brachial variant of Guillain-Barré syndrome, Leptospirosis, Unusual presentation.

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INTRODUCTION

Guillain-Barré syndrome is an autoimmune disorder often considered a postinfectious polyneuropathy involving mainly not only motor but also sensory and sometimes autonomic nerves. It is characterized by progressive symmetrical ascending acute flaccid weakness and mild sensory changes. Progression is often maximal by the end of 4 weeks,¹ and then the condition usually plateaus before improving slowly. Particularly, in cases with an abrupt onset, tenderness on palpation and pain in muscles are common in the initial stages. Affected children are irritable. Weakness can progress to inability or refusal to walk and later to flaccid tetraplegia. Maximal severity of weakness is usually reached by 4 weeks. Bulbar involvement occurs in about half of cases, resulting in respiratory insufficiency. Dysphagia and facial

weakness are often impending signs of respiratory failure.² They interfere with eating and increase the risk of aspiration. The facial nerves may be involved. Occasionally, additional infectious precursors of GBS include mononucleosis, Lyme disease, cytomegalovirus, and *Haemophilus influenzae* [for Miller-Fisher syndrome (MFS)]. There are variants of GBS, namely acute inflammatory demyelinating polyneuropathy, which is the classical variant, acute motor axonal neuropathy, acute motor sensory axonal neuropathy, acute sensory neuropathy, MFS, cervical-pharyngeal-brachial variant (lower cranial nerve palsy mimicking botulism) and Bickerstaff brainstem encephalopathy.³ However, GBS post spirochete illness, leptospirosis is extremely rare. Only few such cases have been reported till date.

CASE REPORT

An 11-year-old female child was brought to the emergency department, Mahatma Gandhi Mission Hospital, Kamothe, Navi Mumbai, India, with chief complaints of fever, yellowish discoloration of urine, and myalgia since 4 days. Child was admitted in pediatric intensive care unit. Soon after admission, the child developed abdominal distension. On neurological examination, child had altered sensorium with preserved reflexes. Examination of abdomen showed liver enlarged 3 cm below costal margin and with smooth surface and rounded margin. Spleen was not palpable. Respiratory and cardiovascular examination was found to be normal.

Complete blood count showed leukocytosis with normal platelets. Liver enzymes were elevated (serum glutamic-pyruvic transaminase – 980; serum glutamic-oxaloacetic transaminase – 4000); serum bilirubin 6.2 (direct 4.2; indirect 2); serum ammonia 100; serum proteins 5.4 (albumin 3.2; globulin 2.2). Child had a deranged coagulation profile (prothrombin time 24.9; international normalized ratio 1.88); Lumbar puncture and serum ceruloplasmin levels were normal. Dark ground illumination was negative. *Leptospira* immunoglobulin M was positive, which confirmed the diagnosis of leptospirosis. Child was started on restricted intravenous fluids, Tab. Doxycycline and other supportive measures. She started responding well to treatment and was started on nasogastric feeds, which were gradually shifted to full oral feeds.

However, in the second week of illness, the child developed drooling of saliva, pooling of secretions, difficulty in

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speech associated with a nasal twang, difficulty in deglutition along with clumsy movement of hands. On examination, child had a weak gag reflex. Direct laryngoscopy was normal. Lower motor neuron bulbar palsy was noted. Provisional diagnosis of cervical-pharyngeal-brachial variant of GBS was considered at this point.

Repeat lumbar puncture was done. It showed cytoalbuminologic dissociation. Cerebrospinal fluid proteins were elevated to more than twice the upper limit of normal, and glucose levels were normal. Fewer than 10 white blood cells/mm³ were found on smear examination. Bacterial cultures were negative. Nerve conduction study of median and ulnar nerves showed decreased nerve conduction velocity. Child was confirmed to have diagnosis of cervical-pharyngeal-brachial variant of GBS. Injection methyl prednisolone was given for 3 days. Gradually, child showed complete recovery without any residual bulbar weakness.

DISCUSSION

Guillain-Barré syndrome is an autoimmune disorder often considered a postinfectious polyneuropathy involving mainly not only motor but also sensory and sometimes autonomic nerves. This syndrome affects people of all ages and is not hereditary. It is a common cause of acute flaccid paralysis in children.⁴ The paralysis usually follows a non-specific gastrointestinal or respiratory infection by approximately 10 days. The original infection might have caused only gastrointestinal (especially *Campylobacter jejuni*) or respiratory tract (especially *Mycoplasma pneumoniae*) symptoms. The syndrome includes several pathological subtypes, of which the most common is a multifocal demyelinating disorder of the peripheral nerves. Evidence from histological examination of peripheral nerve biopsy and postmortem samples suggests that both cell-mediated and humoral mechanisms are involved in the pathogenesis. Immunological studies suggest that at least one-third of patients have antibodies against nerve gangliosides, which in some cases also react with constituents of the liposaccharide of *C. jejuni*. The GBS has been reported after administration of vaccines against rabies, influenza, measles, mumps, rubella, and following administration of conjugated meningococcal vaccine, particularly serogroup C. Other infectious precursors of GBS are infectious mononucleosis, Lyme disease, cytomegalovirus, and *H. influenzae* (for MFS) infections.

Leptospirosis is a spirochete infection of great public health importance in the tropics. The source of infection in humans is usually either direct or indirect contact with the urine of infected animals. These bacteria infect humans by entering through abraded skin, mucous membrane, and conjunctivae. Leptospirosis infection is described as anicteric and icteric form. The septicemic phase of anicteric leptospirosis has an abrupt onset with flu-like

symptoms of fever, shaking chills, lethargy, severe headache, malaise, nausea, vomiting, and severe debilitating myalgia. The immune phase can follow a symptomatic interlude and is characterized by recurrence of fever and aseptic meningitis which manifest as headache, photophobia, and nuchal rigidity.⁴ Complications, such as optic neuritis, uveitis, iridocyclitis, chorioretinitis, and peripheral neuropathy may occur. Nervous system involvement is essentially immune-mediated and gross changes that include leptomeningeal edema, brain and spinal cord congestion, and hemorrhage. Microscopically, perivascular round cell infiltration of small- and medium-sized blood vessels along with patchy demyelination are the prominent features.⁵ In icteric leptospirosis (Weil syndrome), initial manifestations are similar to those described for anicteric leptospirosis. The immune phase is characterized by jaundice, renal failure, thrombocytopenia, and in fulminant cases hemorrhage and cardiovascular collapse.

Two case reports of GBS post leptospirosis have been published as per our knowledge. Bal et al⁶ described classical variant of GBS postleptospirosis infection. Silva et al⁷ described a case of ascending progressive leg weakness with acute pancreatitis postleptospirosis. Our case presented as cervical-pharyngeal-brachial variant of GBS postleptospirosis infection.

CONCLUSION

A case of cervical-pharyngeal-brachial type of GBS due to leptospirosis in an 11-year-old girl is presented. Leptospirosis is an uncommon cause of GBS as per published reports.

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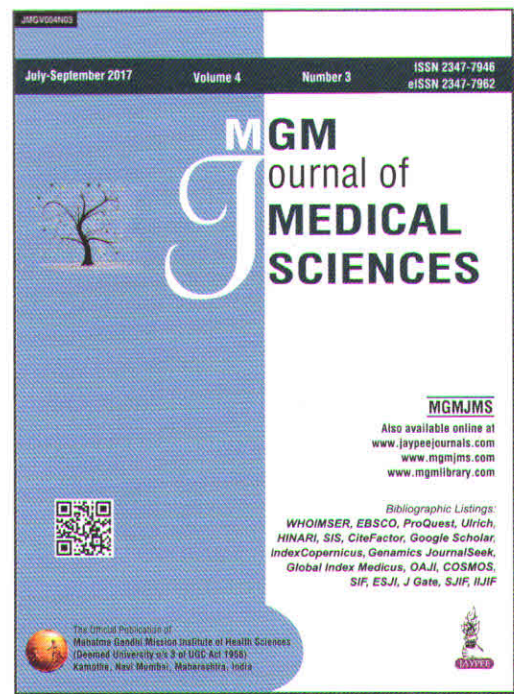
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