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Annals of Medical Science and Research

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CONTENTS

The health of the nation in 2100 – The hope and despair

Since the beginning of this century, we as a nation have made progress in all sectors including health. There has been a significant reduction in under-five and neonatal mortality in the country, reduction in fertility ratio, and increase in life expectancy at birth, although there are substantial variations between the states in the magnitude and rate of decline in these indices.[1,2] This has become possible through various schemes to provide nutrition to women and children, antenatal care of pregnant mothers, ensuring institutional delivery, good neonatal care, universal immunization, and education of girls. India has also made progress in reducing mortality rates from infectious diseases. Despite debates about policies and what we have achieved versus what could have been achieved, these are rays of hope for India.

As Franklin D. Roosevelt said, "We have always held to the hope, the belief, the conviction that there is a better life, a better world, beyond the horizon." The Global Burden of Disease has recently forecasted that continued trends in female educational attainment and access to contraception would hasten declines in fertility and slow population growth worldwide across all societies. A sustained total fertility ratio lower than the replacement level in many countries, including China and India, would have economic, social, environmental, and geopolitical consequences.[3]

Therefore, we are going to experience a change in population dynamics in the next few decades. India's population will rise to its peak by middle of this century to 1.68 billion, and will gradually decline thereafter to 1.1 billion in 2100 [Figure 1]. This will primarily be due to a decline in fertility ratio, which will be 1.3 in 2100 from present-day 2.1. The reduction in fertility ratio is observed in all castes, creeds, religions, and across all socioeconomic strata of Indian society.

The life expectancy will increase from 70.2 in females and 67.8 in males in 2017 to 80.7 and 78, respectively, in 2100. This will have a big impact on the economy as old persons are generally considered as nonproductive and consume more healthcare resources. As the population will age, there will be a reduction in the young working population. However, India will still have the most number of working people (between 25 and 64 years) in the world [Figure 2]. It is also predicted that economic growth will make India the third-largest economy by 2050 in the world.[3]

The number of pediatric and young population will reduce in the next few decades with the rise of elderly population [Figure 3a and b]. Increase in the number of old and retired persons will have a remarkable effect on health care. The burden of infectious diseases will reduce paving the way for the rise of noncommunicable diseases (NCDs). The protracted course of NCDs will increase the burden of people living with disabilities, the economic impact of which will be enormous. As we have been witnessing in Indian society, there is an increase in psychiatric illnesses including depression and suicide due to changes in societal aspirations, family conflict, unemployment, and many more. This will continue to pose a challenge for India in the coming days. The increasing burden of NCDs with more disability-adjusted life years and years of life lost due to these diseases will significantly affect the health resources of the country.

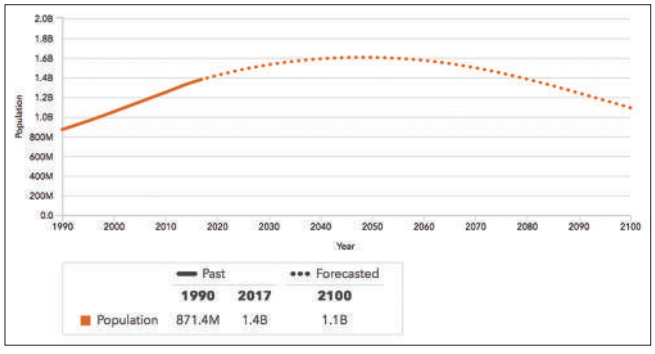

Figure 1: India's population change between 1990 and 2017 and forecasted data based on the Global Burden of Disease 2017 data

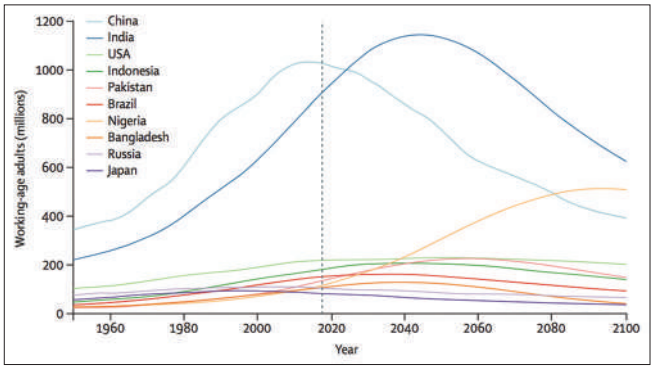

Figure 2: Population age structure for males and females in 1990, 2019 (reference scenario), and 2100 (reference scenario). Forecasted data based on the Global Burden of Disease 2017 results

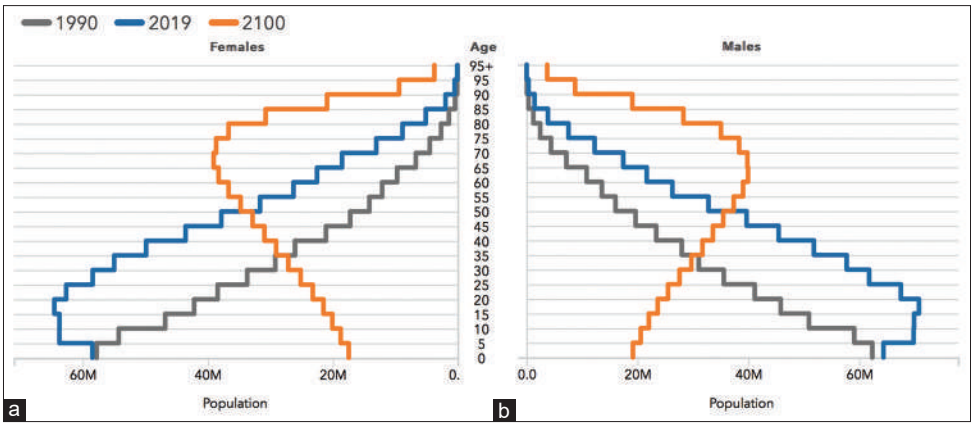

Figure 3: (a and b) Number of working-age adults from 1950 to 2100 in the reference scenario in the ten most populous countries in 2017

As many factors affecting human health are not restricted by geographical boundaries, international agreement is vital to restrict climate change, environmental pollution, poverty alleviation, and control of infections which have the risk of global transmission. Needless to say, we are passing through a time with despair and hopelessness in many fronts.

The inevitable climate change and its consequences on nature and human health are probably the most important issue which is a great cause for concern. The world is going to be warmer by 5°C by turn of this century[4] and its impact on the glaciers, with consequent flooding of coastal areas and frequent occurrences of natural disasters will greatly affect human life in near future.

Second, the socioeconomic disparity across the continents with conflicts resulting in civil wars at the national level and small-to full-scale wars at the regional and global level will also impact human health.

Third, environmental pollution has a great impact on human health. We are already witnessing the rising incidences of NCDs such as cancers, respiratory diseases, stroke, cardiovascular diseases, and dementia. Environmental pollution has been implicated to many of these NCDs.

Fourth, the pandemic of unknown infections, including zoonotic viruses, is also a serious threat to humanity in coming years. The memory of the COVID-19 pandemic is still afresh and future pandemic is looming large on our head.

India's ascend to global platform demands its leadership in all these fronts, ensuring consensus in providing more funds to health and social sectors, and supporting underdeveloped nations so that "Health for All" becomes an achievable goal.

In the coming years, India will conquer many infectious diseases and the darkness of illiteracy. With the largest number of working people, India will become the third-largest economy in the next three decades. However, providing health care to every Indian is still a distant reality. With the rising cost of health care and lack of insurance of vast majority of the population, the dream of universal health care will remain unfulfilled unless we take some important policy decisions urgently. We have been listening to political debates for more resource allocation for public health, and free health care for all Indians. But no one underscores the importance of these, we need to broaden our vision. Health is inseparable from many other aspects of public life. That providing education to all, particularly girls improves maternal and child health indices are well-established. Investing on the universal availability of safe and potable drinking water, proper sewage disposal, improvement of hygiene, and strengthening public distribution system to provide food for all are equally important for the improvement of health of the nation. Technological advancement for lesser dependence on fossil fuel with reduction of carbon emission may not have an immediate impact but will help achieve a healthy world liveable for future generations, a demand which cannot be ignored.

India's progress and rise in the world stage require not only increase in its GDP and defense superiority but also all-round development of all health indices.

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Original Article

Expression analysis of leptin and leptin receptor in prostate cancer and its association with clinicopathological parameters: A case–control study

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Abstract

Aim: The aim of this study is to evaluate the expression analysis of leptin and leptin receptor (LR) in prostate cancer and to determine its association with other clinicopathological parameters.

Materials and Methods: Following the screening of the patients fulfilling the inclusion criterion, prostate biopsy specimens were taken and studied. After histopathological diagnosis, immunohistochemistry was done on paraffin-embedded tissue with suitable antibodies. Results were tabulated and analyzed using suitable variables such as mean, median, standard deviation, and Pearson correlation for trend.

Results: A total of 77 patients were analyzed out of which 45 were benign and 32 were malignant. Expression of leptin and LR was studied in both benign and malignant tissues and a correlation between these two was found in prostate malignancy which was statistically significant.

Conclusion: Our findings concluded that LR expression could be a potential prognostic biomarker for prostate malignancy.

Keywords: Leptin, leptin receptor, prostate cancer, benign prostatic hyperplasia

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INTRODUCTION

Prostate cancer (PCa) stands second in terms of most commonly diagnosed cancer in men with an estimated incidence of 7.3% worldwide, 2.6% in India, and in accordance with cancer-related mortalities it is second only to lung cancers.[1]

Those in Western countries have reported a much higher incidence of PCa than those living in far east,[2] strongly indicating the importance of lifestyle factors in the genesis of this particular cancer. A lifestyle enveloping high-caloric intake from energy condensed diet and sedentary lifestyle leading to obesity has persistently been implied as an important risk factor for this cancer in many international comparison and experimental studies.[3-5]

According to a survey, which was conducted in 2005, obesity is a majorly growing epidemic sharing as much as 33% of the world's adult population load.[6] The fact that obesity increases risk for ischemic heart disease,

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hypertension, and diabetes is known to one and all. Obesity has a strong correlation with various malignancies such as colon, breast, endometrial, pancreatic, renal cell, and esophageal cancers.[7] Although it has been calculated that as large as 14% of the death in men from cancer is due to obesity which intensifies the above statement.[7] However, the link between obesity and PCa risk currently is under debate although there have been some studies using body fat measurement and disease stratification according to PCa have found a strong association between these two.[8]

In particular, the adipose hormone leptin has been shown to be positively associated with PCa. Recently, there has been an upcoming and growing interest regarding the study of the cellular and molecular mechanism of cancer through energy restriction models. Similarly, Berrigan *et al*. and Mai *et al*. concluded that energetic balance and cancer development are correlated, which are further explained by caloric restriction through leptin.[9]

Similarly, various hormones, leptin also requires receptor for performing its action. Therefore, the amount of leptin as well as number of leptin receptors (LRs) on any target cell are vital for its activity.

There have been *in vitro* studies showing leptin as a mitogenic factor in several malignancies. Leptin restores the growth and migration of neoplastic cells *in vitro* and catalyzes the proliferation of PCa probably by suppression of apoptosis, thus accentuating more aggressive biological behavior of malignancy.[10]

The LR Obesity gene Receptor (ObR) belongs to class 1 cytokine receptor family and has two isoforms. Short isoform mediates its transport and its own degradation. The long isoform Obesity gene receptor type b (ObRb) is expressed by hypothalamus and many peripheral cells, responsible for most of the central and peripheral actions. It is interesting to note that both receptors are found in prostate cell membranes.[9]

Leptin through testosterone and other obesity-related factors influences the cellular differentiation and progression of carcinoma prostate.[10]

One of the widely used methods to determine the prognosis of PCa is the Gleason scoring system based on histopathology which correlates with prostate-specific antigen (PSA) value, clinical and pathological staging, and incidence of lymph node and metastases. Although it is one of the most preferred methods for determining the prognosis still, there could always be a margin for subjective error when two different pathologists examine the same sample.[10]

Our study is designed to evaluate and analyze the expression of leptin and LR and to determine its association with other clinicopathological parameters and our hypothesis is that increased expression of both leptin and LR is associated with the progression and aggressiveness of PCa. Such information may be helpful for designing effective prognostic biomarker of disease.

MATERIALS AND METHODS

Patients and samples

The study involved male human participants and was approved by the Institutional Ethics Committee (Memo No. IPGME and R/IEC/2020/280) of IPGME and R, Kolkata. The procedure was initiated after taking the informed and written consent from each of the participants. After screening of the study population by serum PSA and digital rectal examination (DRE), we included all (n = 100) patients who underwent their first transrectal ultrasound (TRUS)-guided prostate biopsy at our institution during the study from December 2019 to December 2020. Patients with active urinary tract infection, H/O prostate surgery, and radiotherapy in a known case of PCa, were excluded from the study. The inclusion criterion for the study included all the patients presenting to the outpatient department with symptoms of lower urinary tract symptoms and suspected DRE finding and raised PSA (≥4 or both). A total of 77 patients (out of 100) were selected for the further study, of which 45 patients were of benign prostatic hyperplasia (BPH) and the rest 32 were of CaP (Carcinoma Prostate). Clinical parameters including patient demographic profile, serum PSA value (in sterile urine), and DRE findings were recorded in a well-prepared chart. TRUS was performed using a Samsung diagnostic ultrasound machine (Model No. SONOACE R7) with a 7.5-MHz transrectal end firing probe. The findings on TRUS were noted for both the right and left lobes with special mention to the features such as the presence of hypoechoic areas, calcifications in the center and periphery of the glands, as well as capsular distortion if any.

Histological evaluation

The number of biopsies taken was documented. A routine 12 core (2 cores from apex, mid-zone, and base of prostate on the periphery of both lobes) biopsies was the standard protocol and we sent all cores separately with proper labeling. Wherever required, we biopsied suspicious areas in addition to the standard 12 core. The core specimens were examined by pathologists at our institution.

Immunohistochemistry

The study of the expression of leptin and LR was done on paraffin-embedded sections of prostate tissue using a suitable antibody (for Ob, A-20 anti-rabbit Ab, sc-842, and ab5593 anti-rabbit Ab for ObR) following the standardized protocol. About 3–5 micrometer paraffin sections were dewaxed, rehydrated, and reacted overnight with primary antibodies at a dilution of 1:100 at 4°C. Further horseradish peroxidase conjugated goat anti-rabbit secondary antibody (sc-2012) was added at a dilution of 1:500. Later, the slide was developed using 3,3'-diaminobenzidine as the chromogen and counterstained with hematoxylin. Scoring was done under a bright-field microscope (Leica DM4000B, Germany). The final evaluation of the expression of leptin (L) and LR was done following the standard procedure by combining the scores of staining intensity (1 = weak, 2 = moderate and 3 = strong) and the percentage of positive cells (<1 = 0, 1–20 = 1, 20–50 = 2, 50–80 = 3, and >80 = 4) (Perrone *et al*.)[11]

Statistical analysis

Data were compiled in an Excel sheet to prepare the master chart and were presented using different statistical methods such as tables and diagrams. For descriptive statistics, mean, median, range, standard deviation, etc., were applied. For inferential statistics, the tests of significance, for example, Chi-square (of association and for trend), Pearson correlation coefficient, etc., were applied using GraphPad Prism v. 8 software Graph Pad PRISM (Version 7, 2016) ILLINOIS, USA.

RESULTS

A total of 77 samples were studied. Out of which, 45 were benign and 32 were malignant. The analyzed samples were from patients with a mean age of 64.26 ± 9.1 years (range, 50–70 years), with an average serum PSA level of 33.6 ± 49.20 ng/ml. In the quantitative analysis, 59.7% ±17.4% of the tumor cores and 58.6% ±20.2% of the nontumor cores were positive for leptin. With respect to LR expression, 74.4% ±17.1% (proportion ± SE) of the tumor cores and 75.4% ±17.1% (proportion ± SE) of the nontumor cores were positive.

We have explained in Table 1 and [Figure 1a and b] that the expression of leptin and LR in biopsy of benign and malignant tissue [Image 1a and b and 2a and b] is not statistically significant.

However, when we study the expression pattern score of leptin [Figure 2a] in both the samples, i.e., benign and malignant tissue, we cannot conclude, as there is no definite trend in these two samples, i.e., either static/increasing/decreasing.

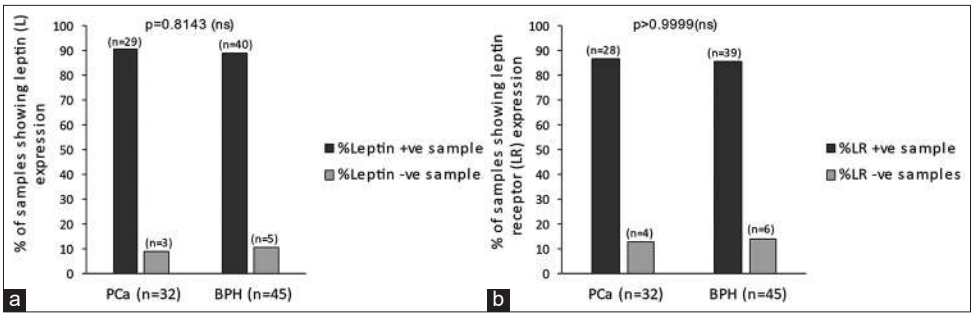

Figure 1: (a) Graphical representation of leptin (L) expression in PCa and BPH, (b) Graphical representation of leptin receptor (L) expression in PCa and BPH

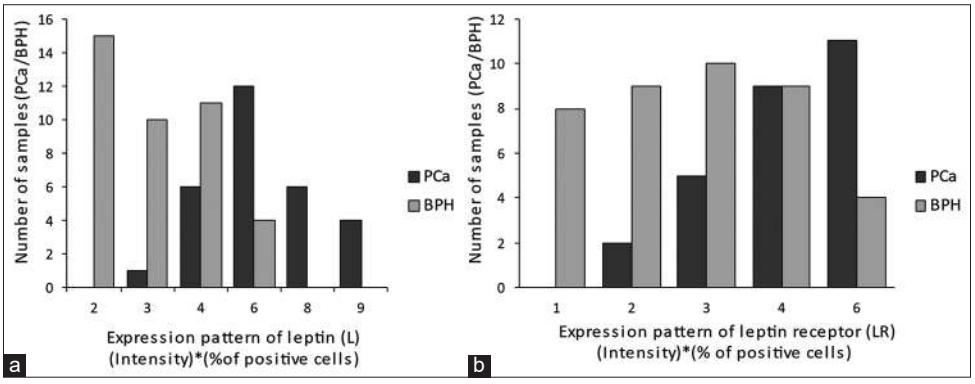

Figure 2: (a) Graphical representation of expression pattern of leptin (L) in PCa and BHP, (b) Graphical representation of expression pattern of leptin receptor (LR) in PCa and BPH

However, when we study the expression pattern score of LR [Figure 2b] in both the samples, i.e., benign and malignant tissue we can conclude that the expression pattern score of LR score, it has a rising trend in malignant tissue but it is not statistically significant.

However, as we study the interrelationship of leptin score and LR score in BPH tissue [Figure 3b, Table 2], we can conclude that there is no statistically significant correlation between these two. On the other hand, we can conclude [Figure 3a,Table 2] that there exists a statistically significant correlation between leptin score and LR score in malignant tissue.

DISCUSSION

All over the world, the prevalence of obesity is markedly increasing. The comorbidities with obesity share an enormous burden on the entire health-care system. Hence, it becomes important to understand the correlation between obesity and many other diseases such as cancer along with the mechanism involved. Calle *et al*. in their prospective cohort study of 900,000 U. S. adults concluded that death due to PCa was more seen in obese people. However, the relationship between obesity and PCa is complicated, because obesity is not only linked with excess body fat but is also associated with several other factors and hormones including testosterone,

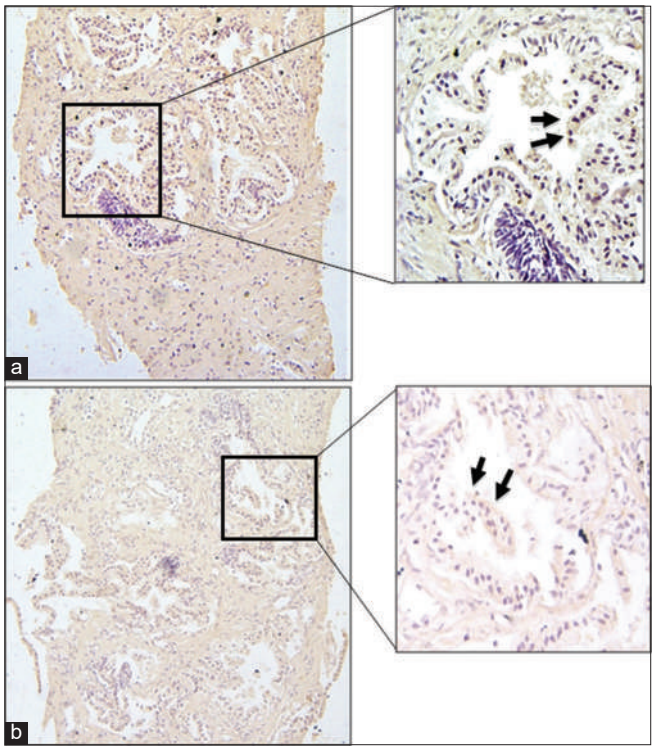

Image 1: (a) Immunohistochemical staining of leptin (L) of prostate epithelial cells in BPH, (b) Immunohistochemical staining of leptin receptor (LR) of prostate epithelial cells in BPH

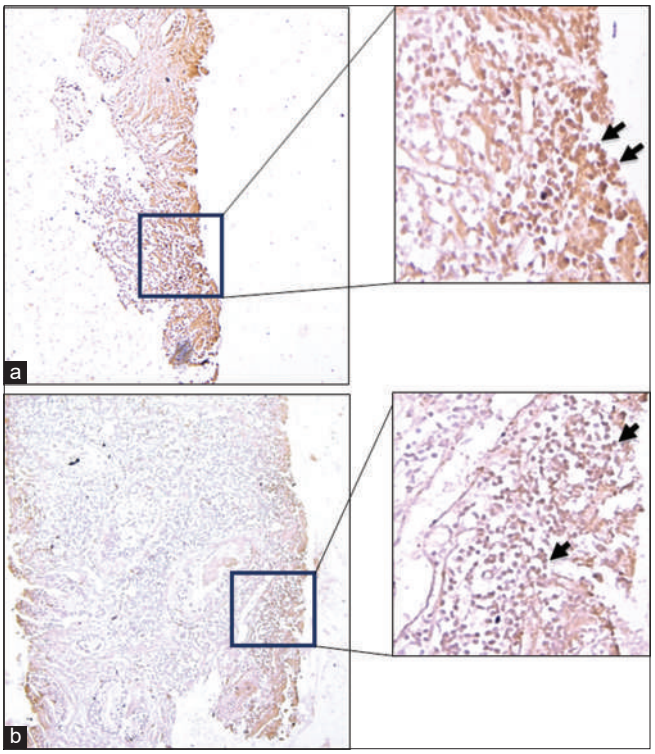

Image 2: (a) Immunohistochemical staining of leptin (L) of prostate epithelial cells in PCa, (b) Immunohistochemical staining of leptin receptor (LR) of prostate epithelial cells in PCa

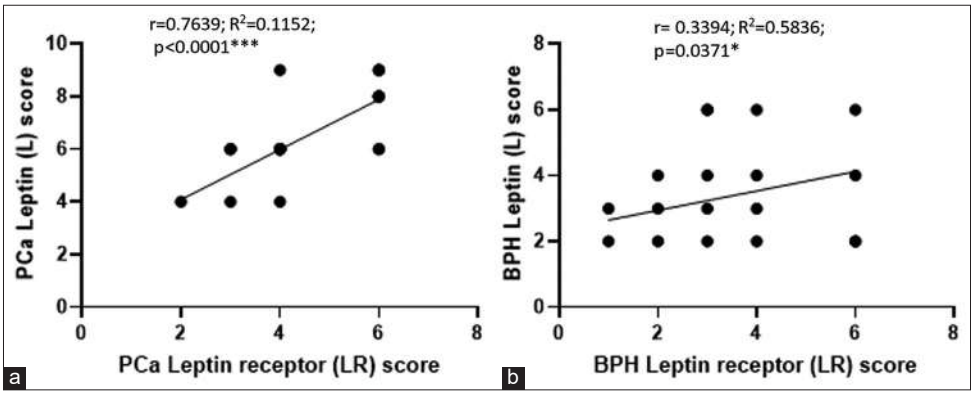

Figure 3: (a) Inter-relationshipof leptin (L) with leptin receptor (LR) in PCa, (b) Inter-relationship of leptin (L) with leptin receptor (LR) in BPH

Table 1: Expression of leptin and leptin receptor

Variables	Benign prostatic hyperplasia, *n* (%)	Cancer prostate, *n* (%)	*P* BPH versus PCa
L	40/45 (89)	29/32 (91)	0.8143 (NS)
LR	39/45 (86)	28/32 (87)	>0.9999 (NS)

NS: Not significant, L: Leptin, LR: Leptin receptor, BPH: Benign prostatic hyperplasia, PCa: Prostate cancer

Table 2: Immunohistochemical findings showing proportions of leptin and leptin receptor positivity in benign prostatic hyperplasia and cancer prostate

Variables	Pearson r	R^2	95% CI	*P* (two-tailed)
BPH	0.3394	0.1152	0.02214-0.5946	0.0371
PCa	0.7639	0.5836	0.5466-0.8848	<0.0001***

***$P < 0.05$ is significant, CI: Confidence interval, BPH: Benign prostatic hyperplasia, PCa: Prostate cancer

estrogen, insulin, insulin-like growth factor (IGF)-1, and leptin, all of these share some degree of link with PCa. In our study, we mainly focused on the expression of leptin and LRs in benign and malignant prostate tissue.[9]

Chang *et al*. in their study reported that more is the concentration of leptin greater the risk of a higher tumor load. Thus, leptin may appear as a risk factor for clinically relevant PCa.[12] Hsing *et al*. in their study reported a statistically insignificant association of leptin with PCa.[13]However, they also reported an association of leptin with PCa in Chinese male with a waist-to-hip ratio >0.87, suggesting the interaction of leptin with other markers related to abdominal obesity, for example, sex hormones or IGF-1.

Par Stattin *et al*. concluded that leptin could be responsible for cancer development by its direct effects in the prostate as high-LR messenger RNA levels have been noted in the prostate. They noted the presence of immunoreactive LRs in normal prostatic cells, high-grade prostatic intraepithelial neoplasia (HGPIN), and prostatic cancer cells. As leptin is related to secondary sexual organ growth during puberty, it is hypothesized that it could influence the development and progression of PCa by its direct effect. In our study, we also found that there is a strong correlation between leptin and LRs in malignant tissue.[14]

Osório *et al*.[10] concluded that leptin is more intensely present in tumors than in hyperplasic tissues; also it is more in locally advanced and metastatic tumors as compared to localized tumors. With this, it could be said that leptin could be used as a predictor of progression and malignancy of disease. Our study also states the same although the difference is not statistically significant.

CONCLUSION

The result of our case–control study suggests that there exists a positive statistically significant correlation between leptin score and LR score in malignant tissue. LR may be used as a prognostic biomarker in prostate malignancy. To establish a confirmation further research in this field is required.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

Correlation between predominantly subclinical peripheral arterial disease in patients with ischemic stroke: A study using ankle–brachial index from rural eastern India

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Abstract

Introduction: Peripheral arterial disease (PAD) decreases arterial perfusion leading to limb ischemia. It is considered one of the markers of subclinical atherosclerosis process. For this reason, it can be a major risk factor for ischemic stroke. Early detection of PAD has an important role in preventing ischemic stroke.

Materials and Methods: This study was carried out in District Hospital, Barasat, Kolkata, from March 2011 to March 2013. Eighty-two patients with ischemic stroke (aged 40–80 years) were recruited. Patients having atrial fibrillation and diabetes mellitus and embolic source were excluded. Ankle–brachial index (ABI) was performed with ultrasonography Doppler in each patient. PAD was diagnosed when the ABI was below 0.9. The severity of stroke was assessed by the National Institutes of Health Stroke Scale.

Statistical Analysis: For continuous variables, analysis of variance was used to compare three or more groups of patients and Student's *t*-test for two groups. Chi-square test or Fisher's exact test was used for categorical variables. For all analytical purposes, a two-tailed $P < 0.05$ was considered statistically significant.

Results: According to ABI, 62 patients had no pad, 13 patients had mild, and 7 patients had severe PAD. High total cholesterol and low-density lipoprotein were significantly associated with low ABI ($P = 0.001$). High total cholesterol levels and low ABI were significantly correlated ($P < 0.001$). A significant association between moderately-low ABI and recurrent stroke was noted ($P = 0.019$).

Conclusion: PAD is significantly associated with recurrent ischemic strokes. Evaluation of ABI for PAD revealed increased risk of recurrent stroke.

Keywords: Ankle–brachial index, peripheral arterial disease, ischemic stroke

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INTRODUCTION

Acute ischemic stroke is a clinical episode of sudden-onset focal cerebral, spinal, or retinal dysfunction lasting for ≥24 h and/or showing ischemic changes on brain imaging (especially diffusion-weighted imaging) irrespective of the time of presentation.[1] Ischemic strokes constitute nearly 87% of all strokes and remain one of the major public health issues with significant morbidity and

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Table 1: Comparison of clinical variables according to the levels of ankle–brachial index in current study

Variables	ABI				Total	*P*
	Normal	Mild PAD	Moderate PAD	Severe PAD		
Hemoglobin (g/dl)	11.14±1.69	10.94±1.21	11.11±2.03	0.00±0.00	11.11±1.64	0.921
WBC count	7630.51±2153.69	7123.08±2354.13	6371.43±2446.57	0.00±0.00	7435.44±2215.56	0.316
Serum sodium (mEq/l)	139.32±8.16	140.69±9.93	137.43±7.68	0.00±0.00	139.38±8.36	0.708
Serum potassium (mEq/l)	4.38±0.58	4.42±0.47	4.26±0.73	0.00±0.00	4.38±0.58	0.834
FBS (mg/dl)	88.39±13.47	89.31±14.85	92.14±9.19	0.00±0.00	88.87±13.29	0.777
PPBS (mg/dl)	124.22±8.32	126.92±12.23	124.14±8.03	0.00±0.00	124.66±8.97	0.615
Total cholesterol (mg/dl)	165.80±43.73	216.92±61.31	204.14±46.01	0.00±0.00	177.61±50.89	0.001**
HDL (mg/dl)	47.42±6.06	43.69±6.21	43.86±6.87	0.00±0.00	46.49±6.28	0.076+
LDL (mg/dl)	100.32±44.45	157.38±63.08	141.71±56.98	0.00±0.00	113.38±53.43	<0.001**

ABI: Ankle–brachial index, PAD: Peripheral arterial disease, WBC: White blood cell, FBS: Fasting blood sugar, PPBS: Postprandial blood sugar, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

Table 2: Distribution of lipids in relation to ankle–brachial index

Variables	ABI				Total (*n*=82), *n* (%)	*P*
	Normal (*n*=62), *n* (%)	Mild PAD (*n*=13), *n* (%)	Moderate PAD (*n*=7), *n* (%)	Severe PAD (*n*=0), *n* (%)		
Total cholesterol (mg/dl)						
<200	53 (85.5)	5 (38.5)	2 (28.6)	0	60 (73.2)	<0.001*
200–280	6 (9.7)	7 (53.8)	5 (71.4)	0	18 (22)	
>280	3 (4.8)	1 (7.7)	0	0	4 (4.9)	
HDL (mg/dl)						
<35	3 (4.8)	1 (7.7)	1 (14.3)	0	5 (6.1)	0.354
35–60	59 (95.2)	12 (92.3)	6 (85.7)	0	77 (93.9)	
>60	0	0	0	0	0	
LDL (mg/dl)						
<70	1 (1.6)	0	0	0	1 (1.2)	0.018*
70–190	52 (83.9)	6 (46.2)	5 (71.4)	0	63 (76.8)	
>190	9 (14.5)	7 (53.8)	2 (28.6)	0	18 (22)	

*Statistically significant, ABI: Ankle–brachial index, PAD: Peripheral arterial disease, LDL: Low-density lipoprotein, HDL: High-density lipoprotein

mortality.[2-4] However, the prevalence of ischemic stroke is somewhat lower in India.[5] Stroke is associated with significant functional disability, psychological, financial and multiple other poststroke complications.[6-8] Peripheral arterial disease (PAD) primarily belongs to the spectrum of systemic atherosclerosis, which decreases arterial perfusion to lower extremities and leading to limb ischemia.[9] It is a treatment-modifiable, potentially disabling yet greatly underdiagnosed illness, affecting over 200 million adults worldwide with or without producing symptoms and hence can escape detection in primary care specialties and even more so in rural-based, resource-poor health-care setups in developing countries.[9,10] Albeit, even in asymptomatic patients with undermined PAD, early detection remains crucial as it can be considered one of the surest markers of a yet-to-be-diagnosed ongoing systemic atherosclerotic process affecting other vascular beds that is critical for life.[9,11,12] For the systemic nature of the atherosclerotic process when one vascular bed (i.e., peripheral arteries) gets affected resulting in PAD, the others (i.e., craniocervical and coronary arteries) will not be spared resulting in cerebrovascular accidents (e.g., ischemic strokes)[13] and heightening of risk of major adverse cardiovascular events (MACEs), i.e., cardiovascular death, myocardial infarction, or ischemic stroke.[12,14] Multiple previous international studies have reported a strong association between ischemic stroke and PAD.[13,15,16] Discussion of the insights from the study by Kolls *et al.* concluded that multiple comorbid conditions (e.g., diabetes mellitus, hypertension, prior stroke, atrial flutter/fibrillation, prior amputation, lower ankle–brachial index (ABI), geographic location, and age) were found to have independent association with occurrence of all-cause stroke.[16] Therefore, for the prevention of all three MACEs, early detection of PAD and starting adequate therapy are a *sine qua non*.[17]

A population-based, cross-sectional telephonic survey revealed the presence of a substantial awareness gap among population in general about PAD.[18] Another descriptive study by Builyte *et al.* concluded recently that patients with PAD are more ignorant about their disease and disease process (i.e., atherosclerosis) and they tend to have less attainment of the overall level of education hindering the early diagnosis and management of the disease.[19] However, unfortunately, the knowledge regarding natural history, diagnosis, and management of PAD amid the primary care physicians and general practitioners worldwide seems to be inadequate too.[20,21]

Till date, there is lack of a reliable, affordable, and widely available diagnostic tool, which can detect PAD as a part of

systemic atherosclerosis with utmost precision, sensitivity, and specificity and predict future vascular events, especially ischemic cerebrovascular diseases.[22] One of the easy methods for the evaluation of PAD is by the estimation of (ABI).[22-24] ABI can be easily evaluated in variety of health setups where an ultrasonography (USG) machine with a Doppler probe is available. With the help of USG Doppler, PAD can be identified at earlier stages and can be managed accordingly. Hence, the evaluation of PAD on large scale and at various health-care systems can help find patients with increased risk of vascular events, especially ischemic cerebrovascular and cardiovascular events,[24] and can potentially reduce the social burden of diseases mentioned.

In spite of multiple studies showing a strong association between ischemic cerebrovascular events and PAD,[13,15,16] the association has been barely evaluated in rural-based health-care system in India. Currently, there is a need for simple investigations, which could detect patients "at risk" of developing new-onset and recurrent ischemic cerebrovascular events. With earlier detection of susceptible patients, they can be potentially put on targeted lifestyle modification and other available treatment modalities.[17,25]

This study was designed to find out the correlation between patients with ischemic strokes and PAD in a rural-based health-care setup with limited availability of resources. PAD was evaluated by the calculation of ABI and patients were classified accordingly.

MATERIALS AND METHODS

Patient population

The study was carried out in the 24 Parganas (North) District Hospital, Barasat, Kolkata, from March 2011 to March 2013, according to the Declaration of Helsinki regarding clinical study using human subjects and after approval of the Institutional Ethics Committee. A total of 82 patients were recruited after sample size calculation according to the following inclusion criteria: ischemic stroke patients aged 40–80 years admitted in the inpatient general medicine ward. Patients having any atrial fibrillation or diabetes mellitus were excluded.

Determination of ankle–brachial index

ABI was measured by USG Doppler method according to the recommendation of the American Heart Association. The patient was kept in supine position for 5 min and remained still during the measurement. The blood pressure cuff was positioned according to the straight wrapping method, with lower edge about 2 cm above the medial malleolus. During measurement, the probe was moved to the position with the clearest signal, and then the cuff was gradually inflated until the disappearance of the signal and then gradually deflated until its reappearance. For the calculation, the highest systolic blood pressure in the leg was divided by the average systolic pressure in the arm. PAD was diagnosed when the ABI was below <0.9.

Ischemic stroke evaluation

The patients were assessed using magnetic resonance imaging with diffusion-weighted imaging and magnetic resonance angiography and transthoracic echocardiography, along with the measurement of hemoglobin A1c and lipid profile. The assessment of the severity of stroke in the patient group was carried out according to the National Institutes of Health Stroke Scale classification.[26] All possible sources of embolism were evaluated and all possible embolic strokes were excluded.

Statistical analysis

The results on continuous measurements were presented on mean ± standard deviation (SD) and the results on categorical measurements were presented in number (%). For continuous variables, analysis of variance was used to compare three or more groups of patients and Student's *t*-test for two groups. Chi-square test or Fisher's exact test was used for categorical variables. For all analytical purposes, a two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Study population demographic

The mean age for the patient group was 62.07 ± 9.24 years. The maximum number of patients (32.9%) was in the age group of 51–60 years. 57.3% of patients were female. According to ABI, 62 patients had no PAD, having a value equal to or higher than 0.9. Thirteen patients were suffering from mild PAD (0.81–0.90) and seven patients from moderate PAD (0.51–0.80). Further, 13 patients had a previous history of ischemic stroke, constituting 15.9% of the study population.

Association between ABI and lipid profile

In females, the ABI value was 0.98 ± 0.14 (mean ± SD), whereas in males, it was 0.97 ± 0.13 (mean ± SD). The difference was not statistically significant ($P = 0.369$). High total cholesterol and high low-density lipoprotein (LDL) were associated significantly with low ABI ($P = 0.001$). The occurrence of mild- and moderately-low ABI was significantly higher in patients with higher total cholesterol ($P < 0.001$), showing a strong association between high total cholesterol levels and low ABI. Further,

LDL levels showed that the occurrence of low ABI (mild and moderately low) increased with an increase in the levels of LDL values ($P = 0.018$).

Ankle–brachial index and its relation with history of ischemic stroke

Previous stroke was present in significantly higher percentage of patients with moderately-low ABI, i.e., 4 out of 7 patients with moderately-low ABI when compared to patients with normal ABI (8 patients out of 62 patients) and with mild-low ABI (1 patient out of 13 patients), showing a moderately significant association between moderately-low ABI and recurrent stroke ($P = 0.019$).

History of ischemic stroke and lipid profile

There was a noticeable increase in the occurrence of stroke in patients with moderately-low ABI when compared to patients with normal and mild-low ABI. As low ABI signifies PAD, there was a significant association between recurrent stroke and PAD. There was a significant association ($P < 0.030$) of high cholesterol with a history of previous stroke. Furthermore, a significant association of ($P = 0.049$) was observed between the presence of a previous stroke and higher LDL values. No association was found between previous stroke and high-density lipoprotein levels. The results are summarized in Tables 1 and 2.

DISCUSSION

In comparison to atherosclerotic vascular disorders in other arterial beds, peripheral arterial disease (PAD) has poorer prognosis.[27] Despite that and evidently high prevalence of PAD in patients with stroke[28] and that of stroke in patients with diagnosed PAD, the epidemiology, management, and preventive strategies are somewhat neglected.[27] Henceforth, customary evaluation for PAD in patients with ischemic stroke is seldom undertaken and thus many cases remain undiagnosed, resulting in an apparently lower prevalence of the entity.[29] In recent times, the fact that the presence of PAD indicates a noticeable high risk of future strokes and that management of PAD has a definite role in primary and secondary prevention of stroke, has been established beyond doubt.[15,16,27-30]

This study in discussion has found that recurrent ischemic strokes were significantly more prevalent in patients with moderately-low ABI compared to patients with normal or mild-low ABI. A remarkable rise of prevalence of recurrent ischemic cerebrovascular events was observed in patients with moderately-low ABI. As moderately-low ABI values signify the presence of moderate PAD.. The current study also has found the prevalence of PAD (having an abnormal ABI) in about one-fourth of patients with ischemic cerebrovascular events. A similar prevalence of PAD (abnormal ABI) was reported in some of the earlier studies on ischemic stroke and PAD measured by either ABI[15,31,32] or computerized tomographic angiography.[29] One-third of these patients having abnormal ABI belonged to moderately-low ABI category, implying that one-third of patients with abnormal ABI (PAD) carried an increased risk of recurrent ischemic strokes. Ratanakorn *et al*. and Meves *et al*. had found a similar increase in recurrent ischemic strokes associated with lower ABI values.[31,33] Hence, the evaluation of ABI for finding PAD in patients with ischemic cerebrovascular events must be done to identify patients with an increased risk of recurrent stroke. These patients with moderately-low ABI can be treated aggressively by available modalities of treatment including hypolipidemic drugs, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, antiplatelets, and lifestyle modifications to decrease the risk of recurrent stroke.[25,34-37]

Patients with mild-low ABI indicating mild PAD were not associated with a significant increase in recurrent stroke when compared to patients who had normal or moderately-low ABI patients. These patients may potentially progress to worsening of PAD and progress to moderately-low ABI due to risk factors associated as shown in a meta-analysis by Sigvant *et al*.[37] Hence, these patients could be potentially targeted for lifestyle modifications and available treatment modalities to decrease or to halt progression to moderately-low ABI.[36,37] These measures in patients with mild-low ABI may reduce social, economical, and psychological burden of recurrent stroke.[34,38,39]

In this study, however, no patient with severely-low ABI was found. The reason for this finding is that probably less number of patients aged more than 70 years were included in the study, and as a matter of fact that with aging, the prevalence of PAD increases.[40] Diabetes mellitus is considered one of the most important risk factors for the development of PAD.[41] Besides, it is also an independent risk factor for the development of new and recurrent strokes.[42,43] To eliminate confounding bias, in the current study, patients with diabetes mellitus were excluded. Furthermore, smoking is considered one of the important risk factors for PAD,[44,45] but the majority of this sample population were nonsmoker female patients. This could be another plausible reason why patients with severely-low ABI were not found in the current study.

Tummala *et al*. reported PAD to be very common yet underdiagnosed entity in rural India,[46] similar to the global

scenario as discussed previously. One definite reason for this is unawareness in part of asymptomatic patients as well as treating doctors and the other is nonavailability of a reliable, simple, precise, sensitive, and specific diagnostic tool for the evaluation of PAD and generalized atherosclerosis. Evaluation of PAD can be done with an assessment of ABI, an easy and affordable screening and diagnostic test that can be used in community as well.[46] For populations at risk, ABI is an excellent screening test for the presence of PAD due to its high sensitivity, specificity, and low cost.[47] The most recent article by Konieczna-Brazis *et al*. concluded ABI measurement to be a first-line tool for the assessment of vascular status[48] among population with atherosclerotic involvement of other vascular territories. They also demonstrated that the prevalence of low ABI correlated significantly with the presence of ischemic cerebrovascular events.[48] Hence, in a resource-poor health-care setup like ours by merely measuring ABI, the risk of atherosclerotic strokes can be predicted, and with the help of comorbidity and lifestyle modifications, the risk of recurrent stroke can be prevented to some extent.

CONCLUSION

Considerable number of patients with ischemic cerebrovascular events (ischemic strokes) present with low ABI, indicating the presence of peripheral artery disease (PAD). The current study concluded that PAD is significantly associated with recurrent ischemic strokes. Hence, the evaluation of ABI for PAD can help us detect patients with increased risk of recurrent stroke. Such patients can be potentially targeted for different treatment modalities or lifestyle modification. It is also concluded that newer modalities of more efficient techniques for identifying PAD in ischemic stroke patients should be developed, which will be cost-effective, available at nearly all health-care setups. Currently, ABI and USG Doppler should be incorporated as routine investigations for patients presenting with either new-onset or recurrent ischemic strokes to potentially reduce social burden and subsequent health consequences, by treating PAD beforehand.

Limitations

The study was carried out at North 24 Parganas District Hospital, Barasat, Kolkata, West Bengal, so similar results may not be reproducible in other geographical areas.

Sample size was limited to 82; hence, similar results may not be necessarily reproducible in large sample studies.

Patients' follow-up, morbidity, and mortality concerns were not included in the study; hence, a comment on those parameters is not possible considering these study population. Patients with diabetes mellitus and atrial fibrillation were excluded from the study; hence, similar results may not be reproducible in patients with ischemic stroke and abovementioned clinical scenarios.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Cancer care during the pandemic period: A hospital-based survey for future reference

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Abstract

Background: Worldwide pandemic due to the novel coronavirus, SARS COVID-19, forced the human race at a stake due to an unprecedented lockdown from March 23 to May 31, 2020. It jeopardized the normal quality of life to all population of India. Special sufferers were the infirmed people who need hospital-based management. Cancer patients were affected mostly as due to the fact that chemotherapy and radiotherapy are cycle specific and hospital specific as patients have to come to the hospital for getting radiation therapy.

Objective: We aimed to assess how cancer patients were affected in a tertiary cancer care hospital.

Methodology: During the lockdown period how much reduction of cancer service at different segments such as the outpatient department, indoor admission, teletherapy, and palliative care were influenced and were compared with the corresponding figures of the nonlockdown period of the previous 3 years were compared.

Results and Conclusion: Around 30% reduction of hospital attendants in cancer follow-up clinics and new patient registration was attributed. More than 30% of patients failed to get radiotherapy compared to the previous years' record. All these figures contributed adversely to upstage presentation in the postlockdown phase with obvious morbidity and mortality.

Keywords: Cancer care, cancer survey, lockdown, pandemic

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INTRODUCTION

The COVID-19 disease caused by the infection of SARS CoV-2 was first reported in Wuhan, China, in December 2019. The virus spread quickly across the world in multiple countries due to modern international connectivity. In India, the first case was reported in January 2020. The rapid rise of active cases led to a nationwide lockdown on March 23, 2020, onward till May 31, 2020. Like many other diseases, cancer sufferers were much affected in the pandemic period due to lockdown. Cancer care is a multidimensional approach consisting of surgery, radiotherapy, chemotherapy, and palliative care in a tertiary care center. The nationwide lockdown halted almost all kinds of transport systems and patients could not reach their treatment centers on scheduled dates. The diagnosis and management of cancer are strictly time sensitive and gets considerably affected by these disruptions. Nearly 70% of patients could not have life-saving surgeries and chemotherapy treatments were also postponed.[1,2] We aimed to assess

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the consequences of the COVID-19 pandemic on cancer care in our institution.

METHODOLOGY

A retrospective, observational study was conducted from March 23, 2020, to May 31, 2020. All the patients who attended the inpatient department (IPD), outpatient department, day-care unit, and teletherapy unit were included in our study. Here, we have collected the attendance of patients and expenses incurred and compared them with that of the mean of the previous years' data. Descriptive statistics were used to assess the losses in health-care delivery and patient footfalls as a consequence of a nationwide lockdown from March 23, 2020, to May 31, 2020. There were no exclusion criteria for the selection of subjects in our study.

RESULTS

A total of 3321 patients attended the radiotherapy department during the lockdown period from March 23 to May 31, 2020. Table 1 shows the comparison between the difference in footfalls during the lockdown period (from March 23 to May 31, 2020) and that of the previous year's data for the same period.

Eighty-eight patients attended the telecobalt unit for external beam radiation therapy (EBRT): 75 patients were treated with curative intent and 13 patients received palliative radiotherapy. In contrast, 280, 310, and 296 patients attended the telecobalt unit in 2019, 2018, and 2017, respectively [Figure 1].

From March 23 to May 31, 2020, 429 patients attended the day-care unit in contrast to 940, 860, and 780 patients, who attended the day-care unit during the same period in 2019, 2018, and 2017, respectively [Figure 2].

294 new patients were registered along with 2044 patients who came for regular follow-up in the outpatient department from March 23 to May 31, 2020. 6678, 5396, and 5082 patients came for regular follow-up in 2019, 2018, and 2017, respectively. Along with those patients, 820, 780, and 670 new patients were registered in the respective years [Figure 3].

During March 23 to May 31, 466 patients were admitted in the indoor patients department, whereas 2384, 1862, and 1539 patients were admitted in 2019, 2018, and 2017, respectively [Figure 4].

The pie charts in figure 5 and 6 show travelling expenses with respect to distance travelled. It is observed that the

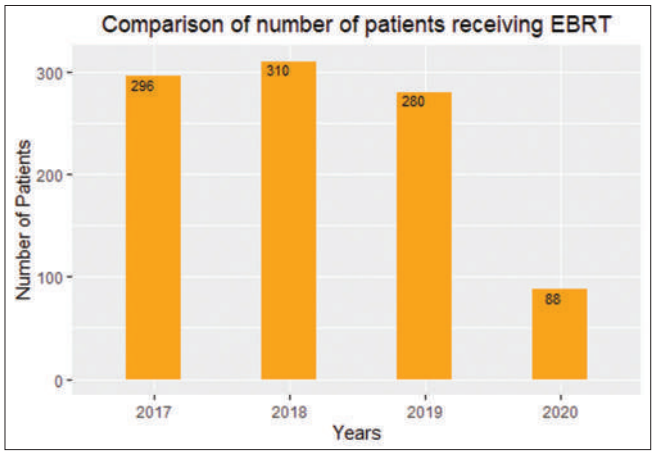

Figure 1: Comparison with respect to EBRT treatment. EBRT: External beam radiation therapy

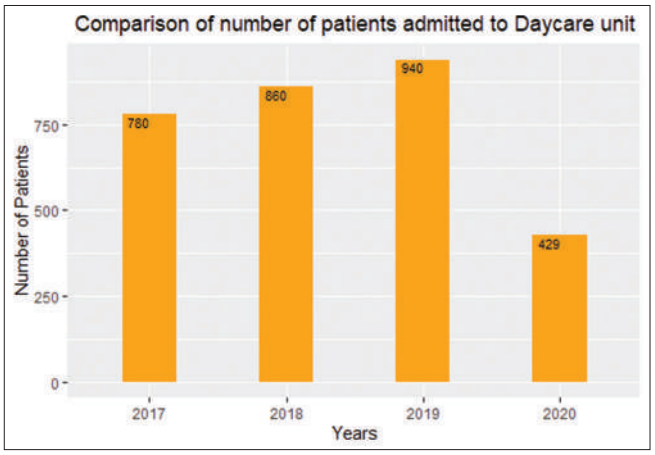

Figure 2: Comparison with respect to total admission in the day-care unit

Table 1: Number of patients in different fields of comparison

Fields of comparison	Years			
	2017 (23rd March to 31st May)	2018 (23rd March to 31st May)	2019 (23rd March to 31st May)	2020 (23rd March to 31st May) lockdown period
Number of patients receiving EBRT	296	310	280	88
Total admission in day-care unit	780	860	940	429
Attendance in OPD				
Follow-up cases	5082	5396	6678	2044
New cases	670	780	820	294
Patients in indoor unit	1539	1862	2384	466

EBRT: External beam radiation therapy, OPD: Outpatient department

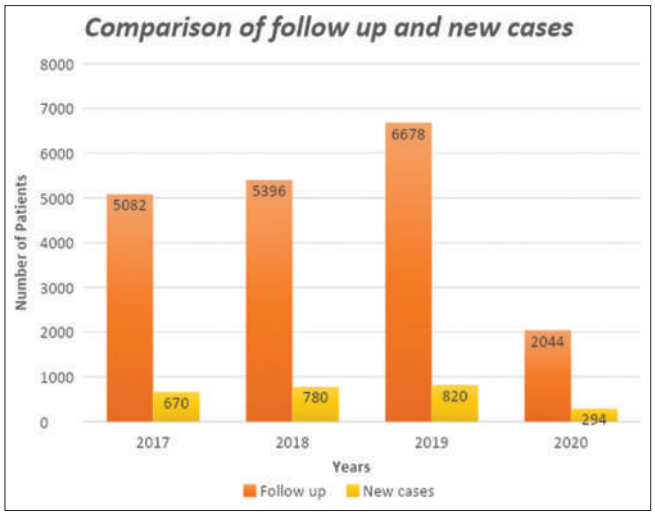

Figure 3: Comparison with respect to attendance in OPD. OPD: Outpatient department

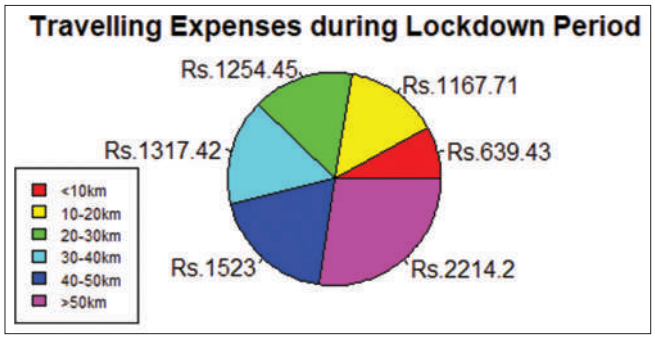

Figure 5: Comparison of traveling expenses during lockdown

average traveling expenses increased to a great extent during the COVID-19 period as compared to the normal period, which may be attributed to the mayhem due to the nationwide lockdown.

DISCUSSION

A decline in the number of patient footfalls cannot be a mere statistics in this pandemic; it is equally a matter of concern. The magnitude of the impact of COVID-19 lockdown on cancer care was emerging globally.[3,4] From the above study, it is evident that during the lockdown period, although the hospital services were fully functional, less number of patients attended the day-care unit as well as were admitted in IPD. Furthermore, less number of patients received EBRT during complete lockdown as compared to the number of patients receiving EBRT in the previous years' same period.

We observed that even though the patient's family members knew that delay in the treatment procedure or interruption during chemotherapy or radiation therapy causes progression of the disease and may upstage the disease

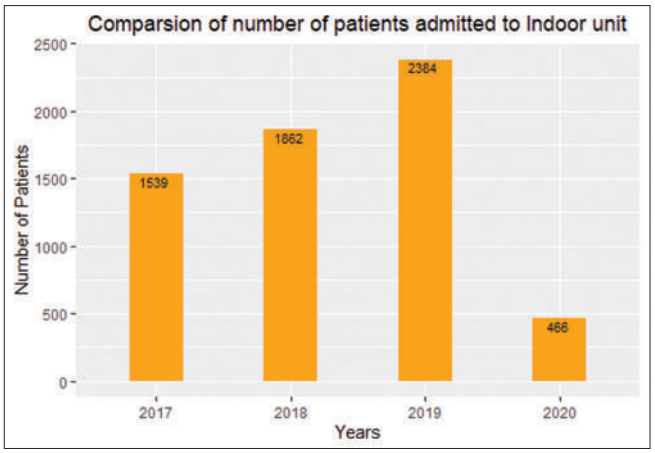

Figure 4: Comparison with respect to indoor unit

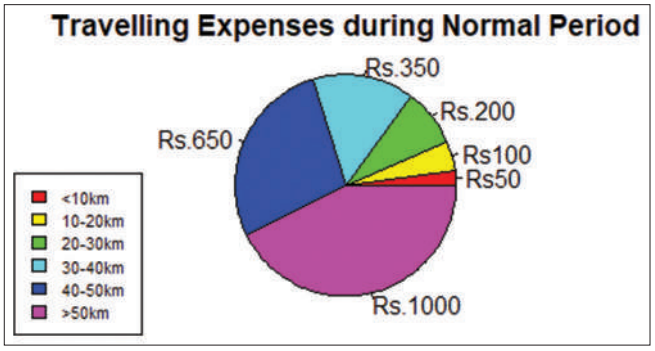

Figure 6: Comparison of traveling expenses during normal days

leading adversely from a curable disease to an incurable, this unforeseen pandemic claimed many lives of patients irrespective of their social status. Traveling expenses added a superlative burden to many cancer-affected families. It is observed that the average traveling expenses increased to a great extent during the COVID-19 period as compared to the normal period which may be attributed to the mayhem due to the nationwide lockdown.

Because the inception of COVID-19 was unpredicted, the patients had to suffer a lot due to the sudden announcement of restrictions in public transport. Coming to the traveling expenses patients could avail the public transport during the normal period. Due to the nationwide lockdown as declared by the government, the public transport system was totally withdrawn and patients had to avail special personal transportation facilities which led to an increase in travel expenses. As cancer is a chronic disease and the patients need to turn up to the health-care institutions multiple times either for receiving chemotherapy, radiotherapy, or for supportive care, these sections of patients had to pay havoc due to the ban on public transport at the cost of deterioration of their own health. COVID-19 is associated with more complications

in cancer patients.[5] Similarly, Patil *et al*. and Chauhan *et al*. also reported a decline in the patients' attendance during the COVID-19 lockdown period.[6,7] More emphasis is to be given on the usage of oral chemotherapy and targeted therapies.[8-10]

CONCLUSION

The pandemic is still in full swing but we have passed through the worst phase. It is high time for the respective authorities to undertake appropriate strategies to analyze the impact of this pandemic and take necessary actions for decentralizing cancer care. Home-based care may be encouraged. The local health-care personnel should be imparted training in basic management of cancer cure. They also should provide mental support to the patients and to their families at this critical period. Teleconsultation should be promoted instead of regular visits to the hospital, as an alternative of routine follow-up as the latter is a mere impossibility. Furthermore, some proactive measures to be undertaken to improve the health conditions of these patients, most of whom had upstaged the disease as a consequence to long-term abstinence from attending hospital for initiation of cancer radical therapy. We have lost many patients who failed to attend our follow-up clinic due to financial constraints and the unavailability of transport systems.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Metabolic syndrome and bladder carcinoma – A cross-sectional study

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Abstract

Background and Objective: Urinary bladder carcinoma is one of the most common carcinomas of the genitourinary tract. Smoking and male sex being an established etiological factor for bladder carcinoma, the rising incidence is seen in nonsmokers as well as in females suggesting other probable etiologies such as metabolic syndrome. Our intention was to know the association between metabolic syndrome and the risk of urinary bladder carcinoma and its histopathological grading.

Materials and Methods: A retrospective cross-sectional study of 201 patients was performed after ethics clearance in a tertiary care hospital in India, between June 1, 2017, and May 31, 2019. The data of patients of urothelial carcinoma bladder were divided into two groups based on the presence or absence of metabolic syndrome and its associated variables for comparison and evaluation.

Results: Of the total 201 patients, 15 patients had metabolic syndrome. In metabolic syndrome patients, ten patients had high-grade tumors and five patients had low-grade tumors. Moreover, in metabolic syndrome negative patients, 145 were of low grade and 41 were of high grade. Body mass index >30, triglyceride levels >150 mg/dL, and high-density lipoprotein level <40 mg/dL were mostly present in patients of metabolic syndrome, and its association was statistically significant.

Interpretation and Conclusion: Metabolic syndrome is associated with high-grade urothelial carcinoma of the bladder. Hence, patients with the risk factors for metabolic syndrome and without urinary symptoms should be properly screened for bladder cancer as there may be bladder cancer in the early stage and its timely diagnosis and intervention can prolong the survival of these patients.

Keywords: Metabolic syndrome, obesity, urothelial carcinoma

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INTRODUCTION

Urinary bladder cancer is one of the most common carcinomas of the genitourinary tract.[1] Although smoking is the most common etiological factor of bladder cancer, there are other risk factors for this disease such as occupational carcinogenic and high arsenic exposure.[2] Bladder cancer is more common in males than females.[3] The molecular basis of urothelial carcinoma has also been explained in various studies[4] that showed mutations in fibroblast growth factor receptor 3 or Rat Sarcoma virus (RAS) gene in low-grade papillary carcinoma and alteration of p53 and pRB in high-grade muscle-invasive carcinoma.

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There is a suspected role of metabolic syndrome in causing urinary bladder carcinoma. Metabolic syndrome is a cluster of metabolic disorders such as, hypertension (blood pressure [BP] >140/90 mmHg), hypertriglyceridemia (triglyceride [TG] >150 mg/dL and high-density lipoprotein [HDL] <40 mg/dL), insulin resistance, and central obesity (waist–hip ratio >0.9 in men and > 0.85 in women and body mass index [BMI] >30 kg/m^2).[5] There are some studies which show the association between metabolic syndrome and urothelial carcinoma of the bladder[6] and also with a higher grade of tumor[7] but this association is not proven yet.

MATERIALS AND METHODS

This retrospective cross-sectional study was performed in a tertiary care hospital in eastern India after approval from the institutional ethics committee. We retrospectively analyzed the data of patients who were diagnosed with urothelial bladder cancer between June 1, 2017, and May 31, 2019, applying total enumeration. Assuming 29% prevalence of metabolic syndrome as per the study by Ozbek *et al*.[8] and applying the formula:

$$N = Z^2 \times p \times (1\text{-}p)/e^2$$

where, Z = 1.96 for 95% confidence interval; *P* = expected true proportion and e = desired precision (0.05) in a population of 547 (last 3 years average number of urinary bladder cancer patients operated in our institute). Finite population correction was done as per Thrusfield M, sample size was 201.

The objective of this study was to determine the association between metabolic syndrome and urothelial carcinoma of the bladder as well as the grade of urothelial carcinoma determined by the WHO 2004/2016 classification of urothelial carcinoma.[9] The patients were diagnosed as having metabolic syndrome[10] according to the National Cholesterol Education Program–Adult Treatment Panel 3 (NCEP-AT3) criteria[11] which are as follows - patients fulfilling any three of the following five criteria:

a. BMI ≥30, or waist circumference >40 inches (male) and >35 inches (female)*
b. Fasting blood sugar >100 mg/dl or taking antidiabetic treatment
c. Serum TG levels >150 mg/dl or taking treatment
d. HDL cholesterol <40 mg/dl (male) or <50 mg/dl (female) or taking treatment
e. Systolic BP >130 mmHg or diastolic BP > 85 mmHg or taking treatment.

*As waist circumference was not available, BMI was evaluated in all subjects.

All five criteria aforementioned were considered in our study.

Statistics

Data were statistically analyzed using MedCalc version 15.8 (Mariakerke, Belgium, MedCalc Software bvba, 2015) software. Categorical variables have been summarized as counts and percentages, and numerical variables have been expressed as mean and standard deviation. Fisher's exact test or Chi-square test was employed to compare independent proportions. Odds ratios with corresponding 95% confidence intervals have been presented and were relevant. For subgroup comparison, a two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Observations made were formatted in tabular form [Tables 1-3]. The total population for the study was 201. Of the total 201 patients [Figure 1], 15 patients were having metabolic syndrome and were included in the study following NCEP-AT3 criteria and 186 patients were without metabolic syndrome. Of the total study population, 165 were male and 36 were female. Ten male patients and five female patients were diagnosed with metabolic syndrome [Tables 1 and 3, Figure 1], out of which, in metabolic syndrome patients, 10 samples were of high grade and five samples were of low-grade

Table 1: Multivariate analysis of patients of metabolic syndrome and without metabolic syndrome along with odds ratio and *P* value; gender as a variable is showing confounding effect

Parameter	Metabolic syndrome		OR (95% CI)	*P*
	MetS+	MetS−		
Male	10	155	0.40 (0.13-1.25)	0.152
Female	5	31		
Diabetes mellitus+	14	25	112.7 (14.06-903.31)	<0.001
Diabetes mellitus−	1	161		
HTN+	14	36	58.33 (7.43-458.21)	<0.001
HTN−	1	150		
Smoking+	8	161	0.18 (0.06-0.53)	0.003
Smoking−	7	25		
High TG (>150)	15	12	216.25 (25.29-1778.59)	<0.001
Low TG (≤150)	1	173		
Low HDL (≤40)	15	10	262.5 (31.44-2191.78)	<0.001
High HDL (>40)	1	175		
Low-grade urothelial	5	145	7.07 (2.29-21.86)	<0.001
High-grade urothelial	10	41		
BMI ≥30	14	6	82.13 (22.26-303.09)	<0.001
BMI <30	5	176		

OR: Odds ratio, CI: Confidence interval, MetS: Metabolic syndrome, HTN: Hypertension, TG: Triglyceride, BMI: Body mass index, HDL: High density lipoprotein

tumors [Tables 1-3 and Figure 1]. In metabolic syndrome negative patients, 145 were of low-grade tumors and 41 were of high-grade tumors [Tables 1-3]. The mean age of patients of metabolic syndrome was 64.1 ± 14.1 years, whereas the mean age in patients without metabolic syndrome was 61.1 ± 15.2 years [Table 3]. TG value above 150 mg/dL was present in a total of 27 patients, out of which, 15 were in patients of metabolic syndrome and 12 were present in patients without metabolic syndrome. This association was statistically significant ($P < 0.001$) [Tables 1 and 3]. HDL values <40 mg/dL were present in a total of 25 patients, out of which, 15 had metabolic syndrome and 10 were without metabolic syndrome. This association was also statistically significant ($P < 0.001$) [Tables 1 and 3]. In patients with metabolic syndrome, five patients (33.34%) had tumors of low grade, whereas ten patients (66.67%) had tumors of high grade, and in patients without metabolic syndrome, 145 patients (77.95%) had tumors of low grade, whereas 41 patients (22.05%) had tumor of higher grade. This association was statistically significant ($P < 0.001$). Odds ratio was calculated for various putative risk factors [Tables 1 and 2]. As per the odds ratio, the association between metabolic syndrome and urothelial cancer development was significant.

Table 2: Multivariate analysis of patients of low-grade and high-grade urothelial carcinoma along with odds ratio and *P* value; gender as a variable is showing confounding effect

Parameter	Tumor grade		OR (95% CI)	*P*
	High	Low		
Male	44	121	1.09 (0.48-2.50)	<1.0
Female	9	27		
Diabetes mellitus−	37	125	2.11 (1.00-4.43)	0.0065
Diabetes mellitus+	14	25		
HTN−	34	117	2.11 (1.06-4.19)	0.041
HTN+	19	31		
Smoking−	18	14	0.38 (0.17-0.81)	0.015
Smoking+	55	114		
Low TG (≤150)	41	133	2.60 (1.12-5.99)	0.0033
High TG (>150)	12	15		
Low HDL (≤40)	40	136	0.32 (0.13-0.75)	0.013
High HDL (>40)	12	13		
BMI <30	42	139	6.15 (2.30-16.40)	0.001
BMI ≥30	13	7		
MetS−	43	143	6.65 (2.15-20.51)	<0.001
MetS+	10	5		

OR: Odds ratio, CI: Confidence interval, MetS: Metabolic syndrome, HTN: Hypertension, TG: Triglyceride, BMI: Body mass index, HDL: High density lipoprotein

Table 3: Multivariate analysis of patients of metabolic syndrome and without metabolic syndrome

Parameters	Bladder cancer		*P*
	With MetS	Without MetS	
Total	15	186	-
Age (mean±SD) in years	64.1±14.1	61.1±15.2	-
Male	10	155	
Female	5	31	
Diabetes+	14	25	<0.001
Diabetes−	1	161	
Hypertensive+	14	36	<0.001
Hypertensive−	1	150	
Smoking+	8	161	0.003
Smoking−	7	25	
TG (≥150)	15	12	<0.001
TG (<150)	1	173	
HDL (≤40)	15	10	<0.001
HDL (>40)	1	175	
Low grade (%)	5 (33.34)	145 (77.95)	
High grade (%)	10 (66.67)	41 (22.05)	
BMI (mean±SD)	31.2±4.1	25.1±2.2	

MetS: Metabolic syndrome, TG: Triglyceride, BMI: Body mass index, SD: Standard deviation, High density lipoprotein

DISCUSSION

Urinary bladder carcinoma is one of the most common carcinomas occurring in the population. Smoking is the biggest etiological factor for bladder carcinoma. Apart from smoking, various occupational exposures and arsenic content in water are the other contributing factors for the development of bladder carcinoma.[12] Males are more predisposed to bladder cancer than females.[3] However, in our study, gender was a confounding factor as the maximum number of cases included in the study were male.

Metabolic syndrome has also been found as an etiological factor for bladder cancer,[13] as it is seen that in many obese patients who are not exposed to etiological risk factors, still developed bladder cancer. Deranged lipid profile and increased secretion of insulin-like growth factor-1 are the main reason for carcinogenesis in obese patients. One possible explanation of carcinoma development in obese patients is that more pro-inflammatory cytokines and recruitment of macrophages lead to tumor development.[14] This finding also supported the work done by Xu *et al*. who found a clear association between obesity and bladder cancer.[15] Koebnick *et al*. also supported this finding in their study.[16] However, an increased number of urinary tract infections also has a role in etiopathogenesis of urothelial

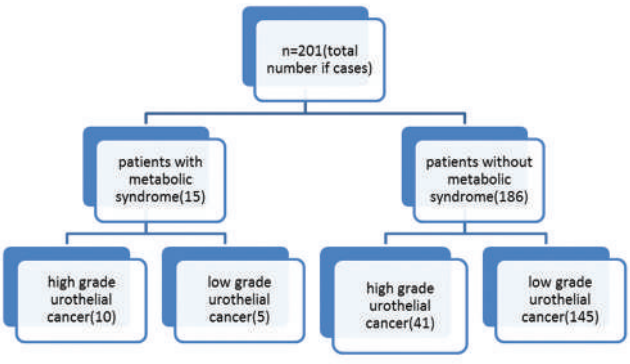

Figure 1: Distribution of high- and low-grade urothelial cancer in patients with and without metabolic syndrome

carcinoma in metabolic syndrome patients.[6] However, there is no clarity regarding mechanisms for the association between metabolic syndrome and urothelial carcinoma of the bladder. Association of diabetes with bladder cancer is also mentioned in some literature such as Larsson *et al*. who showed that high glucose levels were prevalent in urothelial carcinoma patients.[17] In this study also, we found the same association between diabetes and bladder cancer.

There are many studies in the literature which show the different associations of TGs and cholesterol with urothelial carcinoma. Some studies show the inverse relationship between cholesterol with bladder cancer such as the study conducted by Schatzkin *et al*.[18] However, majority of studies support our results of a clear direct association between triglyceride and cholesterol with urothelial carcinoma of the bladder. The cause of the association between low HDL and bladder cancer is not clearly known. Hence, physicians should screen these patients regarding tumor development.

In our study, it was seen that metabolic syndrome was associated with high-grade urothelial carcinoma of the bladder. This is supported by few studies such as which show that there is a strong association between higher stage and higher grade of tumor with metabolic syndrome.[7,11] However, low-grade carcinoma was more common with nonmetabolic syndrome patients in the present study and, there are some studies which show that non-muscle invasive bladder tumors are more common in bladder cancer.[19] Hence, we have to explore further and also take care of other risk factors for carcinoma bladder apart from metabolic syndrome.

In this study, there is a proven association between bladder cancer and combined effect of all the above-mentioned etiological factors, which was seen in very few literatures. Esposito *et al*. showed a weak association between bladder cancer and metabolic syndrome.[20] However, in our study, there is a strong correlation between metabolic syndrome and urothelial carcinoma of the bladder. This conforms to the results of Nagase *et al*. who showed a strong association between metabolic syndrome and urothelial carcinoma of the bladder.[21] In our study, there is a correlation between individual components of metabolic syndrome and urothelial carcinoma of the bladder.[22]

However, this study has some limitations because it is retrospective in nature. A prospective study has a clear advantage over this type of study as selection bias is absent and researchers can collect data on suspected risk factors while they monitor for new cases.

CONCLUSION

The conclusion of this study is that urothelial carcinoma of the bladder has a strong association not

only with metabolic syndrome but also individually with diabetes, hypertension, and deranged lipid profile. Urinary bladder carcinoma in metabolic syndrome patients is often of high grade and poor prognosis. Hence, patients with these risk factors and without urinary symptoms should be properly screened for bladder cancer.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Original Article

Magnitude of dyslipidemia in type 2 diabetes

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Abstract

Background: Dyslipidemia in diabetes is very common and important contributing factor behind cardiovascular disease. This study shows the magnitude of dyslipidemia in type 2 diabetes whose glycemic control is optimal.

Methodology: One hundred and thirty type 2 diabetes individuals with HbA1c <7% who were not on statin, were included in this study. Fasting lipid profile was estimated. Demographic characters and risk factors were recorded.

Results: The mean age, duration of diabetes, and body mass index were 46.88 ± 9.32, 4.43 ± 4.58, and 24.54 ± 3.44, respectively. The prevalence of dyslipidemia was 88.46% in our study group. The most common pattern of dyslipidemia was combined dyslipidemia (46.1%) followed by isolated dyslipidemia (36.5%).

Conclusion: The prevalence of dyslipidemia is very high despite good glycemic control in type 2 diabetes.

Keywords: Diabetes, dyslipidemia, insulin resistance

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INTRODUCTION

Diabetes mellitus (DM) is a common cause of dyslipidemia, which in turn is an important risk factor for atherosclerosis and coronary heart disease.[1,2] Insulin resistance and insulin deficiency have been identified as causes of dyslipidemia in patients with DM.[3] Even in the absence of overt hyperglycemia or abnormal glucose tolerance, there is an abnormality in lipid metabolism.[4] The spectrum of dyslipidemia in DM can include all the various types of dyslipidemia identified in the general population. However, the characteristic feature of diabetic dyslipidemia is a combination of high-plasma triglyceride (TG) concentration, low-HDL cholesterol concentration, and increased concentration of small dense low-density lipoprotein cholesterol (LDL-C) particle.[5] Insulin resistance represents the main cause of this disorganized metabolic milieu characteristic of the metabolic syndrome and the type 2 DM (T2DM).[3,6,7] Many studies were done to look at dyslipidemia without emphasizing on the glycemic influence which has an enormous impact on lipid metabolism. We, therefore, conducted this study to evaluate the spectrum of dyslipidemia in patients with T2DM after achieving optimal glycemic control.

METHODOLOGY

This study was conducted at the Department of Endocrinology, NRS Medical College and Hospital, Kolkata, after ethical clearance. It was a cross-sectional hospital-based study. A total of 130 nonpregnant, type 2 diabetes individuals, aged 18 to 65 years with optimal

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glycemic control were included in the study after satisfying the inclusion and exclusion criteria. Optimal glycemic control was defined by fulfilling the following three criteria, i.e., fasting plasma glucose is ≤130 mg/dl, postprandial glucose is ≤180 mg/dl, and glycated hemoglobin is ≤7.0%. Patients suffering from other causes of secondary dyslipidemia and who were on lipid-lowering drugs were excluded from this study. All patients were evaluated clinically and case record forms were filled up. Fasting blood samples were analyzed for total cholesterol (TC) by enzymatic cholesterol oxidase/peroxidase method, TG by enzymatic glycerol kinase/peroxidase method, high-density lipoprotein cholesterol (HDL-C) by precipitation method, low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald's formula (TC − HDL-C-TG/5) which is not applicable when plasma TG is >400 mg/dl. If TG was >400 mg/dl, LDL-C was measured directly. Glycosylated hemoglobin (HbA1c) was measured by High Performance liquid Chromatography (HPLC) method.

The descriptive analysis of the data was done using Statistical software, namely SPSS version 19.0 IBM, US. Graphs and tables were generated using Microsoft Word and Excel. Unpaired *t*-test and multiple regression ANOVA were used for statistical analysis. $P < 0.05$ was considered statistically significant.

RESULTS

A total number of 130 patients with controlled type DM in our study were studied. Seventy-four (56.9%) patients were male and 56.2% (73 out of 130) were from urban areas. The mean age, duration of diabetes, and body mass index (BMI) were 46.88 ± 9.32, 4.43 ± 4.58, and 24.54 ± 3.44, respectively. The characteristics of the study population are given in Table 1.

The prevalence of dyslipidemia was 88.46% (115 out of 130) in our study group. The most common pattern of dyslipidemia was combined dyslipidemia – 46.1% followed by isolated dyslipidemia 36.5%. Among the combined dyslipidemia the most common subtype was increased LDL-C and decreased HDL-C [Table 2].

Age, gender, BMI, socioeconomic status, duration of diabetes, and smoking were not significantly related to dyslipidemia in our study.

DISCUSSION

DM is a common secondary cause of hyperlipidemia and the characteristic feature of it is a combination of high plasma TG concentration, low-HDL-C concentration, and increased concentration of small dense LDL-C particles. Dyslipidemia was present in 88.47% of diabetes individuals in our study which is comparable to the study done by Udawat *et al.* where it was 89%.[8] The most common pattern of dyslipidemia in our study was combined dyslipidemia of increased LDL-C and decreased HDL-C (46.1%) which is comparable with the study done by Parikh *et al.*[9] Increased TG and decreased HDL-C were found in 28.3% of the population in this study.

Table 1: Demographic characters, blood glucose, and lipid profile of study individuals

Parameters	Mean±SD
Age	46.88±9.32
Gender (%)	
Male	74 (56.9)
Female	56 (43.1)
Rural/urban (%)	
Rural	57 (43.8)
Urban	73 (56.2)
Duration of DM	4.43±4.58
Exercise	
Yes	47
No	83
Smoking	
Yes	46
No	84
Hypertension	
Yes	30
No	100
BMI	24.54±3.44
FBG	102.10±14.01
PPBG	138.8±23.46
HbA1c	6.32±0.57
Total cholesterol	188.16±48.03
LDL-C	112.3±37.19
Non-HDL-C	142.34±45.39
HDL	
Male	46.20±12.07
Female	46.09±12.23
TG	157.2±83.56
Albumin: Creatinine	47.16±161.15

DM: Diabetes mellitus, BMI: Body mass index, FBG: Fasting blood glucose, PPBG: Postprandial blood glucose, HbA1c: Glycosylated hemoglobin, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, SD: Standard deviation

Table 2: Prevalence of dyslipidemia with its various types

Combined dyslipidemia: 40.77% of total study populations and 46.1% of the dyslipidemic patients (53/115)
Combined dyslipidemia: ↓HDL-C, ↑LDL-C–20/53=37.7%
Combined dyslipidemia: ↑LDL-C,↑TG–18/53=34%
Combined dyslipidemia: ↑TG, ↓HDL-C–15/53=28.3%
Mixed dyslipidemia: 15.4% of total study population and 17.4% of the dyslipidemic patients (20/115)
Isolated dyslipidemia: 32.3% of total study population and 36.5% of dyslipidemic patients (42/117)
↑LDL-C: 50% (21/42)
↑TG: 9.5% (4/42)
↓HDL-C: 40.5% (17/42)

LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglyceride, ↑ and ↓: Increase and decrease

In our study, we found hypertriglyceridemia in 48.6%, LDL hyperlipoproteinemia in 69.5%, and decreased HDL-C dyslipidemia in 60.0% of type 2 diabetic patients, whereas in a study by Udawat *et al.*, it was 22%, 76%, and 58%, respectively.[8] A study done by Parikh *et al.* showed that the most common pattern of dyslipidemia is high-LDL-C and low-HDL-C among both males and females which is consistent with our findings.[9]

We found that good glycemic control has a modest effect on lipid parameters in type 2 diabetics. Literature also confirmed that TG and HDL-C levels often may remain abnormal despite improved glycemic treatment[10] and in population studies, dyslipidemia was not related to levels of glycemic control.[11]

There was no significant correlation observed with risk factors such as age, gender, socioeconomic status, exercise status, smoking status, hypertension, BMI, duration of DM, and HbA1c. It indicates that in controlled T2DM, dyslipidemia is not significantly affected by individual confounding factors studied both in rural and urban populations.

There have been different study results regarding the metabolic control of DM which is generally indicated by HbA1c and serum lipid levels. In some studies, a positive correlation between HbA1c and serum lipid profiles was reported.[12] In the present study, we found a high prevalence of dyslipidemia despite good glycemic control.

CONCLUSION

The magnitude of dyslipidemia in controlled type 2 diabetes is very high (88.6%) despite optimal glycemic control. Increased LDL-C and decreased HDL-C (37.7%) is the most common pattern of dyslipidemia in this study cohort.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Management of female anorectal malformations: Our experience

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Abstract

Anorectal malformations (ARMs) simply mean absent or malformed anal opening. Its management consists of proper knowledge of anatomy, identification of defect, and appropriate surgical management and follow-up. Anatomy and defects are different and complex in female ARM. We are discussing six cases of different female ARMs with their rare and complex anatomy analysis and their surgical management. In this series, according to the international ARM classification system (Krickenbeck), we have chosen patients of both "major" and "rare" variety for discussion. This series will give an idea about the definite and complete management of female ARM patients in the light of recent advances in a tertiary care center like IPGMER.

Keywords: Abdominoperineal pull-through, anorectal malformations, cloaca, H-type fistula, posterior sagittal anorectoplasty, pouch colon

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INTRODUCTION

Anorectal malformations (ARMs) are a class of congenital anomalies that are represented by a wide spectrum of defects, some relatively mild and some quite severe.[1] The reported incidence of ARM is 1 in every 2500–5000 live births but may be even more frequent in certain developing countries.[2-4] Chatterjee from Kolkata calculated the incidence of a regional variety of ARM-like congenital pouch colon (CPC).[5]

In general, the male: female ratio associated with ARM is almost equal, with a 56:44 male: female ratio.[2]

For ages, research is going on classifying the defects for their management and prognosis. The most recent classification system which is internationally accepted is "Krickenbeck Classification". Krickenbeck consensus (2005) guides us the classification [Table 1], grouping of surgical techniques [Table 2], and scoring for follow-up of ARM. According to this system, there are seven "major clinical groups" and few "rare/regional anomalies."

In IPGMER and SSKM, a tertiary care center for pediatric surgery, both male and female ARM patients are being treated successfully throughout the year. We are sharing our experience of management of few female ARM patients in the light of recent advances in ARM management. In this series of six cases of female ARM patients, we are discussing the management of three cases of "major clinical group" and three "rare/regional anomalies" based on the international ARM classification system.

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PERINEAL (CUTANEOUS) FISTULA

This 9-month girl was diagnosed at birth as a "perineal fistula" as the rectal orifice is located anterior to the center of the sphincter but posterior to the vestibule of the genitalia (in the perineal body) [Figures 1 and 2].[7]

She underwent emergency colostomy just after birth and was following up in outpatient department (OPD) for workup and management of associated anomalies and adequate weight gain for definitive surgery. We went for definite surgery to make neo-anus at an expected position within the sphincter and the surgical procedure is posterior sagittal anorectoplasty (PSARP) [Figure 3].

Neo-anus is formed and subsequent colostomy closure was done to maintain bowel restoration after 6 months. The patient is following up in OPD with good bowel continence. This girl with ARM was managed by staged procedures (colostomy creation-PSARP-colostomy closure) and all stages were completed within 15 months of age.

Table 1: Standards for diagnostic procedures: International Classification (Krickenbeck)[6]

Major clinical groups	Perineal (cutaneous) fistula
	Rectourethral fistula
	Bulbar
	Prostatic
	Rectovesical fistula
	Vestibular fistula
	Cloaca
	No fistula
	Anal stenosis
Rare/regional variants	Pouch Colon
	Rectal atresia/stenosis
	Rectovaginal fistula
	H type fistula
	Others

Table 2: International grouping (Krickenbeck) of surgical procedures for follow-up[6]

Operative procedures	Perineal operation
	Anterior sagittal approach
	Sacroperinal procedure
	PSARP
	Abdominosacroperi-neal pull-through
	Abdominoperineal pull-through
	Laparoscopic-assisted pull-through
Associated conditions	Sacral anomalies
	Tethered cord

VESTIBULAR FISTULA

This girl had an anatomical defect vestibular fistula where the anal opening was within the vestibule [Figures 4 and 5].

Although single-stage PSARP (primary PSARP) is a well-practiced procedure, we did staged procedure for this girl also. Here, the definitive surgery is the same PSARP but the perineal body formation and vaginal dissection are of utmost importance.

CLOACA

This girl (now age 1 year 6 months) attended at birth with a complex anomaly with ARM. Anatomically her urinary, vaginal, and anal opening made a confluence to make a "common channel" and came out as a single opening [Figure 6].

At neonatal age, she underwent "transverse colostomy" to relieve bowel obstruction along with "cystostomy" for urinary obstruction [Figure 7]. "colpostomy" was not required here. We assessed the length of the common channel by cysto-genitoscopy and it was measured > 3 cm length. Hence, we did an abdominal approach and "abdominal pull-through" was done to create neo-anus. "Total urogenital mobilization" was done for exteriorization of urogenital confluence.

RECTAL ATRESIA

This girl presented at neonatal age with normal anal opening with abdominal distension and no passage of stool. On per rectal examination, the catheter could not be negotiated beyond 3 cm and was diagnosed clinically with rectal atresia. Emergency colostomy was done to relieve obstruction and was following up in OPD for a definitive procedure. At 1 year of age, PSARP was done and after removing the rectal membrane [Figure 8] neo-anus was placed at a normal anal position. Colostomy closure was done subsequently after few months.

H-TYPE FISTULA

This girl presented at OPD at 4 months of age. She had a normal anus but was passing stool from both anal and vaginal openings [Figure 9].

The patient was diagnosed with "H-type fistula" or "perineal canal" (not perineal fistula) which is again a rare anomaly where there is a fistulous communication between the bowel and vagina at the perineal level. We did colostomy at 4 months of age and did definite surgery at age 1 year.

Surgery was again PSARP with identification of fistula and ligating it. Neo-anus is repositioned after PSARP. After colostomy closure, the girl is passing stool normally.

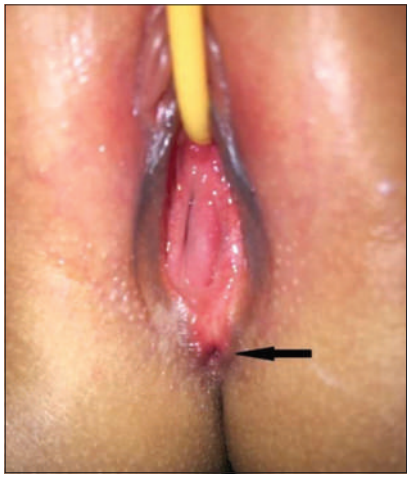


Figure 1: Ectopic anal opening at the perineum (Arrow)

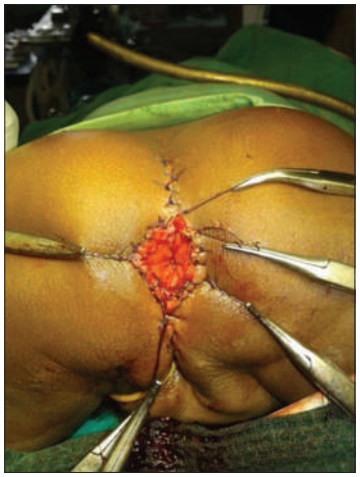


Figure 3: Neo-anus after PSARP (patient is in prone position). PSARP: Posterior sagittal anorectoplasty

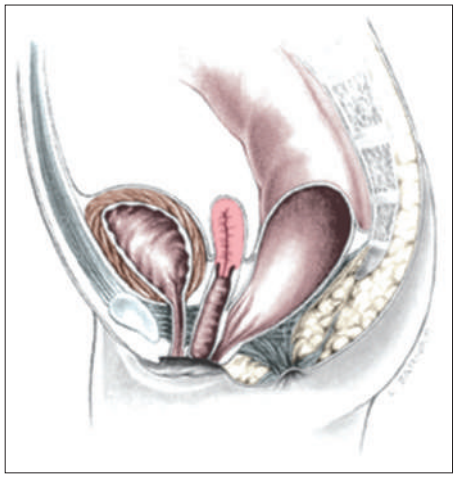


Figure 5: Schematic diagram of vestibular fistula[7]

POUCH COLON

This girl presented with an absent anal opening with abdominal distension at neonatal age. She underwent colostomy to relieve obstruction and a pouch colon was

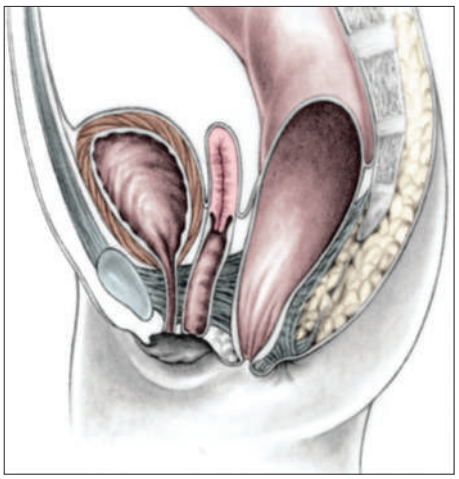


Figure 2: Schematic diagram of anterior ectopic anus[7]

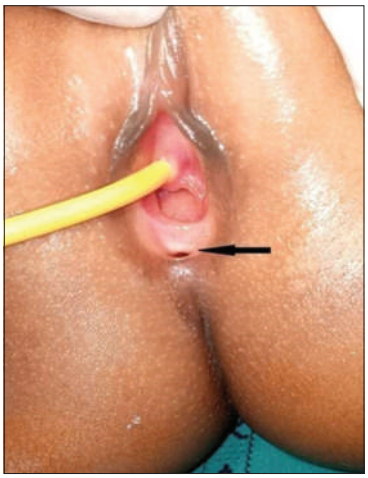


Figure 4: Vestibular fistula (marked with Arrow)

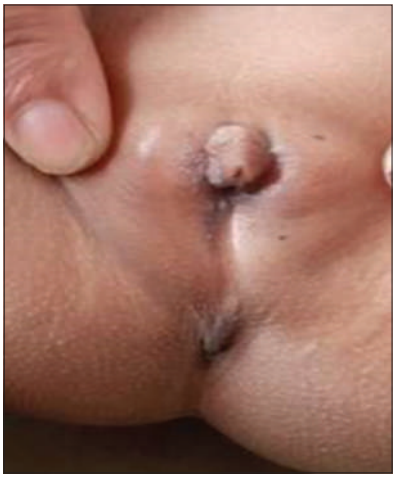


Figure 6: Cloaca- single opening, no anal opening

diagnosed (type 4) which is a dilatation of the distal colon with or without a fistulous connection with the urinary bladder. At neonatal age, we exteriorized the normal part of the distal colon and colostomy was made [Figure 10].

During definitive procedure at age 1 year, we excised the distal pouch [Figure 11] after ligating the fistula and proximal "normal" distal colon is pulled through and neo-anus is formed. We completed the procedure within 1 year of age.

DISCUSSION

ARM represents a complex group of congenital anomalies resulting from abnormal development of the hindgut, allantois, and Mullerian duct, leading to incomplete or partial urorectal septal malformations. Approximately 36.4% are isolated lesions and 63.6% are associated with other anomalies.[2,8] Chromosomal defects are associated with 8% and family history may be present.[2,8,9]

The initial diagnosis of the imperforate anus is almost always made during the first newborn physical examination. The absence of an anal opening is usually fairly obvious. Occasionally, a perineal fistula may be missed. Now two important points to be noted in the first 24 h of life: (1) The first point is whether a "colostomy" should be opened, deferring the repair of the defect until later in life, or to proceed with "definitive repair" during the newborn period without a protective colostomy. Physical examination, especially the perineal inspection, will provide enough clinical evidence to reach a decision about the need for a diverting colostomy in over 90% of the patients. (2) The second point is whether the patient needs urgent treatment for an associated defect.[1] The decision-making is different in male [Table 3] and female children [Table 4].

"Perineal fistula" is the lowest defect. The rectum is located within most of the sphincter mechanism. Only the lowest part of the rectum is anteriorly mislocated [Figure 2]. The

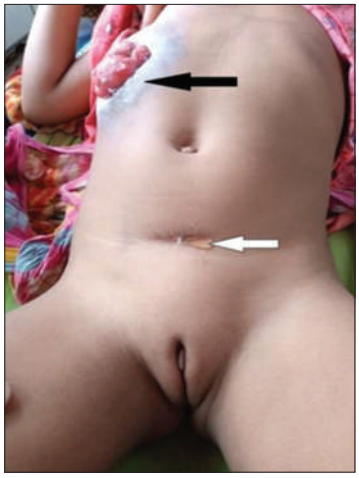


Figure 7: Transverse colostomy (black arrow) and cystostomy (white arrow)

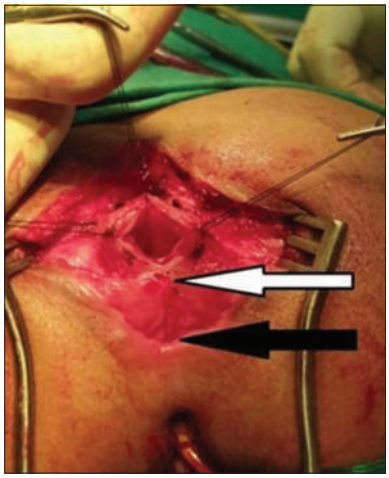


Figure 8: Rectal Atresia, rectal membrane (white arrow) separating proximal bowel, and distal anus (black arrow)

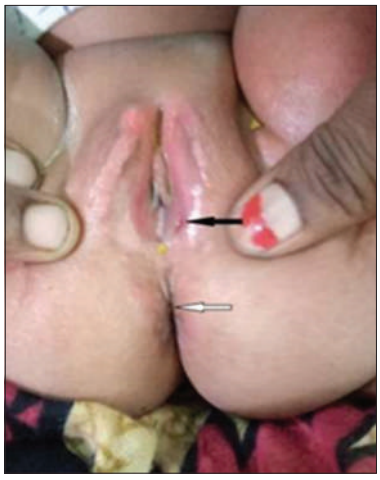


Figure 9: H-Type fistula, normal anal opening (white arrow), fistulous opening (black arrow), and stool staining

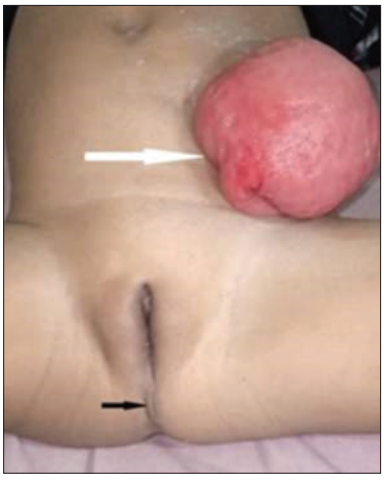


Figure 10: Pouch colon, prolapsed pouch in colostomy (white arrow), and imperforate anus (black arrow)

terms covered anus, anal membrane, anterior ectopic anus, and bucket-handle malformations all refer to rectoperineal fistulas.[7]

"Rectovestibular fistula" is the most common defect in females and has an excellent functional prognosis. On meticulous inspection, a normal urethral meatus and a normal vagina, with a third hole in the vestibule, which is the rectovestibular fistula are observed [Figure 5].

Many patients do very well with a primary neonatal operation (primary PSARP) without a protective colostomy. However, a perineal infection followed by dehiscence of the anal anastomosis or perineal body, or recurrence of the fistula provokes severe fibrosis that may interfere with the sphincter function. If these complications occur, the patient may have lost the best opportunity for an optimal functional result because secondary operations do not render the same prognosis as a successful primary operation. Thus, a protective colostomy is still the best way to avoid these complications for most surgeons.[7]

"Cloacal malformations" represent the extreme in the spectrum of the complexity of female malformations. Here, the distal portions of the rectum, vagina, and urinary tract fuse and create a single common perineal channel. The diagnosis of a cloaca is a clinical one. This defect should be suspected in a female born with imperforate anus and small-looking genitalia [Figure 6]. Careful separation of the labia discloses a single perineal orifice. The length of the common channel varies from 1 to 7 cm and is very important for operative and prognostic implications. A common channel of < 3 cm [Figure 12] usually means that the defect can be repaired with a posterior sagittal operation without opening the abdomen.

Common channels longer than 3 cm [Figure 13] are more complex, mobilization of the vagina is often difficult, and some form of vaginal replacement may be needed during the definitive repair.[7] A single procedure for separating all openings is known as posterior sagittal anorecto-vagino-urethroplasty.

"Rectal atresia" is a rare type of ARM constituting 1%–2% of the ARM. However, an incidence of 14% was reported from the southern part of India at one stage[11,12] thus this has been kept under "rare/regional variety." Rectal atresia is characterized by the presence of the proximal rectum and a well-formed distal anus that is in its normal location and has a normal appearance, which is about 1–3 cm in depth separated by a membrane commonly.[11] For rectal atresia, an end-to-end anastomosis after removing the membrane with PSARP gives satisfactory results.[11]

"H-type fistula" or "perineal canal" is a fistula between a normal anorectum and the vestibule. Although it is rare, elsewhere is relatively common in India.[13] The treatment is fistula closure with a protective colostomy followed by colostomy closure. During fistula closure, PSARP is an accepted procedure.

CPC is defined as an anomaly in which all or part of the colon is replaced by a pouch-like dilatation, which communicates distally with the urogenital tract through a large fistula and is seen particularly in Asia – thus it has been put under the regional variety of ARM. Chatterjee from Kolkata reported an incidence of 2%.[5] The mesentery of this pouch is short and poorly developed, the wall is very thick, the taenia coli are absent or ill

Table 3: Clinical algorithm for males with imperforate anus[10]

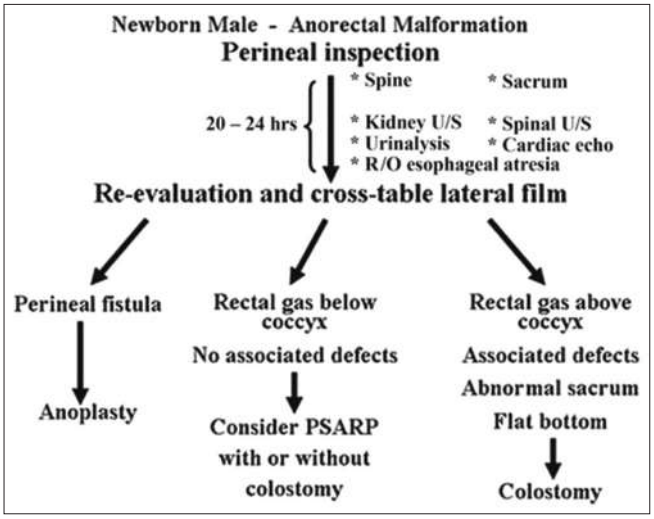
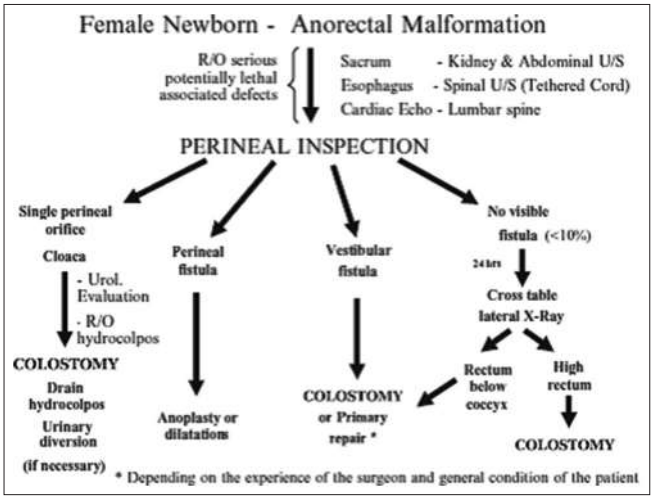


Table 4: Clinical algorithm for females with imperforate anus.[10]*



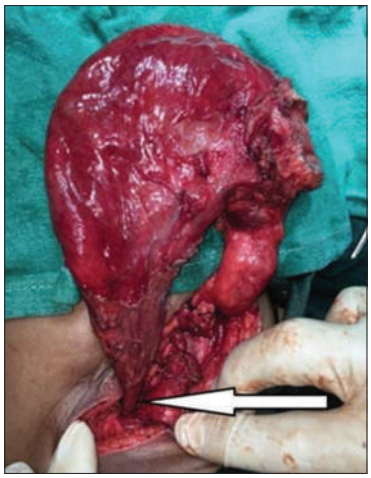


Figure 11: Pouch during dissection, fistulous communication with bladder

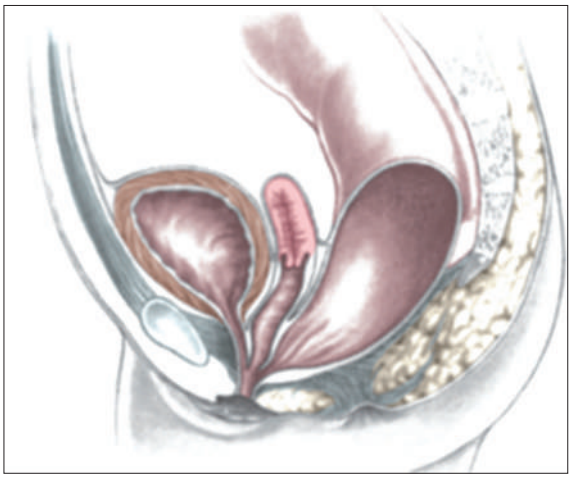


Figure 12: Cloaca with short (<3cm) common channel[7]

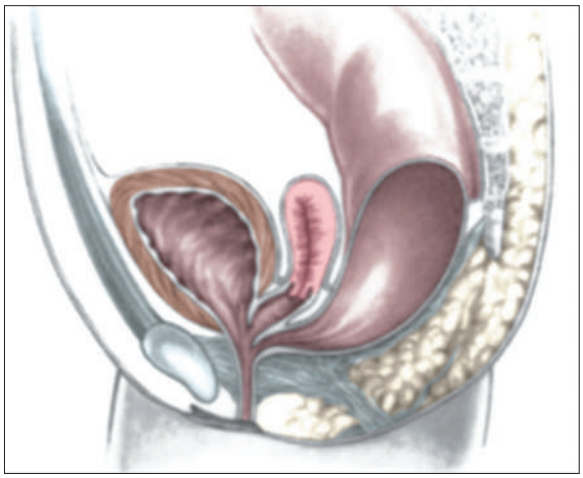


Figure 13: Cloaca with long (>3 cm) common channel[7]

defined, and haustration and the appendices epiploicae are absent. The main pouch is supplied by the branches arising from the superior mesenteric artery, which forms a leash of vessels around it.[14] There are four types of CPC depending on anatomy (Narsimha Rao *et al*.[15]). Repair of CPC consists of excision of the pouch after ligation of fistula and pull-through bowel to form neo-anus. Some prefer coloplasty (tubularization of dilated colon/pouch), followed by PSARP. In our case, we preferred the first procedure, i.e., ligation of fistula, excision of the pouch, and abdominoperineal pull-through.[14]

INFERENCE

ARM forms a significant load on the surgical services, particularly in developing countries, not only in the emergency situation but also in terms of long-term corrective procedures. Although there have been major advances in the management of these children during the past 15 years, these patients still represent a continuing challenge as a result of the significant reconstructive problems involved, as well as the fact that a significant number suffer from fecal and urinary incontinence, as well as the possibility of sexual inadequacy in later life.

A complete management of ARM requires knowledge of the embryological defect, environmental effect, management from early diagnosis till completion of treatment, postoperative long-term follow-up, and knowledge about bowel management along with management of associated anomalies. For all these factors, a long-term study with a larger population is required and we are hopeful to bring our contribution of work to the research of ARM in future.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Series

Labial adhesions: A novel therapeutic approach

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Abstract

Labial adhesion is a common condition found in girls before puberty. All the patients (n = 15) in this series were diagnosed clinically, and routine blood and urine examinations were normal. Mometasone cream was applied topically over the labial adhesions with a positive therapeutic response within 3–8 weeks of treatment. Recurrences of adhesions were found only in two patients who discontinued the treatment after recovery, and repetition of the treatment for 8 weeks solved the issue. Nonsignificant side effects were seen only in two patients. Hence, it can be concluded that mometasone cream is an effective method of treatment for labial adhesions.

Keywords: Labial adhesion, mometasone cream, topical

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INTRODUCTION

Before puberty, labial adhesion is a common condition in girls; labial synechia and labial agglutination are other names for this condition.[1] It is caused by the midline fusion of the labia minora, and it is usually asymptomatic; it is commonly first noticed by mothers during a regular physical examination by a doctor.[2] They most usually arise between the ages of 3 months and 3 years and are mostly an acquired disorder in girls, they are caused by inflammation that creates a thin bluish semipermeable membrane to adhere to the labia minora. Although labial adhesions are normally asymptomatic, they can cause postvoid dribbling or vaginal voiding, which is linked to a urinary tract infection, as well as discomfort when the bladder is evacuated.[3,4] It is commonly treated with estrogen cream and has a low recurrence rate.[5-7] The use of 0.05% betamethasone cream as a topical therapy has shown to be effective.[8] In tough cases of labial adhesions, manual separation and small surgical treatments are required.[9,10] There is a scarcity of data on the use of mometasone cream as a topical treatment for labial adhesions. The study's objective is to apply topical mometasone cream to cases of labial adhesion and assess the efficacy of this intervention.

CASE REPORT

The age group of the patients (n = 15) was 3 months to 4 years. All the patients in this series were diagnosed clinically. On physical examination, all the patients were normal except their labial adhesions [Figure 1]. Routine laboratory blood examination and urine examination reports were normal. Informed Consent from parents/guardians was taken before the application of the treatment. All the pros and cons about the medication were well explained to the parents/guardians before the

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application of the treatment. Initially, mometasone cream was applied topically over the adhesions twice daily for 2 weeks. Partial opening of the adhesions was noticed within 2 weeks in almost all the cases except three cases which had taken 4 weeks for partial response [Table 1]. After 3 weeks of exposure of mometasone cream, six patients showed total removal of adhesions and four patients had taken 4 weeks, one patient had taken 5 weeks, two cases had taken 6 weeks, and the remaining two cases had taken 8 weeks for full response to treatment [Figure 2]. Mometasone cream application once daily was continued for another 3–4 weeks for all the patients. Two patients discontinued the treatment after full removal of adhesions, and recurrence of adhesions was found in these cases. Again, they applied the same treatment till the full clearance of the adhesions and continued for another 3–4 weeks. No recurrence was found in these cases. For follow-up, 13 patients maintained their regularity, whereas two patients did not attend. Minor but nonsignificant side effects were seen only in two patients, but the treatment was continued after counseling and verbal assurance of the parents.

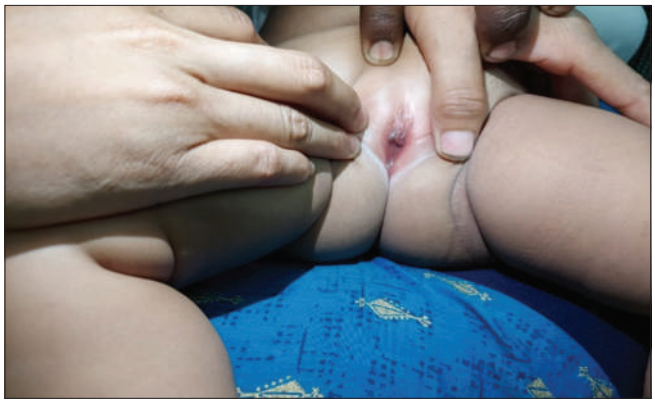

Figure 1: Labial adhesion

DISCUSSION

All the patients in this series were normal on physical examination except their labial adhesions. Mometasone cream was applied topically over the adhesions with a good therapeutic response within 3–8 weeks of treatment, and very minor side effects were noted only in two cases. According to a study by Leung *et al*., 20 girls were treated with estrogen cream. They all showed good therapeutic response with the treatment and minimum number of recurrences.[7] In our study, we have only two cases with recurrences who discontinued the treatment after full removal of adhesions and reinstitution of treatment till the full clearance of the adhesions and continued for another 4 weeks, and the problem was solved.

A total of 49 girls were enrolled in Soyer's study. They were all given estrogen cream to use. The vast majority of them were cured.[5] In a 2006 study involving 107 girls, the use of estrogen cream resulted in a 79% success rate and roughly 40% recurrences among those who were given recurrent exposure to estrogen cream.[11]

Labial adhesions can also be treated with a topical 0.05% betamethasone cream. In a trial, 19 girls with labial

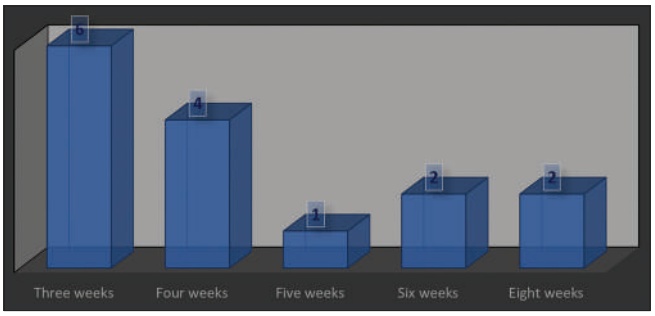

Figure 2: Response to treatment of patients (n = 15) after using mometasone cream

Table 1: Features of congenital labial adhesion patients (n=15)

Age of the child	Total duration of application of mometasone cream (weeks)	Adhesion opened after (weeks)	Follow-up done up to the age of	Recurrence	Adverse effects
3 months	8	4	9 months	No	No
8 months	6	3	11 months	No	No
10 months	6	3	12 months	No	No
3 months	6	3	6 months	No	No
3.5 years	11	8	4.5 years	Yes	Not significant
5 months	3	3	Not done	No	No
2.5 years	7	4	3 years	No	No
4 months	3	3	9 months	No	No
8 months	9	6	3 years	No	No
4 years	11	8	Not done	No	Not significant
4 months	6	4	7 months	No	No
2 years	6	6	3 years	Yes	No
2 years	8	5	2.5 years	No	No
6 months	7	4	11 months	No	No
1 year	6	3	2.5 years	No	No

adhesions who had previously failed treatment were given topical 0.05% betamethasone cream for 4–6 weeks and saw positive improvements.[8]

Another study in 2011 comparative effects of topical estrogen cream only, betamethasone cream only, and a combination of the two were observed by the researchers. Total 131 children with labial adhesions were included. Treatment was applied for 4 weeks on an average. Nevertheless, no substantial variances among these groups were experienced.[12]

Mometasone is a synthetic topical glucocorticoid receptor (GR) agonist with anti-inflammatory, antipruritic, and vasoconstrictive properties. Mometasone cream is a potent topical corticosteroid. It is used in inflammatory skin conditions such as severe eczema and dermatitis. Regarding the mechanism of action, mometasone cream being steroid in nature , attaches to cytoplasmic glucocorticoid receptors (GRs), the receptor and mometasone complex translocate into the nucleus, where the gene expression for various anti-inflammatory proteins is induced. This is done through inducing the lipocortin/annexin I (ANXA 1) levels.[13]

CONCLUSION

In our study, we have used mometasone cream for the treatment for labial adhesion cases and an effective therapeutic response was observed with negligible side effects. It can be concluded that mometasone cream can be used effectively for the treatment for labial adhesions.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Report

Phenytoin-induced hypertrichosis and gingival hyperplasia

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Abstract

Increased hair growth may be due to hirsutism or hypertrichosis. Hirsutism is the growth of excessive terminal hair in androgen-dependent areas in females, whereas, hypertrichosis is excessive hair growth anywhere in the body in both males and females. Both these entities, although similar in presentation, have varied etiologies and required a distinct diagnostic approach. Gingival or gum hyperplasia can be a presentation of various conditions including drug induced. We would like to report the case of a young boy on phenytoin who had presented to our outpatient services with increased hair growth and gingival hyperplasia.

Keywords: Gingival hyperplasia, hypertrichosis, phenytoin

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INTRODUCTION

Hypertrichosis is defined as excessive hair growth anywhere on the body, in males or females. Hirsutism, however, is the growth of terminal hair in androgen-dependent areas in females. Differentiating between these entities is vital as they both entail a varied approach to evaluation. Hypertrichosis may be generalized or local, congenital or acquired and may entail growth of lanugo or vellus or terminal hair. Hypertrichosis is equally common in both males and females.[1] Drug-induced hypertrichosis is one of the common etiologies for generalized hypertrichosis. Gingival hyperplasia though not obvious on clinical examination, must be looked for in suspicious cases such as malignancies, infiltrative disorders, and adverse effects of drugs.

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The authors would like to report a case of a young male child who presented to our outpatient services with increased hair growth and gingival hyperplasia due to phenytoin.

CASE REPORT

A 9-year-old boy presented to the endocrinology outpatient department with a complaint of hair growth all over the body for the past 1 year. He also complained of thickening of gums for the same duration. He was a known patient of generalized epilepsy since the age of 7 years and was being treated with a combination of antiepileptics including phenytoin 50 mg thrice daily since diagnosis. He did not have any history of height acceleration or history suggestive of precocious puberty. There was no history of intake of

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any drugs including exposure to androgens. There was no family history of excess hair or similar presentation in family members.

On examination, the boy was 100 cm tall and weighed 25 kg. The boy was short and his parents were also short, suggestive of familial short stature He had hair growth all over his body, most prominent over the back, buttocks, arms, and thighs [Figure 1a]. He had bushy eyebrows. There was no moustache, beard, pubic hair, or axillary hair. On oral examination, he had thickened gums which were overhanging beyond the teeth insertion, suggestive of gum hyperplasia [Figure 2]. There was no gum discoloration or bleeding from gums. Dentition was normal for age. His tanner staging was prepubertal and there were no bony or skin lesions.

The above were pointing to phenytoin-induced hypertrichosis and gum hyperplasia. For the sake of exclusion, routine investigations showed normal liver, renal, and thyroid function tests. Blood levels of androstenedione, testosterone, and prolactin were also normal for age and sex. A request to the treating neurologist was made for phenytoin discontinuation with alternative antiepileptics, if permissible. The benign nature of the presentation was explained to the parents and reassured. Phenytoin was stopped by the treating neurologist and at 1 month follow-up hypertrichosis had nearly disappeared [Figure 1b].

DISCUSSION

Excess hair growth can be due to hirsutism or hypertrichosis. The two are distinct entities and must be clearly identified. The term "hirsutism" was used by Wilkins[2] in females for excess growth of sexual hair in a male distribution. Hypertrichosis, on the other hand, is generalized growth of body hair all over the body or may be localized to a body area.[3] Hirsutism is the growth of terminal, coarse, and pigmented hair in areas of sexual hair growth. Hypertrichosis represents fine, long, and lightly pigmented hair. Hirsutism, particularly in prepubertal children can be a due to androgen excess from adrenal hyperplasia, adrenal tumors, ovarian tumors, or androgen exposure. This may be accompanied with virilization in girls. Hypertrichosis can result from systemic illnesses such as hypothyroidism, anorexia, and porphyria and most commonly drugs such as minoxidil, phenytoin, penicillamine, and cyclosporine.[4] Increased hair growth has been reported in 8%–12% of individuals on phenytoin therapy,[5] usually developing within the first 2–3 months of treatment. Treatment of hypertrichosis involves treatment of the cause and reassurance. For drug-induced cases, like in our case due to phenytoin, hypertrichosis disappears rapidly on drug discontinuation. Gum or gingival hyperplasia is caused by inflammatory conditions, infiltrations like leukemia, and a number of drugs such as phenytoin, cyclosporine, and calcium channel blockers. Our patient had both hypertrichosis and gingival hyperplasia due to phenytoin and excellent improvement following drug withdrawal.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

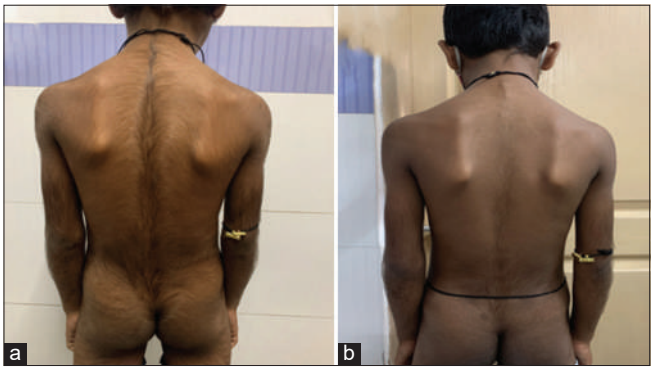

Figure 1: Boy on phenytoin at presentation with hypertrichosis all over his back in the form of fine nonterminal hair (a). The same boy showing significant improvement 1 month after stopping phenytoin (b)

Figure 2: Gingival (gum) hyperplasia at presentation in the boy on phenytoin

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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Case Report

Hemangioblastoma, a rare tumor of supratentorial and infratentorial regions: A report of two cases with review of literature

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Abstract

Hemangioblastoma (HBL) is a rare benign neoplasm arising from the vascular stromal cells. It is a WHO Grade 1 neoplasm with solid and cystic components. In majority of the cases, it is a sporadic tumor, and in few cases, association with Von Hippel–Lindau syndrome has been found. Here, we present two separate cases of intracranial HBL. One tumor is from the supratentorial region and another one is from the infratentorial region. Although infratentorial HBL is commonly found, supratentorial HBL is very rare. Microscopical similarity with metastatic clear cell renal cell carcinoma can be a diagnostic pitfall.

Keywords: Central nervous system, hemangioblastoma, supratentorial

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INTRODUCTION

Among the benign neoplasms of the central nervous system, hemangioblastomas (HBLs) are a rare entity, accounting for only 2.5%.[1,2] Molecular biological investigation on the cell origin of HBL revealed stromal cells as the cell of origin and the Von Hippel–Lindau (VHL) gene 3p26-p25 as the responsible one.[3] HBL affects the cerebellum in majority (16%–69%) of the cases, other sites are brain stem (5%–22%), spinal cord (13%–53%), and cauda equina (11%). Supratentorial HBL is rare only seen in 1%–5% of cases.[2,4] In majority of cases, HBL is sporadic in occurrence (75%) and a certain number has a genetic association of VHL disease (15%).[5]

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CASE REPORT

Case 1

A 32-year-old male presented with headache, vomiting, and loss of sensorium for 2 months. The patient was well oriented. General examination was apparently normal. Vitals were stable with blood pressure of 140/80 mmHg. On neurological examination, left-sided both limbs showed a decrease in power. On magnetic resonance imaging (MRI), a moderate-sized pial-based heterogeneous neoplasm (51 cm × 47 × 32 mm) in the right temporoparietal region with solid enhancing and cystic nonenhancing with mixed T2, FLAIR hypointense, T1 hypointensity to isointensity was detected. To rule out VHL, other tests such as chest X-ray, abdominal ultrasonography, and fundoscopic

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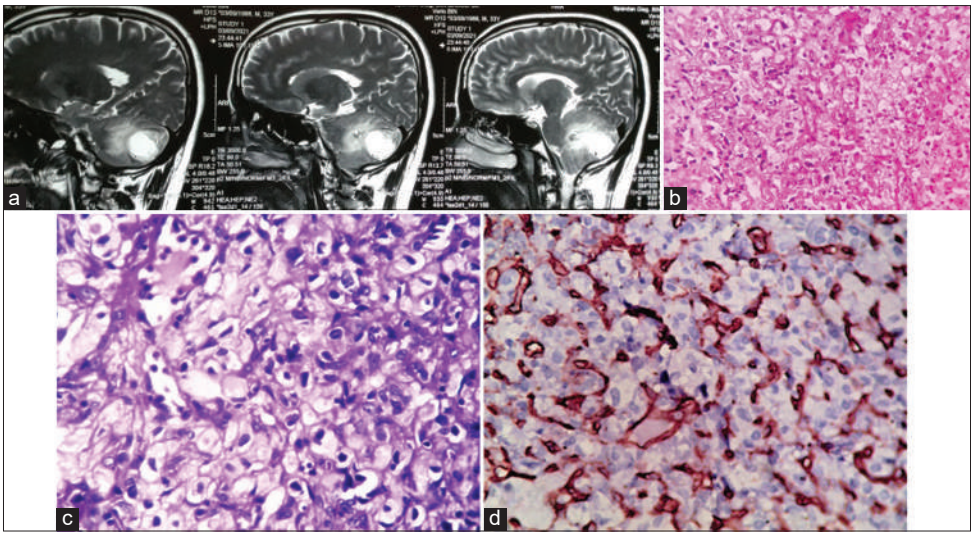

Figure 1: (a) MRI of infratentorial lesion. (b) Supratentorial hemangioblastoma. ×400, H and E showing stromal cells with fine vascular septa. (c) Infratentorial hemangioblastoma. ×400, H and E showing stromal cells with fine vascular septa. (d) CD34 IHC, ×400, showing membranous positivity. MRI: Magnetic resonance imaging, IHC: Immunohistochemistry

examination were done. All investigations were normal. On blood examination, hemoglobin was 15 g/dl and white blood cell (WBC) was 13568 cells/mm^3; differential was normal. Platelet was 1.8 lac/mm^3. Other tests were normal. Neurosurgical excision was undertaken, and the tissue was sent for biopsy. On histopathological examination, the diagnosis of HBL was confirmed.

Case 2

A 33-year-old male presented with severe headache and intermittent loss of sensorium and loss of balance. Like the previous case, the patient was well oriented with severe intention tremor. Blood workup revealed hemoglobin of 14 g/dl and WBC –16458/mm^3; differential count showed neutrophilic leukocytosis; platelet was 2.1 lac/mm^3. Other tests such as chest X-ray, abdominal USG, and fundoscopic examination were within normal limits as the previous case. On working up, MRI revealed a complex SOL (27 mm × 26 mm × 25 mm) at the right cerebellum, having enhancing solid and peripherally enhancing cystic components. Edema associated with the lesion caused fourth ventricular compression resulting in supratentorial ventriculomegaly. After neurosurgical excision, the tumor tissue was sent for biopsy. On histopathological examination, it was diagnosed as HBL.

DISCUSSION

HBL is a benign (WHO Grade 1) tumor mainly of sporadic incidence; in minority of cases, it is associated with VHL syndrome. In both of our cases, it was sporadic as other associated pathologies were not present. Entities such as clear cell renal cell carcinomas, pheochromocytomas, paragangliomas, and pancreatic neuroendocrine neoplasm were not present in these cases.[6]

Supratentorial HBL was first reported by Bielschowsky in 1902.[7,8] As per a review by Pandey *et al.* from 1902 to 2015, a total of 57 cases of supratentorial HBL without associated VHL were found.[9] After reviewing the literature, it revealed that supratentorial HBL affected a wide range of patients from the age group of 3 months to 80 years. However, a maximum number of cases belonged to the age group of 20–30 years and 40–50 years. Only one case of supratentorial HBL in an infant was seen. This fact probably points to the rarity of this condition in infancy. There is a male preponderance also. Most of the tumors were found to be solid, and only a minor <1/3 fraction were cystic.[9] The present case, however, had both the cystic and solid components. As per literature, supratentorial HBL is seen in locations such as cavernous sinus, optic nerve, frontal, parietal, temporal, occipital, third ventricle, lateral ventricle, pituitary, pituitary stalk, suprasellar, hippocampus, falx cerebri, corpus callosum, meninges, and choroidal fissure. In the present case, the lesion was in temporoparietal pial-based mass. As per Rocha *et al.*, supratentorial HBL having meningeal involvement is even rarer.[10]

Symptoms of supratentorial HBL depend on the location and pattern of growth of the tumor. The most common symptoms seen in patients are seizure and headache.[11] In the present case, the patient had headache, vomiting, and loss of sensorium.

The most accepted hypothesis about the pathogenesis of this condition is a mutation in the VHL gene that encodes the VHL

protein. VHL protein is of importance in the proteosomal degradation of hypoxia- inducible factor 1- alpha(HIF-1). In the mutation of VHL protein, the HIF-1α and its products accumulated the cell forms hypervascular tumor tissue.[12]

Radiological diagnosis is based on MRI findings. A solid nodule with adjacent cystic component is usually found. In T1-weighted sequence and with gadolinium contrast, the nodule appears hyperintense and homogeneous. On T2-weighted sequence, the cystic component appears hyperintense. The supratentorial lesions are solid cystic with a smaller cyst component. While the infratentorial in contrast the infratentorial lesion have a large cystic component.[11,13] In the case presented here, the supratentorial tumor was solid cystic in MRI [Figure 1a]. The infratentorial lesion, however, had a peripherally enhancing cystic component that caused compression of the fourth ventricle resulting in ventriculomegaly of the third ventricle. Radiologically, supratentorial HBL closely resembles angioblastic meningiomas.[14] Thus, without histological examination, it is not possible to identify HBL.

Histologically, the solid part of the tumor is formed by blood vessels of various calibers lined by a single layer of endothelium [Figure 1b and c]. The space between the vascular channels is filled with stromal cells, which represent the principal neoplastic component. These may be relatively sparse and evenly distributed around the rich capillary meshwork (the reticular variant) or form large contiguous sheets of clear epithelioid cells (the cellular variant). Small foci of extramedullary hematopoiesis are seen in roughly 10% of cases. Stromal cells generally have bland, oval-to-bizarre, degenerate-appearing, hyperchromatic nuclei with ample, vacuolated, clear cytoplasm containing lipid and glycogen accumulation. Immunohistochemical profile overlaps with other differentials such as renal cell carcinoma. However, endothelial markers such as CD34 are positive in HBL [Figure 1d]. Other immunohistochemical markers like inhibin-alpha, glucose transporter-1, podoplanin D2-40, and vimentin are highly positive. Positivity for the vimentin supports the hypothesis that HBLs have a mesenchymal origin. Other histochemical markers that are negative are cytokeratin, gliofibrillar acid protein, and epithelial membrane antigen.[15]

CONCLUSION

HBL is a rare tumor often causing diagnostic pitfalls. Supratentorial HBL is a rare entity, hence high index of suspicion is necessary for its timely diagnosis. Though proper history, clinicoradiological correlation and tumor morphology can solve the problem.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Osteopetrosis: A rare case

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Abstract

Osteopetrosis is a rare inherited metabolic bone disease characterized by failure of osteoclasts to resorb bone leading to impairment of bone modeling and remodeling. The defect in bone turnover results in skeletal fragility despite increased bone mass, hematopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, and growth failure. It has two major clinical forms: an autosomal dominant benign type or an autosomal recessive malignant type. The recessive form is usually fatal whereas the dominant type is more compatible with life. A rare autosomal recessive (intermediate form) is more prevalent and has less severe presentation. A 12-year-old boy presented with short stature, bilateral progressive vision loss, and backache. X-ray of nondominant hand for bone age estimation showed bone in bone formation. Followed which skeletal survey was done which showed characteristic radiological findings suggestive of osteopetrosis. Osteopetrosis is a rare disease transmitted by autosomal dominant or recessive inheritance having variable penetrance. We report here intermediate form of osteopetrosis. Although the genetic test is used to differentiate between the subtypes, diagnosis is mainly radiological.

Keywords: Metabolic bone disorder, osteopetrosis, short stature

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INTRODUCTION

Osteopetrosis also known as marble bone disease or Albers-Schonberg disease named after the German radiologist reported first description of the condition in 1904.[1] It is characterized by the failure of osteoclasts to resorb bone leading to impairment of bone modeling and remodeling. The defect in bone turnover results in skeletal fragility despite increased bone mass, hematopoietic insufficiency, disturbed tooth eruption, nerve entrapment syndromes, and growth failure. The estimated prevalence is 1 in 100,000–500,000 birth.[2] It is present as either an autosomal dominant benign type or an autosomal recessive malignant type. In the recessive form, caused by biallelic mutation of any one genes involved in osteoclast function or differentiation namely TCIRG1, CLCN7, OSTM1, SNX10, PLEKHM1, TNFSF11, TNFRSF11A; the child is severely symptomatic early in life and usually fatal. The dominant type, caused by a heterozygous missense mutation of CLCN7 gene on the other hand is more compatible with life. However, an intermediate type[3] due to carbonic anhydrase II deficiency is more prevalent in practice and has less severe presentation.

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CASE REPORT

A 12-year-old boy presented with poor gain of height noticed since 6 years of age along with bilateral progressive vision loss and backache. He was born out of nonconsanguineous marriage, with a birth weight of 1.6 kg by normal vaginal delivery at term, cephalic presentation with uneventful perinatal and antenatal history. There was no history of headache, nausea, vomiting, polyuria, and any chronic systemic illness. There was no history of head injury, radiation present. On anthropometry, height is 118.5 cm (< 3rd percentile) with standard deviation score (SDS) -4.33 and height age of 6.5 years. weight is 21 kg (< 3rd percentile), SDS -1.86 and weight age 6.5 years. Midparental height 162.75 cm and target height 164.8cm with SDS -1.13. Upper segment 62.5cm , lower segment 56cm. The child was prepubertal and bilateral testicular volume is 2 ml. Systemic examination is within normal limit, except presence of caries teeth, and visual acuity of finger counting in bilateral eyes. X-ray hand was done for bone age estimation, which shows bone in bone formation [Figure 1]. In view of these typical imaging findings, the skeletal survey was done, which shows the base of skull sclerosis [Figure 2] hypoplastic sinuses, reduced medullary cavity of long bones, erlenmeyer flask deformity of long bones [Figure 3] sandwich vertebra [Figure 4]. In view of characteristic imaging findings suggestive of osteopetrosis, further investigations were done for complications screening. Magnetic resonance imaging (MRI) LS SPINE done showed compression of nerve roots with disc bulge at L4-5 and L5-S1, straightening of the lumbar spine, and diffuse decreased bone marrow signal-intensity suggestive of myelofibrosis. Computed tomography brain done which shows communicating hydrocephalus. Pure tone audiometry showed a mild conductive loss in the right ear. Complete blood count showed only anemia with other cell lines remaining unaffected. Other baseline investigations are given in Table 1. Visual evoked potential showed bilateral optic atrophy. In view of the clinical diagnosis of osteopetrosis, the skeletal survey of the sibling was done, which also shows characteristic radiological findings, though he was asymptomatic with normal height for age.

DISCUSSION

Clinical manifestation of osteopetrosis ranges from asymptomatic to fatal course depending on the mode of inheritance. Our index case had clinical features consistent with an intermediate form of disease whereas his elder sibling is asymptomatic which denotes that the disease was likely inherited as autosomal recessive form with varying severity in the family members. The main features are short stature, visual and hearing loss, nerve entrapment syndromes, anemia, and hepatosplenomegaly. The characteristic clinical features of different types of osteopetrosis are given in Table 2.

Short stature is due to impaired longitudinal growth and dysmorphic craniofacial appearance is caused by macrocephaly and bossing of the forehead.[4] Due to continued bone formation, hematopoiesis is affected resulting in bone marrow failure, pancytopenia, and compensatory extramedullary hematopoiesis leading to hepatosplenomegaly, increased susceptibility to infection. The abnormally thickened bone also causes narrowing of cranial foramina resulting in nerve entrapment and hence facial palsy, deafness, and blindness.[5] The decrease in height age and bone age along with weightage could be explained by associated decrease in appetite and hence malnutrition secondary to systemic involvement of the disease and associated suspected renal tubular acidosis.

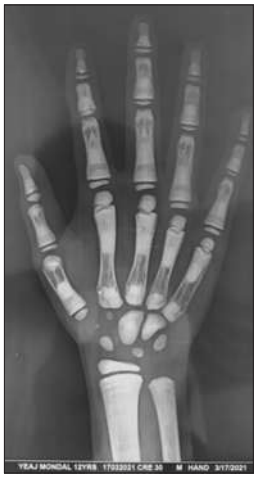

Figure 1: X-ray hand showing bone in bone formation

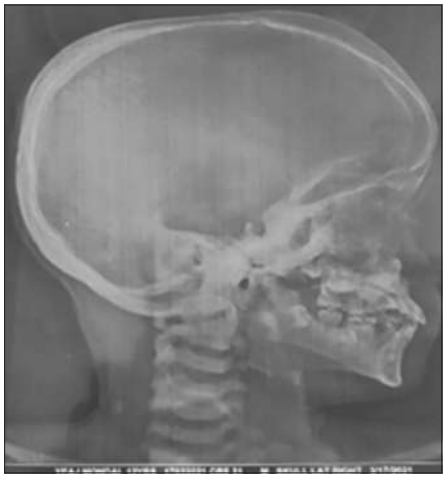

Figure 2: X-ray skull showing sclerosis of base of skull

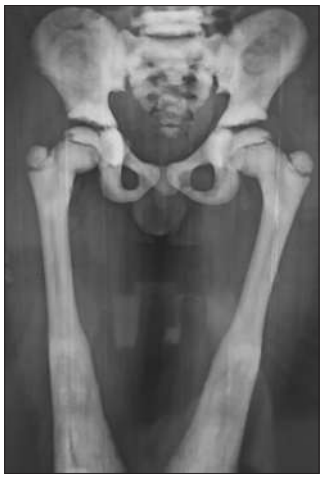

Figure 3: X-ray leg showing Erlenmeyer flask deformity of long bones, narrowing of medullary cavity

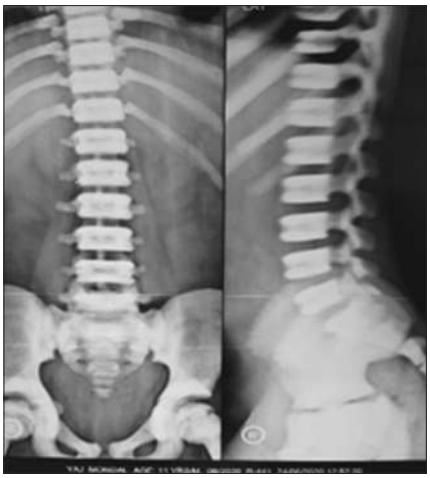

Figure 4: X-ray spine showing sandwich vertebra

Diagnosing osteopetrosis is mostly relied on skeletal radiology. On plain radiographs, osteopetrosis can present as osteosclerosis or dense bones. Four classic features appear in radiographs of patients: (1) diffuse sclerosis, affecting the skull, spine, pelvis, and appendicular bones; (2) metaphysis long bone defects known as "Erlenmeyer flask deformity," and characteristic lucent bands; (3) "bone-in-bone" appearance of the vertebrae and phalanges; and (4) sclerosis of skull base, pelvis, and vertebral end plates, giving rise to "sandwich" vertebrae, and "rugger-jersey" spine.[6] Genetic testing can be used to confirm the diagnosis and distinguish between various osteopetrosis subtypes, but not done in our case due to economic constraints.

The differential diagnoses include other disorders which can cause osteosclerosis, such as pyknodysostosis, hypervitaminosis D, Paget's disease, bone metastasis of breast or prostate cancer, fluoride, lead or beryllium toxicity.

Hematopoietic stem cell transplantation (HSCT) is the only treatment for osteopetrosis. HSCT using HLA identical donors results in 73% 5 years disease free survival.[7] Interferon-gamma 1b (IFNγ1b) treatment has been tried in patients with osteopetrosis variants unresponsive to HSCT or as a bridging therapy to transplantation. IFNγ1b leads to improvement in immune function, increased bone resorption, and increase in bone marrow space.[8] Other medications which can be administered in osteopetrosis include (1) Vitamin-D supplements which stimulate the dormant osteoclasts, resulting in bone resorption and (2) corticosteroids-stimulate bone resorption. While some may be asymptomatic, many of these patients require orthopedic surgery at some point in their lives for fractures.

Table 1: Baseline relevant investigations

Biochemical Test	Values (Reference range)
Urine pH	6 (4.6-8)
Blood pH	7.41 (7.35-7.45)
pCO_2	22.6 mmHg (35-45)
Serum HCO_3	17 mEq/L (22-30)
Serum chloride	106 mEq/L (96-106)
Anion gap	14 mmol/L (8-16)
TSH	2.3 miu/ml (0.4-4.5)
Free T4	1.2 ng/dl (0.8-1.8)
Calcium	9.72 mg/dl (8.5-10.5)
Phosphorus	4.0 ng/dl (3.5-4.5)
Serum potassium	4.7 mEq/L (3.5-5.5)
25 (OH) Vitamin D	16 ng/ml (<20 ng/ml)
8 AM cortisol	15 ug/dl (5-25)
LH	<0.01 miu/ml (0.8-7.6)
FSH	1.3 miu/ml (0.7–11)
IGF1	348 ng/ml (173-420)
LDH	>2078 IU/L (105-333)

IGF1: insulin like growth factor 1, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, LDH: Lactate dehydrogenase, TSH: Thyroid stimulating hormone

Table 2: Clinical classification of osteopetrosis

Characteristics	Adult onset	Infantile	Intermediate
Inheritance	Autosomal dominant	Autosomal recessive	Autosomal recessive
Bone marrow failure	None	Severe	None
Prognosis	Good	Poor	Poor

CONCLUSION

Although osteopetrosis is a rare disease, the diagnosis should be considered in children presenting with short stature, nerve entrapment syndromes, anemia, and radiological survey is required to confirm the diagnosis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to

be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Electric wire as an aid for masturbation: Report of a case with review of literature

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Abstract Masturbation by insertion of electric wire is rarely reported in the literature. Here, we are presenting a case of electric wire in the urinary bladder, which was inserted as an aid to masturbation.

Keywords: Cystoscopy, foreign body, masturbation

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INTRODUCTION

Selfinflicted foreign bodies in the male urethra and urinary bladder are a rare emergency in urology. The reason associated with the insertion of foreign bodies into the genitourinary is sexual.[1] In adults, this is commonly caused by the insertion of objects used for masturbation and is frequently associated with mental health disorders.[2] We report a case of insertion of electric wire into the urethra and urinary bladder as an aid of masturbation.

CASE REPORT

A 38-year-old male presented with the inability to void associated with pain in the penis. He inserted an electrical wire into his urethra for masturbation 4h earlier. He had a history of getting sexually erotic after inserting a thin electric wire into his urethra. Since the past 5 years, he was doing this practice of inserting electric wire, and after masturbation, he would pull the wire out. This time after repeating the same act, he was unable to pull the wire out. He had made several unsuccessful attempts to remove it. On physical examination, the two ends of the wire were observed in the urethral meatus [Figure 1]. After getting his formal consent, the patient was taken to the operating room. A plenty of local anesthetic gel was used, ventral meatotomy was done, and the wire was pulled out with some difficulties with the use of artery forceps [Figure 2].

This procedure in the emergency department was performed under local anesthetic only, without any sedation. A single dose of intravenous amikacin was given. After the patient passed urine normally, he was discharged with an appointment for follow-up, cystoscopy and uroflowmetry, and advised for psychiatric referral, but the patient did not follow-up.

DISCUSSION

A large number of selfinflicted foreign bodies have been reported in the male urethra and urinary bladder.[3] There is abound in literature on foreign body bladder such as needle, bullet, magnet, safety pin, animal feather, pieces of candle, thermometer, chewing gum, toothbrush, and electric wire.[4] The most common reason for selfinsertion

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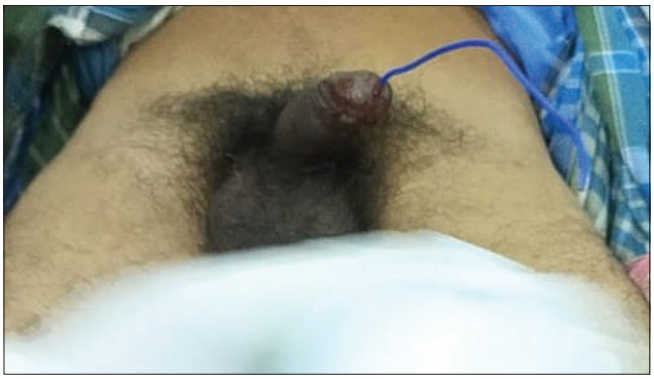

Figure 1: Electric wire into urethra

of a foreign body into the male urethra is of erotic or sexual nature, especially masturbation or sexual gratification.[1] A mental illness or drug intoxication may also be the reason.[2] According to Kenney's theory, the initiating event is the coincidentally discovered pleasurable stimulation of the urethra, followed by repetition of this action with objects of unknown danger, driven by a particular psychological predisposition to sexual gratification.[5] In the majority of cases, the patient feels guilty and humiliated; therefore, he postpones the search for medical help.[1,3]

There are a variety of symptoms including urinary frequency, dysuria, nocturia, hematuria, gross bleeding from the urethra, difficulty in voiding, or complete urinary retention.[1,2] After taking a good history, investigation such as an X-ray or ultrasonography[2,6,7] or rarely by computed tomography scan can be done. Cystoscopy is the best and most commonly used modality, not only to confirm, but also to remove most of the foreign bodies.[3]

There are various methods of removal of foreign bodies depending on the location and type of the foreign body such as cystoscopy, urethrotomy, or cystotomy.[1] In our case, the foreign body found to be inserted into urethra from external urethral meatus; it was smooth with no metal wires sticking out. We successfully removed the foreign body with meatotomy.

CONCLUSION

The removal of foreign bodies of the urogenital system is a rare case. Underlying psychiatric illness may be present. A trial for removal of foreign body under local anesthesia with forceps should be given; if failed, then advanced procedure like cystoscopy or open procedure should be tried. Postremoval of the foreign body, the urethra should

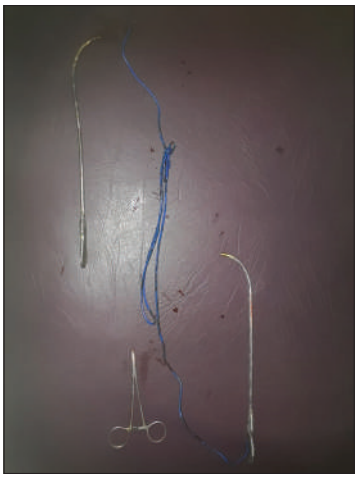

Figure 2: Removal of electric wire

be assessed with urethroscopy and uroflowmetry to rule out urethral injury. A psychiatric assessment should be done to rule out any underlying abnormality.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's guardian has given consent for images and other clinical information to be reported in the journal. The guardian understands that name and initial will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Familial hypercholesterolemia

A 5-year-old girl born out of nonconsanguineous marriage presented with yellow-white extensive flat-topped lesions over both buttocks suggestive of xanthomas, which were present for the last 1 year. There was no history of shortness of breath or chest pain. The father had tendon xanthomas over both tendon Achilles. Her mother had no such lesions. Her paternal grandfather died of stroke at the age of 55 years. There was no history of atherosclerotic cardiovascular disease(ASCVD) in the other family members. On examination, the girl was healthy-looking with large xanthomas over both buttocks [Figure 1a]. She did not have any tendon xanthomas or xanthelasma. All her pulses were equally palpable, and the cardiac examination was essentially normal. Her father had tendon xanthomas over both ankle joints [Figure 1b]. Investigations revealed total cholesterol of 913 mg/dl, serum triglyceride (TG) 158 mg/dl, serum low-density lipoprotein (LDL) 695 mg/dl, and serum high-density lipoprotein (HDL) 66 mg/dl. Her father had total cholesterol of 355 mg/dl, serum TG 122 mg/dl, LDL 246 mg/dl, and HDL 49 mg/dl. Her mother had total cholesterol of 324 mg/dl, serum TG 110 mg/dl, LDL 220 mg/dl, and HDL 51 mg/dl. Electrocardiography and echocardiography were essentially normal for the girl. The provisional diagnosis was familial hypercholesterolemia which was confirmed by clinical exome sequencing, The final diagnosis was familial hypercholesterolemia type 1. The culprit mutation was a homozygous variant c. 666C>A (p.cys222Ter) on exon 7 of chromosome 19. The patient and both her parents were initiated on tablet atorvastatin 20 mg once daily at bedtime. At 3 months, her lipid profile was still deranged. Hence, atorvastatin was increased to 40 mg once daily and tablet ezetimibe 10 mg once daily was also added. At last follow-up, her cholesterol was 770 mg/dl, TG 104 mg/dl, LDL 593 mg/dl, and HDL 61 mg/dl.

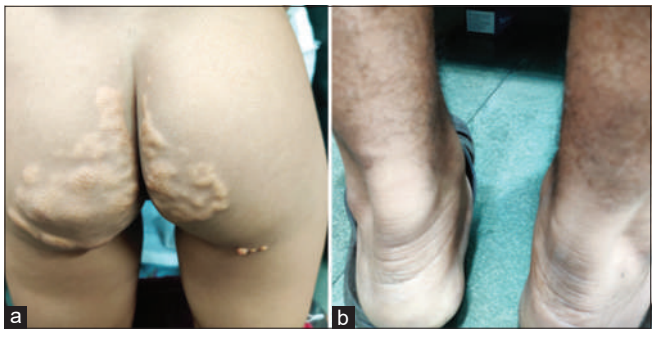

Figure 1: The child with flat yellowish xanthomas over both buttocks (a), the father with tendon xanthomas over both Achilles tendons (b)

Homozygous familial hypercholesterolemia is a disorder of lipoprotein metabolism caused by mutations in the LDL receptor gene, leading to an absence of functional receptors on the cell membrane, causing decreased uptake of LDL into the liver from blood, resulting in increased levels of LDL-cholesterol (LDL-C). In 1939, familial hypercholesterolemia was first described by Muller.[1] In cases with familial hypercholesterolemia, high cholesterol may manifest as xanthomas on the eyelids, tendons of the elbows, knees, hands, and feet.[2] The diagnosis in our case was made based on Simon Broome Register criteria.[3] Treatment is often difficult despite advances in lipid-lowering therapies.[4] The 2019 ESC/EAS Guidelines for the Management of Dyslipidemias suggests that statin treatment should be initiated as early as 6–10 years of age along with healthy lifestyle measure. Proprotein convertase subtisilin/kexin type 9 (PCSK9) inhibitors can be used in some of the children with homozygous familial hypercholesterolemia; however, it would likely be ineffective in our patient as she is harboring LDL-null mutation. Recommended goals for children >10 years of age are LDL-C <3.5 mmol/l (135 mg/dl) or at least a 50% reduction from the baseline.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient's parents have given consent for images and other clinical information to be reported in the journal. The patient's parents understand that the names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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