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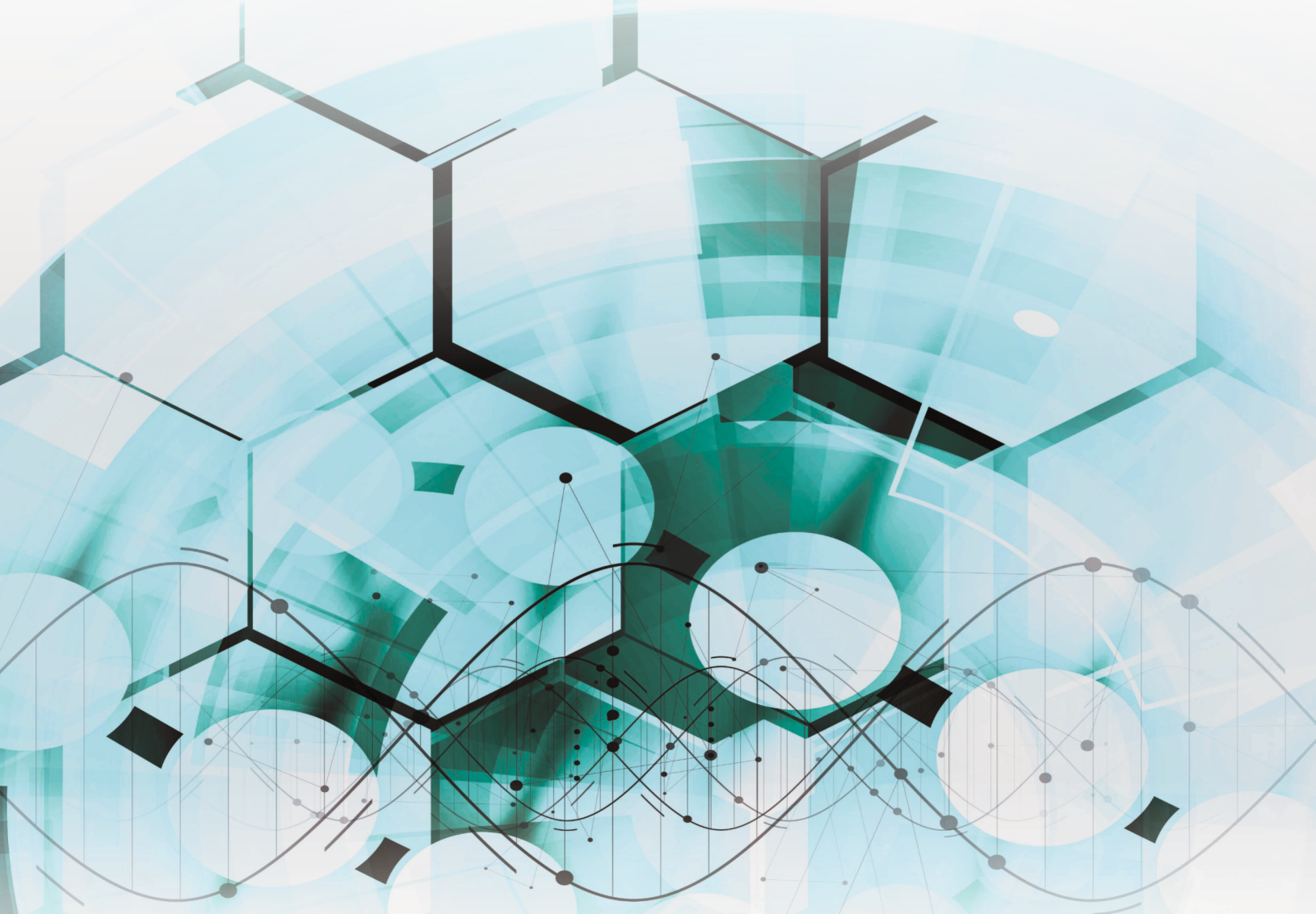

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CONTENTS

COVID pandemic: An unchartered terrain

The severe acute respiratory syndrome coronavirus (SARS-CoV-2) pandemic reportedly originated from Wuhan city, China, in December 2019 which later on was declared as a pandemic by the WHO on January 30, 2020. Since then, it gradually spread over the world, and the whole health-care delivery system had got stunned at the beginning but gradually got adopted and changed itself to face the unprecedented threat against humankind and its existence. This global pandemic has subjected health-care workers (HCWs) to an extremely high risk of infection through direct workplace exposure, coupled with increased workload and psychological stress. While HCWs represent less than 3% of the population in developed countries and less than 2% in almost all developing and underdeveloped countries, around 14% of COVID-19 cases reported to the WHO are among HCWs. In some countries, the said proportion can be as high as 35%. Thousands of HCWs infected with COVID-19 have lost their lives worldwide.

Limited availability of personal protective equipment (PPE) kits at the beginning of pandemic and enhanced workload increased the risk of both contracting and transmitting the infection. PPE is often double-layered, uncomfortable, and suffocating. It must be worn for several hours at a stretch without providing any scope for consuming food, drinking, or even using the washrooms. Most of the users get dehydrated from excessive sweating and also develop skin complaints from retention of moisture inside and excessive hand cleaning. There was evidence of considerable psychological burden on HCWs, including posttraumatic stress disorder and depression. Particularly, the psychological stress of infecting their near and dear ones after returning from workplace was always a mental burden on them.

HCWs working in high-risk departments such as intensive care unit, respiratory wards, and 24-h fever clinics are directly exposed to SARS-CoV-2 patients and are threefold more vulnerable. High morbidity and mortality associated with the infection; in addition to the abrupt, fast, and unpredictable nature of deterioration, medical workers experience feelings of helplessness. This gets extended when one experiences loss of a coworker after getting infected with COVID.

To provide 24-h care, hospitals organized staff rotations in shifts and HCWs must often work for inhumanly long hours. SARS-CoV-2 has brought a flood of patients with varieties of complex management needs, placing an even greater strain on health-care systems and adding workload to the HCWs. In the COVID-only hospitals, the medical personnel often got mentally fatigued by seeing only COVID-infected patients day and night, and the failure to see patients with any other ailment created a sense of clinical depression.

Similarly, the SARS-CoV pandemic has demonstrated increasing rates of mental health outcomes in nurses as compared to doctors. The reasoning behind this may be multifactorial. Nursing staff may have increased possibilities of physical contact with infected patients compared to other HCWs. Given the morbidity associated with the disease, all are likely to experience increased "Emotional Labor." This refers to the mental effort of suppressing emotions such as fear and concern while displaying optimism and empathy.

"No country, hospital, or clinic can keep its patients safe unless it keeps its health workers safe. WHO's Health Worker Safety Charter is a step toward ensuring that health workers have the safe working conditions, the training, the pay, and the respect they deserve."

The role of telemedicine has grown in many countries since the start of the COVID pandemic. Often, it has allowed ailing people to consult with physicians without leaving their homes during lockdowns and avoids spreading or contracting the virus, thereby breaking the chain of infection. In much of the developing world with weaker health-care systems, and particularly in India during the recent surge, telemedicine has played a far more vital role. Judicial use of tele-consultation in COVID cases not only eliminates the mental stress of the doctors, but the patient or their relatives also get ample time to take valued opinions of the medical personnel.

It is necessary to achieve herd immunity through vaccination globally to prevent SARS-CoV-2 from continuing to mutate, becoming more resistant to current vaccines and causing more periods of mass fatality. We have taken the challenges of offering the vaccine to those who need it most and preventing disparities in vaccination access. For the vaccines to work to its highest efficacy,

access should not be dictated by the social or economic status of the citizen. We have followed the rule that those at high risk should be vaccinated first with less vulnerable groups receiving their vaccine aftermath.

We are duty bound and firmly determined to overcome this pandemic by educating the people about the importance of COVID-19 vaccination and other available health-care measures to overcome the potential adverse events. Educating people helps build trust in the decision of HCWs without which, the world will not be able to overcome the pandemic and return to "normal" life it deserves.

Practically, with the entire humanity, the HCWs are also going through a hitherto unchartered path. All the turns and pebbles of this path provide valuable learning. Hope, our learning makes us stronger to deal with such situations more efficiently.

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Launching of a new platform of academic discourse

Institute of Post Graduate Medical Education and Research (IPGMER), the erstwhile Presidency General Hospital or PG Hospital, was established in 1707 by the East India Company and continues to be one of the premier health-care and academic institutes of the country. This hospital is also the oldest general hospital in the Indian setup for the practice and research in modern medicine.

The institute has a glorious record of fundamental research in various fields of medicine. It was from here that Hare, Cunningham, Lewis, and Ronald Martin had put their mark in medical treatment and research.[1-7]

This hospital had hosted the works of the epoch-making discovery of "Cycle of Malarial Parasite" by the first Nobel laureate from India (1902), Sir Ronald Ross, who also received the Barclay Memorial Medal from the Asiatic Society, Calcutta (1903), thus ending the myth of the "mal-air" established a scientific pathogenetic basis for one of the dreaded killer diseases of the world. The campus proudly bears the testimony of the historical event as engraved in the "Gate of Commemoration," which was unveiled by Lord Lytton (1927), the then Governor-General of India.

Michael Madhusudan Dutta, the eminent poet, was the first native Indian to be admitted to this hospital on June 22, 1873, where he died on June 29, 1873. Dr. Surendranath Ghosh was the first native Indian doctor appointed in the then PG Hospital.

In the postindependent years, PG Hospital had reincarnation in the form of the first Post Graduate Medical Institute in Eastern India in 1957, when it came to be known as the IPGMER. It was inaugurated by Pandit Jawahar Lal Nehru, the first Prime Minister of India, on January 16, 1957. Undergraduate medical training was introduced here later in 2004. In its years as a medical teaching institute, it had many great luminaries who followed the path of their eminent predecessors.

Catering to the health needs of a very large proportion of the world population over the years, we have always felt the need for scientific data harvesting in this part of the world. India being the unique melting pot holds a fifth of the world's population, which has been churned through the ages of migrations resulting in a multiethnic, multiracial diaspora spread across its extreme geographical and cultural diversities. Apart from being an anthropological marvel, it offers a unique challenge and scope to the clinicians and scientists to study disease processes with multitudes of variations in its agent, host, and environmental factors that need not match the existing western texts. Thus, we believe that systematic documentation of the health records, disease patterns, and health solutions available across the diverse strata of this country can not only contribute but also significantly influence and enrich the world of medical literature.

There is immense potential and enthusiasm in the pursuit of academic exercises in medicine in India and in the state of West Bengal in particular. However, we strongly felt the need of an integrated effort in motivating and nurturing the young minds, as well as providing a platform to document the high-quality academic and health research works that are undertaken at regional and national levels and to help them achieve better coordination with the international fora. The illustrious history of this organization acts as a motivation for us to excel, and it is befitting that IPGMER would lead the endeavor, as has always been its legacy.

The idea of the *Annals of Medical Science and Research (AMSR)* was thus conceived.

The *AMSR* is devoted to basic, clinical, epidemiological, and experimental studies of the various disciplines of medical and health sciences. It seeks to contribute significantly to the pathogenesis, diagnosis, prognosis, and effective treatment or prevention of diseases.

The *AMSR* will document the scientific contribution and novel findings of Theoretical and Applied Research, Quantitative and Qualitative Research, Preventive and Therapeutic Research, Educational Research, Interesting facts and Observations, Current Topics, etc. *AMSR* also acts as a platform of research data repository to facilitate reproducibility and data reuse with recognition and citation of the source and encourages open source sharing of software, code, models, algorithms, protocols, methods, and other useful research materials.

It will not be out of place to note that as we are moving through the scripts and scriptures of medical literature

to present the inaugural issue of this Journal, we are also witnessing a history being created as the whole world is plagued by a health crisis of pandemic proportion in the form of COVID-19. It has shown beyond any doubt that our only hope of fight back lies with timely and appropriate medical research. The results influence not only the practice of health sciences but also impact the major social, political, and economic decisions touching every aspect of our survival and well-being.

We contemplate making *AMSR* an effective platform of rich and resourceful interaction among academicians on classic as well as recent development in the field of medicine. The young aspirant gets the opportunity to act together with the "old mate in the profession" for enrichment of ideas, thoughts, and methodologies. Let *AMSR* becomes the launch pad of newer scientific ideas, research aptitudes of the budding medicos and an exchange podium of interesting information, historical backdrop of crucial scientific discoveries and viewpoint of science, and more. We sincerely hope that *AMSR* will contribute greatly toward inculcation of the philosophy of reflective inquiry among the medical fraternity of our country.[8]

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Variant of *CALCR* gene (rs2301680) associated with the risk of calcium urolithiasis: A preliminary study

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Abstract

Background: Urolithiasis is a global health burden. It is a complex disease resulting from the complex interactions of epidemiological, genetic, and environmental factors.

Objective: Earlier studies showed a majority of the renal stone patients in West Bengal were diagnosed with calcium-containing stone. Here, in this study, we aimed to find out the association between single-nucleotide polymorphism (rs2301680) of *CALCR* gene with urolithiasis risk.

Methodology: A case–control study was performed with 20 renal stone patients admitted to the Department of Urology, Institute of Post Graduate Medical Education and Research, Kolkata. The equal number of age-, sex-, and ethnicity-matched healthy individuals were also enrolled. Clinical parameters were recorded through a questionnaire. Peripheral blood was drawn from every individual in ethylenediaminetetraacetic acid (anticoagulant) containing vials. DNA was extracted from the blood using a QIAamp Blood Kit (QIAGEN, Hilden, Germany) as per the manufacturer's instruction. Amplification of the desired region of *CALCR* gene was performed using polymerase chain reaction (PCR) using specific primers. The PCR products were sequenced bidirectionally using the BigDye Terminator kit v3.1 (Applied Biosystems, Foster City, USA) in ABI Prism 377 DNA Sequencer (Model 3700; Applied Biosystems, Foster City, USA).

Results and Conclusion: Clinical results showed a higher level of urinary calcium in patients than controls. The allelic and genotypic frequency analyses revealed a probable association of rs2301680 of *CALCR* with the risk of urolithiasis in our study population. However, our sample size is very small and further studies with larger samples are required to conclude the association of this SNP with urolithiasis.

Keywords: *CALCR*, SNP, urolithiasis

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INTRODUCTION

Urolithiasis is a global urological problem. It involves stone formation in any portion of the human urinary system. Stone forms by successive physicochemical events of supersaturation, nucleation, aggregation, and then retention[1] of stone-forming crystals such as calcium oxalate (CaOx), calcium phosphate (CaP), uric acid, cysteine, or magnesium–ammonium phosphate. Major risk factors that contribute to stone formation and

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its recurrence include low urine volume, hypercalciuria, hyperoxaluria, hypocitraturia, and hyperuricosuria. Stone formation is also associated with climate, age, sex, body weight, race, and ethnicity. Another mechanism of urolithiasis is an imbalance between the promoters and inhibitors of crystallization compounds such as citrate, magnesium, and molecules such as nephrocalcin and Tamm–Horsfall glycoprotein. The deficiency of inhibitors also increases the chance of the disease.[2]

Kidney stones are usually asymptomatic until and unless they obstruct the urinary passage. Lifetime prevalence of the disease is about 10% in adults. Multiple factors such as epidemiological, biochemical, metabolic, nutritional, socioeconomic, drug induced, and genetic risk factors are all responsible for urolithiasis.[3]

Among the kidney stones, calcium stones constitute ~75%, struvite stones ~15%, uric acid stones ~6%, and cystine stones ~1%–2%.[2] Furthermore, about 80% of calcium kidney stones are CaOx. The remaining 20% stones are CaP and a mixture of both CaOx and CaP. Hypercalciuria is the most common abnormality in calcium urolithiasis patients.

Our previous study showed a significant association of rs1801197 of *CALCR* with urolithiasis in the population of West Bengal, India.[4] Moreover, we had performed a case study (n = 5) to check CALCR protein expression in the stone affected the region of the biopsy kidney tissue as compared to adjacent control tissue and observed variant genotypes for rs2301680 along with SNP rs1801197 and rs1042138 of *CALCR*.[5] In this study, we have screened SNP rs2301680 with the risk of calcium urolithiasis in kidney stone patients of West Bengal.

METHODOLOGY

Urolithiasis patients (n = 20) were recruited from the Department of Urology, Institute of Post Graduate Medical Education and Research (IPGME and R), Kolkata, West Bengal, under the supervision of Dr. Dilip Kumar Pal. The study protocol was approved by the Institutional Ethical Committee. Prior consent was obtained from each of the patients and/or families before collecting samples. Both male and female patients of age group 18–70 years were recruited who had reported a spontaneous urinary stone expulsion or when stone was observed on ultrasound/X-ray of the kidney or patients with a history of surgical stone removal or lower urinary pH (<5.5) or urinary tract stones of >5 mm diameter. Patients taking drugs affecting electrolyte or citrate handling (steroids, diuretics, Vitamin D, bisphosphonates, etc.), endocrine or other metabolic disorders in addition to stone disease, patients with abnormal serum creatinine, abnormal serum electrolyte concentration, and recurrent urinary infections or obstructive nephropathy were totally excluded from the study. The control group (n = 20) was selected from age- and sex-matched healthy individuals of the same geographical region and socioeconomic status, who had no evidence of diseases at physical examination, negative personal and familial history of kidney stones, absence of hypercalciuria, normal serum creatinine, and serum calcium concentrations.

Data such as age, gender, drinking and dietary habits, daily urine output, height, body weight, serum calcium, urea, and urinary calcium were acquired from both the patients and controls. Peripheral blood sample (approximately 2 ml in ethylenediaminetetraacetic acid vial) was collected from the study participants and their genomic DNA was extracted using QIAamp Blood Kit (QIAGEN, Hilden, Germany). The purity and concentration of extracted DNA were checked by NanoPhotometer (Implen, Implen GmbH, Munich, Germany). Specific oligonucleotide primers [Table 1] were designed for rs2301680 [location shown in Figure 1] using integrated DNA technologies and Primer 3 software.

Polymerase chain reaction (PCR) was carried out in 30 μL reaction mixture consisting of 100 ng genomic DNA, 0.5 μL of forward and reverse primer (10 mmol/L), 0.5 μL of dNTP (10 mmol/L), 1 μL $MgCl_2$ (50 mmol/L), 2.5 μL PCR buffer (×10), and 0.5 μL of Taq polymerase (5 units/μL). PCR was performed in a thermocycler (Applied Biosystems, Veriti 96-well thermal cycler, Model No. 9902) in the following condition – denaturation at 94°C (5 min), followed by 44 cycles of denaturation for 30 s, then annealing of primer at 64°C for 30 s, then extension at 72°C for 1 min and finally extension at 72°C for 5 min

PCR fragments were checked and purified from agarose gel. Then, the PCR products were subjected to bidirectional sequencing to detect the genotypes, using a Taq Dye Deoxy Terminator sequencing kit (PE Applied Biosystems, City, USA) with an ABI Prism 377 DNA Sequencer (PE Applied Biosystems). Pairwise sequence alignments between sequences of the case and control individuals were performed to find the best-matching piecewise (local) or global alignments of two query sequences using clustalW program (EMBL-EBI, Hinxton, England).

Chi-square test was used to test the allelic and genotypic associations of the SNP rs2301680. Hardy–Weinberg equilibrium of the SNP in the case and control individuals

Table 1: Primer sequence

Primers (5'–3')	GC content	Primer length	Amplicon length	Annealing temperature
Forward (F): GAGGGCCTCAGGTATAACAATC	50	22	509 bp	64°
Reverse (R): CTGGGTAGACCACAAACACTAA	48.5	22		

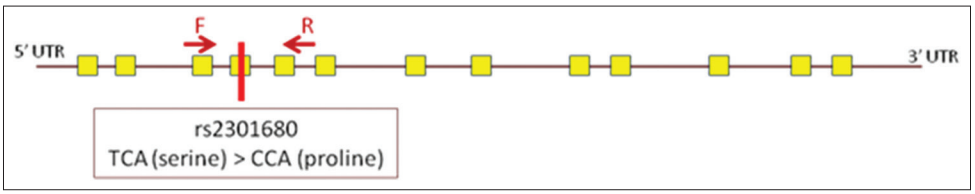

Figure 1: Schematic representation of the position of the SNP and location of the primers

was examined using this test. The tests were done using GraphPad InStat software (GraphPad InStat software, San Diego, CA). Odds ratio (OR) and 95% confidential interval were calculated using the same software.

RESULTS

The comparison of control individuals and kidney stone patients is presented in Table 2.

Among the 20 patients, 80% were males and 20% were females showing approximately 4:1 sex ratio in our study population. The BMI was 22.28 ± 2.38 kg/m^2 for kidney stone patients and 22.09 ± 2.65 kg/m^2 in controls, showing no significant difference between the two groups. Daily urine output was found to be significantly ($P < 0.0001$) low in patients as compared to controls [Table 2].

Then, PCR products were first checked in 1.5% agarose gel and then the genotypes for rs2301680 of *CALCR* gene were determined by doing forward and reverse strand DNA sequencing of the PCR products. Representative chromatogram for the SNP is shown in Figure 2.

Comparison of allelic and genotypic frequencies between patients and controls population

In the studied group, wild genotype TT was observed in 14 controls and 9 kidney stone patients. The variant CC genotype was found in six patients, as compared to three controls. The data are presented in Table 3.

Significant high "C" allele distribution in patients (0.42) was observed compared to controls (0.22) against rs2301680 (Ser17Pro) [Table 3]. Our result suggests that "C" is the risk allele ($P = 0.056$; OR = 2.55; 95% confidence interval [CI]: 0.96–6.73) for kidney stone formation in this study group [Table 4]. Genotype CC for rs2301680 was noted in 30% of cases as compared to 15% of controls ($P = 0.0398$) [Table 5]. Moreover, individuals with CC genotype showed about two and half times increased risk (OR = 2.59; 95% CI: 0.49–13.61) in our population toward the formation of urolithiasis.

DISCUSSION

The etiopathogenesis of urolithiasis is multifactorial. Alongside the environmental factors, genetical aspects play a significant in the pathophysiology of the disease. Research findings on different ethnic populations of the world revealed the association of polymorphisms in several genes such as *CASR, CALCR, PTH, VDR, TRPV5, OPN, MGP, AQP1, SLC34A1, CLDN14,* and *KLOTHO*[6] with the kidney stone disease. In this study, we have examined the possible association between rs2301680 of *CALCR* gene and the risk of development of urolithiasis in West Bengal population of India.

Majority of the kidney stone patients in West Bengal are hypercalciuric. Hence, it is assumed that the disease results from an alteration in calcium homeostasis regulating pathway. *CALCR* gene is attributable to the synthesis of calcitonin receptor. It interacts with the hormone calcitonin, which inhibits the activity of osteoclasts in the bone tissue. This in turn decreases calcium release into the bloodstream and also regulates the phosphates and calcium reabsorption in the renal tubules.[7] Polymorphisms or mutations in *CALCR* gene might influence disease development. The association of SNP rs1801197 with urolithiasis has been established in populations of India,[4,8] Brazil,[9] Iran,[7] and Russia.[6]

The present study is the first report on the possible association of SNP rs2301680 with urolithiasis risk. Our preliminary data indicates the frequency of variant genotype CC is double (30%) in patient group, as compared to controls (15%). Significant high frequency of allele "C" was noted in urolithiasis patients (0.42) as compared to controls (0.22). "C" was found to be the risk allele. Here,

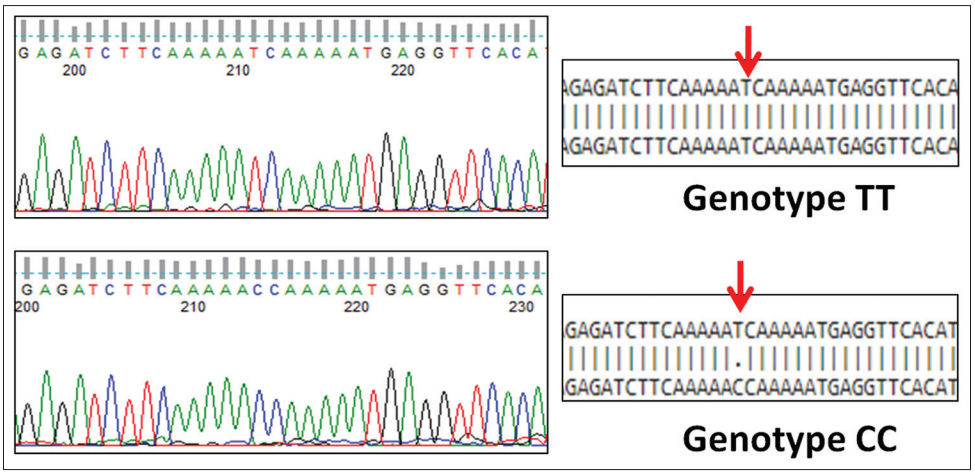

Figure 2: Chromatogram sequencing of CALCR SNP rs2301680

in this study, 2.55-fold (with 95% CI 0.96–6.73) increased risk of kidney stone formation was noted in individuals carrying "C" allele compared to those carrying allele "T". Therefore, the allelic change from "T" to "C" for rs2301680 of *CALCR* gene can be predicted as a risk factor for kidney stone development in the population of West Bengal ($P = 0.032$; OR = 2.55; 95% CI: 0.96–6.73).

Genotypic analysis revealed that variant genotype CC was noted in 6 (30%) patients, as compared to 3 (15%) controls. Individuals with CC genotype were at about three times increased risk ($P = 0.0398$; OR = 3.11; 95% CI: 0.62–15.71) toward developing urolithiasis.

In conclusion, our preliminary study indicates rs2301680 (TCA > CCA) of *CALCR* might be a potential genetic marker for recognizing subjects at risk of urolithiasis in the West Bengal population. As this SNP causes amino acid change from serine (polar, uncharged) to proline (nonpolar, hydrophobic); hence, rs2301680 needs to be studied extensively with larger sample size, supported by functional analysis to provide conclusive evidence.

Author contributions

PM and MD conceptualized and designed the research study; PM performed the experiments; PM analyzed the data; MD contributed essential reagents/materials/analysis tools; DKP provided blood samples along with clinical data; PM drafted the manuscript with important intellectual inputs from DKP; MD critically revised the manuscript.

Compliance with ethical standards

Ethical approval

This study was approved by the Institutional Ethics Committee (Memo No. INST/IEC/2016/374 dated 06.06.2016) of (IPGME and R), Kolkata, West Bengal, India.

Table 2: Comparison of characters between controls and patients

Characteristics	Control (*n*=20)	Patient (*n*=20)	*P*
Age (years)	39.6±9.85	43.0±11.752	0.3277
Gender, *n* (%)			
Male	14 (70)	16 (80)	0.9922
Female	6 (30)	4 (20)	
BMI (kg/m^2)	22.09±2.65	22.28±2.38	0.8177
Serum urea (mg/dL)	25.74±6.50	29.20±13.41	0.0626
Serum calcium (mg/dL)	9.03±0.54	9.05±0.61	0.9378
Urinary calcium excretion (mmol/day)	5.6±0.49	7.48±0.37	**<0.0001**

BMI: Body mass index, (To compare continuous independent variables [age, body mass index [BMI], and all clinical parameters] within controls and patients, unpaired two-sided Student's t-test was used. Nonparametric variables [gender, place of living, lifestyle, and food habit] were analyzed using Mann–Whitney U-test.All data expressed as mean SD ± (standard deviation) and P < 0.05 is considered to be statistically significant and marked in bold.)

Table 3: Allele and genotype frequency of controls and patients

	Control (*n*=20)	Patient (*n*=20)
Individuals with "TT" genotype	14	9
Individuals with "TC" genotype	3	5
Individuals with "CC" genotype	3	6
"TT" genotype frequency (%)	70	45
"TC" genotype frequency (%)	15	25
"CC" genotype frequency (%)	15	30
"T" allele frequency	0.78	0.58
"C" allele frequency	0.22	0.42

Informed consent

Signed informed consent was obtained from each study participant included in the study.

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Table 4: Comparison of allele frequency between controls and patient

Allele	Allele frequency		OR (95% CI)	*P*
	Control (*n*=20)	Patient (*n*=20)		
T	0.78	0.58	2.55 (0.96–6.73)	0.056
C	0.22	0.42		

CI: Confidence interval, OR: Odds ratio

Table 5: Comparison of genotype frequency between controls and patients

Genotype	Control (*n*=20)	Patient (*n*=20)	Model	Adjusted odds ratio (95% CI)*	*P*
TT	70%	45%	Codominant		
TC	15%	25%	TT versus TC	2.59 (0.49–13.61)	**0.0398**
CC	15%	30%	TT versus CC	3.11 (0.62–15.71)	
			Dominant		
			TT versus TC + CC	2.85 (0.78–10.47)	0.1077
			Recessive		
			TT + TC versus CC	2.43 (0.51–11.51)	0.0526

CI: Confidence interval, $P < 0.05$ is considered statistically significant and marked in bold. Chi-square test was used to compare genotype frequencies between controls and patients. * OR adjusted for age, gender, BMI, place of living, lifestyle, and daily water intake and food habits.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Association of tobacco addiction, oxidative stress, and abnormal seminogram profile among middle-aged Indian males

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Abstract

Background: The impact of tobacco addiction and oxidative stress on male fertility has been studied globally, but the findings are often controversial. Moreover, data pertaining to socioeconomic background of India are very limited in this regard.

Objective: In the present study, we attempted to explore the association of tobacco addiction, oxidative stress, and abnormality of seminogram parameters among middle-aged Indian males.

Materials and Methods: Male counterparts of 147 infertile couples were investigated and classified into addicted and nonaddicted groups on the basis of tobacco addiction history. Physical parameters, such as sperm count, motility, and morphology of sperm, were done in Sperm Quality Analyzer. Seminal malondialdehyde (MDA) was measured by thiobarbituric acid method. Association of tobacco addiction and seminogram profile was tested by Chi-square test. MDA levels were compared in groups by unpaired Student's *t*-test. Correlation among the parameters was checked by the coefficient of correlation. Everywhere, $P < 0.05$ was considered statistically significant.

Results: Among 147 candidates, 87 were addicted and 60 were nonaddicted. On seminal analysis, 47 showed normal and 100 abnormal seminogram. The Chi-square test showed a significant association between tobacco addiction and abnormal seminogram ($P < 0.05$). The mean MDA level in nonaddicted group was 1.46 ± 0.56 nmol/ml, whereas in addicted group, it was 2.28 ± 0.71 ($P < 0.05$ in unpaired Student's *t*-test). A significant negative correlation was found between MDA level and sperm count, motility, and morphology ($P < 0.05$ in each case).

Conclusion: The present study concludes that tobacco addiction may be associated with an abnormal seminogram profile and oxidative stress may be an underlying factor.

Keywords: Male infertility, oxidative stress, tobacco addiction

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INTRODUCTION

Although, traditionally, the female counterpart is held responsible for the failure to conceive, in reality, the male reproductive capacity was found to be deficient in at least 50% of infertile couples.[1] Therefore, the evaluation of male fertility potential merits attention when investigating

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Table 1: Distribution of smokers and nonsmokers with normal and abnormal seminogram profiles and result of the Chi-square test

Seminogram profile	Addicted	Nonaddicted	Total	*P* (by Chi-square test)
Normal seminogram	22	25	47	<0.05 (degree of freedom=1)*
Abnormal seminogram	65	35	100	
Total	87	60	147	

*Significant

Table 2: Comparison of seminogram parameters between addicted and nonaddicted groups

Seminogram parameters	Addicted group	Nonaddicted group	Result of unpaired students *t*-test
Sperm count (millions/ml)	27.55±10.37	92.95±29.15	<0.01*
Sperm motility (%)	28.25±12.11	58±8.02	<0.05*
Normal sperm morphology (%)	30.02±4.97	40.12±6.29	<0.05*

*Significant

any couple for infertility. Numerous factors may influence male fertility, among which oxidative stress has created much interest among the researchers recently. Oxidative stress occurs when the delicate balance between the production of reactive oxygen species (ROS) and inherent antioxidant capacity of any system is distorted. ROS are highly reactive oxidizing agents belonging to the class of free radicals containing one or more unpaired electrons,[2] which are continuously being generated through various metabolic and pathophysiologic processes in our system. The excess of ROS can damage the living cell at different levels such as cell membrane, cellular proteins, and nuclear DNA, leading to different morbidity.

Human spermatozoa are especially susceptible to ROS as their plasma membrane contains polyunsaturated fatty acid in abundance which can undergo a chain of chemical reactions after getting attacked by ROS, called lipid peroxidation, which is grossly damaging to the sperms. They also lack cytoplasm to generate robust preventive and repair mechanism against ROS.[3]

One of the important markers of oxidative stress is malondialdehyde (MDA), which is an end product of lipid peroxidation. High level of MDA represents high lipid peroxidation rate, which may cause changes in sperm and diminish fertility.[4] However, there is controversy about the seminal MDA activity and the sperm quality. Suleiman *et al.* demonstrated that the MDA concentration in the seminal plasma was not correlated with sperm concentration and motility, which contradicts the findings of a number of previous studies.[5]

Lifestyle behaviors, such as smoking, tobacco chewing, alcohol abuse, and environmental pollutants, further enhance the generation of ROS and thus may cause destructive effects on various cellular organelles such as mitochondria and sperm DNA. However, the impact of tobacco addiction on seminal quality has seldom been systematically studied. Often, the findings of the studies are mutually contradictory. In some studies, smoking was found to be associated with low sperm count but higher sperm motility,[6] whereas some other studies showed that smoking may cause a reduction in progressive motility of sperms.[7] Thus, the reports regarding the exact effect of smoking on seminal quality are still controversial. Therefore, in the present study, we attempted to explore whether smoking has got any deleterious effect on seminal quality and whether oxidative stress has any role into it.

MATERIALS AND METHODS

It was a cross-sectional study done at the Reproductive Biology Unit of the Physiology Department of Mahatma Gandhi Institute of Medical Sciences, Wardha, Maharashtra. The entire study was done with due permission from the Ethics Committee of the Institute (ref no: 29/07/9.01.07 dated 30/12/06), and written consent was obtained from each participant before inclusion. All participants were first selected randomly using a computer-generated random number table from each day's OPD attendance of the reproductive biology unit, and then they were further screened as per mentioned inclusion and exclusion criteria.

Inclusion criteria

Male counterparts of the couples attending the reproductive biology unit with complaints of infertility (both primary and secondary infertility) and 30–58 years of age were included. The total number of candidates included was 147. Persons having their BMI in the range of 23–25 were only included in the study.

Exclusion criteria

Subjects with varicocele, hydrocoele, undescended testes, cryptorchidism, or any other structural abnormality or any history of surgical intervention in the genitourinary tract which may interfere with male fertility were excluded from the study. Subjects with any acute febrile (>38°C body temperature) illness or a history of similar episode in the last 6 months or treatment history with drugs such as cancer chemotherapy, nitrofurantoin, niridazole, colchicine, or any hormonal preparation which may directly suppress the spermatogenesis were also excluded from the study. Complete azoospermics were excluded from the study. Participants with any other addiction than

tobacco (smoking or chewing) such as alcohol and cannabis were also excluded from the study. Persons with other relevant histories such as usage of recreational drugs, such as marijuana and anabolic steroids, occupational exposure of heat, use of agricultural pesticides in farming, history of hereditary subfertility in the family, and history of intake of any antidepressant drugs were also excluded from the study.

Study design

After taking a detailed history of addiction and lifestyle behaviors, present and past illness, as well as medical and surgical managements, the selected male partners were taken for a thorough surgical examination of the genitourinary system to rule out the exclusion criteria. Only participants with normally developed genitorurinary organs were included in the study.

On the basis of tobacco addiction history, participants were divided into two groups:

1. Addicted: Those who smoke or use any tobacco product for sucking, chewing, or snuffing either daily or occasionally for more than 12-month duration[7].
2. Nonaddicted: Those who are not in the use of any kind of tobacco ever.

Semen samples were collected by masturbation after 3 days of sexual abstinence. After complete liquefaction at 37°C, each sample was mixed well. The following physical parameters were assessed thereafter:

- Routine semen analysis was done by Sperm Quality Analyzer (SQA II B, M. E. S. Ltd., Israel) for sperm concentration, motility, and morphology, and according to the WHO guideline(1), grouped into two categories with the following criteria:
    1. Normal seminogram (showing normozoospermia): Sperm count >20 million/mL, forward progressive motility in >50% sperms, and normal morphology in >30% sperms
    2. Abnormal seminogram (showing oligo-, astheno-, or teratozoospermia).

After evaluation of physical parameters, the whole semen sample was centrifuged at 3000 rpm for 10 min. Then, without disturbing the pellet at the bottom, supernatant seminal plasma was taken for the estimation of malondealdehyde (MDA).

Estimation of malondialdehyde by thiobarbituric acid method

Principle

The assay was done by thiobarbituric acid (TBA) method and was based on acid-catalyzed decomposition of lipid hydroperoxides to MDA, which reacts with TBA to form a chromogen evaluated spectrophotometrically at 530 nm.

Method

MDA levels were measured by TBA method.[4] 0.1 ml of seminal plasma was added to 0.9 ml of distilled water in a glass tube, to it 0.5 ml of TBA reagent was added and then heated for 1 h in a boiling water bath. After cooling, the tube was centrifuged for 10 min at 4000 rpm, and the supernatant absorbance was read on a spectrophotometer at 534 nm.

Statistical tools applied

The association of semen quality and addiction habit was verified by the Chi-square test. MDA levels of different subgroups were checked by unpaired Student's *t*-test. Everywhere, $P < 0.05$ was considered statistically significant. The association of seminal MDA level and seminogram parameters (count, motility, and normal morphology) was tested by coefficient of correlation (*r*-value).

RESULTS

A total of 147 male counterparts of the infertile couples attending the reproductive biology unit of physiology department were investigated. Among them, 87 were found to have tobacco addiction history and 60 were nonaddicts. After seminal analysis for sperm count, motility, and morphology, 47 were found to have normal and 100 were found to have abnormal seminogram profile.

The mean MDA level in the nonaddicted group was 1.46 ± 0.56 nmol/ml, whereas in the addicted group, it was 2.28 ± 0.71 nmol/ml ($P < 0.05$ in unpaired Student's *t*-test). A significant negative correlation was found between seminal MDA and sperm count ($r = -0.57$), motility ($r = -0.58$), and percentage of sperm with normal morphology ($r = -0.6$) ($P < 0.05$ in each case).

DISCUSSION

It is now evident from different research works that free radical-induced injury to the sperm plays a major role in the pathogenesis of male infertility. About 40% of men attending infertility clinics show detectable ROS level in their semen.[1] The vulnerability of human spermatozoa to oxidative injury[8] is due to the fact that these cells are particularly rich in unsaturated fatty acid. Such an abundance of unsaturated lipid is necessary to create the membrane fluidity required for the membrane fusion events of fertilization such as acrosomal exocytosis and sperm–oocyte fusion. It has been found that over one-third of all men are addicted to some form of tobacco globally.[9]

Smoking has been shown to be associated with an array of adverse health outcomes such as cardiovascular disease, respiratory disease, and cancer of the lungs, bladder, esophagus, and stomach. Recently, the relationship between tobacco addiction and reproductive health has become the theme of various studies in various parts of the globe. In our study, we found an association between tobacco addiction and abnormal seminogram profile. Our finding is corroborative with number of previous studies,[9] which also found some negative impact of tobacco smoking on male fertility potential. Nicotin and other toxins liberated in cigrette smoke are the mediators of smoking induced damage to the male fertility potential.[9] All such mediators may induce inflammatory response, leukospermia, and production of ROS, leading to oxidative stress that ultimately leads to damage to various cellular components such as sperm cell membrane, acrosomal cap, and sperm DNA. Ultimate effects may render sperms nonfunctional causing subfertility.[10] On the contrary, there are certain studies which found positive effects of tobacco smoking on sperm motility.[6,11] However, our study is further supported by Fuentes *et al*., who found that paternal smoking contributes to decreased *in vitro* fertilization success rates.[12] There is also evidence of improvement in male fertility potential after cessation of nicotine addiction.[10]

In recent times, it has been established through various studies that oxidative stress has a definite role in the pathogenesis of male infertility. MDA being the end product of lipid peroxidation reflects the extent of oxidative stress in any system. An important finding of our study is an elevated level of seminal MDA in the addicted group, which, on the other hand, shows higher percentage of abnormal seminogram profile. This clearly signifies that smoking or tobacco addiction may lead to oxidative stress that may ultimately lead to abnormal seminogram in males. Our study finding is supported by number of previous researches[13,14] that also demonstrated a negative impact of oxidative stress on seminogram parameters. The mechanism by which MDA leads to poor semen quality may be multifaceted. ROS-induced sperm damage can be responsible for a gross deterioration of semen quality. It can decrease sperm motility presumably by a rapid loss of intracellular ATP which leads to axonemal damage, decreased sperm viability, and increased midpiece morphological defects that may produce deleterious effects on sperm capacitation and acrosome reaction.[2] Moreover, oxidative damage can also cause DNA fragmentation, base degradation, and cross-linking of proteins with loss of function in sperms.[3] Overall effects lead to increased apoptosis (programmed cell death) in sperms with excess oxidative damage.

Human spermatozoa, because of abundant content of polyunsaturated fatty acids in their cell membrane and very scanty antioxidant support from the cytoplasm, are very much susceptible to oxidative stress. Excess amount of lipid peroxidation produces high levels of spermicidal cytotoxic end products such as MDA which may cause defective changes in sperm and diminish fertility.[4]

Furthermore, the lipid peroxides formed as well as their degradation products (hydroxyalkenals, malonaldehyde, etc.) can cause irreversible arrest of motility and midpiece morphological defect.

Free radical-induced oxidative injury to the spermatozoa not only affects its physical parameters but also induces poor sperm function by altering signal transduction mechanism and damaging DNA, protein, lipid, and other cellular components, which ultimately lead to impaired fertility.

Contrary to these facts, there are some other studies which failed to demonstrate any significant correlation of seminal MDA with sperm concentration and motility.[5]

However, as supported by most of the previous studies, the present study emphasizes deleterious effect of tobacco addiction on male fertility potential. It also indicates that oxidative stress as revealed by higher MDA level in the addicted group may be one of the responsible factors for their abnormal seminogram profile Tables 1 and 2.

Surprisingly, we also found a considerable number of abnormal seminogram among the nontobacco addicts. Other than tobacco addiction, there can be a wide variety of lifestyle factors that could potentially influence sperm quality. These lifestyle factors may include the use of recreational drugs, such as marijuana and anabolic steroids; obesity; psychological stress; advanced parental age (between 35 and 50 years); diets consisting of processed meat, full-fat dairy products, alcohol, coffee, and sugar-sweetened beverages; and genital heat stress resulting from scrotal hyperthermia due to various reasons, such as cycling and occupational heat exposure which may be responsible for poor semen quality even in the tobacco nonaddicted group. These factors can affect sperm quality in various ways, remarkably by inducing inflammatory milieu, oxidative stress, apoptosis of sperm, etc.[15] Moreover, other than congenital or acquired conditions, a substantial proportion of subfertility may be idiopathic in origin.[16]

Therefore, although we excluded persons with all documented and accepted factors for poor semen quality, still there may be various underlying factors, information

of which could not be elicited and hence not excluded. These may be the reason for poor semen quality even among nonaddicted group.

CONCLUSION

The present study concludes that tobacco addiction may be associated with abnormal seminogram profile and oxidative stress may be one of the underlying mechanisms for the derangement of seminogram parameters in tobacco users. Hence, abstinence from tobacco abuse may be advocated for improving semen quality.

Limitations of the study

1. After centrifugation of whole semen, the pellet containing the cellular portions should have been analyzed along with supernatant plasma for biochemical markers. However, due to time constraints, we could not explore cellular pellet; only seminal plasma was used for oxidative marker
2. Although MDA is the end product of the peroxidative process, basal levels of MDA may not reflect the exact status of oxidative damage in tissue. This is because MDA can be further metabolized to malonic acid semialdehyde and further to acetate and acetyl CoA. There are better markers for assessing actual oxidative stress, for example, protein carbonyls and F2 isoprostanes, but due to logistic constraints, we explored only MDA level.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

Lupus in elderly: An observational study

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Abstract

Introduction: Lupus is an autoimmune disease with multisystem involvement. The disease may be seen in the elderly, and due to nonspecific presentation in this age group, only a high degree of suspicion helps diagnose cases. Moreover, in the presence of several comorbidities in the elderly, the management of lupus often becomes difficult and challenging, resulting in increased morbidity and mortality.

Aims and Objectives: To evaluate the presentation, organ damage, and outcomes of lupus in elderly patients.

Materials and Methods: About 50 ($n = 50$) lupus patients above 50 years of age were evaluated with respect to their presentation, organ damage, and outcomes.

Results: The female-to-male ratio was 2.8:1, and the majority of them had nonspecific presentations such as fatigue, weakness, weight loss, and low-grade fever. The musculoskeletal system was seen most commonly involved, followed by cutaneous and neurological involvement. These patients had several comorbidities such as diabetes, hypertension, and dyslipidemia in various combinations, and all these, besides lupus, contributed to increased morbidity and mortality in comparison to lupus in the younger.

Conclusions: Lupus in the elderly needs a strong suspicion, and the presence of comorbidities in addition to organ damage by the disease itself really makes a challenge for the treating physician.

Keywords: Lupus, organ involvement, elderly population, outcomes

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INTRODUCTION

Lupus is an autoimmune disease with multisystem involvement. The disease is common in childbearing age, probably due to some hormonal influences, but may also be occurred in older age groups. Late-onset lupus is defined as onset of the disease above 50 years of age and is seen in about 12%–18% of cases.[1] Age at disease onset has a great impact on clinical manifestations of lupus.[2] As the geriatric population increases worldwide due to increased life expectancy, there will be more detection of late-onset lupus in future. Besides, late-onset lupus is reported to have a more insidious onset, nonspecific presentations and maintain a relatively lower disease severity.[3] Therefore, diagnosis is often delayed and sometimes can be a challenging task for the treating physicians. Hence, a high index of suspicion is always required to diagnose lupus in elderly subjects. There are also striking differences observed between late onset and lupus in young adults and these are declining female to male ratio, relatively less renal involvement, more non-specific symptoms such as weight loss, anorexia and more serositis, lung involvement, sicca symptoms, neurological involvement(headache, cognitive impairment etc.) and hematological involvement (cytopenia, anemia etc).[4] Lupus nephritis and central nervous system involvement are also less

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Table 1: Presenting symptoms of lupus patients

Symptoms	No. of Patients (%)
Weakness	37 (74)
Myalgia	32 (64)
Arthralgia	30 (60)
Fatigue	28 (56)
Weight loss	21 (42)
Fever	12 (24)
Dry eyes and mouth	11 (12)
Cognitive dysfunctions	9 (18)

Table 2: Spectrum of organ involvement

Organs	No of cases(%)
Musculoskeletal	31 (62)
Cutaneous involvement	29 (58)
Nervous system	15 (30)
Pulmonary involvement	12 (24)
Renal involvement	11 (22)
Cardiovascular	22 (44)

Table 3: Comorbidities in elderly lupus patients

Types of co-morbidities	No of cases(%)
Diabetes	28 (56)
Hypertension	20 (40)
Hypothyroidism	15 (30)
Dyslipidemia	22 (44)
Hyperuricemia	20 (40)

Table 4: Laboratory abnormality of elderly lupus patients

Laboratory parameters	No of cases(%)
Anemia	40 (80)
Leukopenia	14 (28)
Thrombocytopenia	25 (50)
ANA (Hep2)	50 (100)
ds-DNA	33 (66)
SSA	10 (20)
SSB	6 (12)
Rheumatoid factor	9 (18)
Anti Sm	5 (10)
Hypocomplementemia	6 (12)

ANA: Antinuclear antibody, ds-DNA: Double-stranded DNA, SSA: Sjogren's syndrome related antigen A, SSB: Sjogren's syndrome type B, Sm: Smith

frequently encountered in the late-onset group.[5] Moreover, the presence of multiple comorbidities (e.g., diabetes mellitus, hypertension, hypothyroidism, and dyslipidemia) in various combinations might be confounding factors and also challenging for the treating physician because of decreased tolerance of immunosuppressive drugs and increased mortality.[6]

Objectives

The objective of this study is to evaluate the presentation, organ damage, and outcomes of lupus in elderly patients.

MATERIALS AND METHODS

This was a prospective observational study, where diagnosed lupus patients (as per the new ACR/EULAR criteria, 2019) aged above 50 years were evaluated in the NRS Medical College, Kolkata, with consent from each patient, for 2 years (March 2018 to March 2020). The inclusion criteria were age above 50 years, diagnosed lupus, and willing to participate in this study, and the exclusion criteria were those having end-stage renal diseases, malignancies, and not willing to give consent for this study. The institutional ethics committee gave permission for conducting this study. They were assessed with respect to age, sex, marital status, drug history, social history, modes of presentation, spectrum of organ involvement, and the presence of comorbidities (such as diabetes, hypertension, hyperlipidemia, and hypothyroidism). Laboratory tests included were routine blood examination, thyroid functions, immunological tests like ANA , anti- ds DNA, anti-Sm antibodies, serum complements, and renal biopsy where indicated.

RESULTS

In this study, the majority of patients were found to be above 65 years of age and the female-to-male ratio was 2.8:1 (female 37 and male 13 patients). The presenting symptoms were nonspecific and were weakness in 37 (74%), myalgia in 32 (64%), arthralgia in 30 (60%), fatigue in 28 (56%), weight loss in 21 (42%), fever in 12 (24%), dry eyes and mouth in 11 (22%), and cognitive dysfunction in 9 (18%) cases [Table 1].

Regarding the spectrum of organ involvement, musculoskeletal involvement was observed in the majority of cases, in about 31 (62%) patients. These were polyarthralgia in 25 (50%), body ache in 23 (46%), low back pain in 22 (44%), and proximal muscle weakness in 12 (24%) cases. Cutaneous involvement was the second most common and seen in about 29 (58%) cases. These were painless oral ulcers in 23 (46%), photosensitivity in 20 (40%), discoid lesions in 5 (10%), and Raynaud's phenomenon in 10 (20%) cases. Involvement of other organs observed were -lungs in 12 cases(24%) in the form of pleural effusion in 10 cases(20%), interstitial lung disease in 5 cases(10%), and pulmonary arterial hypertension in 3 cases (6%). Neurological involvement was seen in 15 cases (30%) in the form of non-specific headache in 10 cases (20%), peripheral neuropathy in 9 cases (18%), cognitive involvement in 7 cases (14%), seizure in 6 cases (12%) and dementia in 4 cases (8%).

Renal involvement was seen in 11 cases (22%), with nephrotic range proteinuria in 7 cases (14%) and subnephrotic proteinuria in 8 cases (16%) and urinary

active sediments containing cellular and red blood cell casts in 6 (12%) cases. Cardiovascular involvement was seen in 22 (44%) patients in the form of ischemic heart disease in 20 cases (40%), pericardial effusion and pericarditis in 7 cases (14%), and cardiomyopathy in 3 cases (6%) [Table 2]. Disease activity as per the SLEDAI scale was low in all most all the patients, and the average time interval required to diagnose all these patients was 4 ± 2.5 years. Another important observation noted that about 30 patients (60%) had co-morbidities in various combinations, of these 28 had diabetes (56%), 20(40%) had hypertension, 22 (44%) had dyslipidaemia in the form of hypertriglyceridemia in 12 cases(24%). Regarding serum uric acid level, 20 (40%) patients had asymptomatic hyperuricemia with the average serum uric acid level of 8 ± 2.4 mg/dl [Table 3].

Laboratory abnormalities observed were anemia in 40 cases(80%), mostly normocytic normochromic type, thrombocytopenia in 25 cases (50%), ANA detected in all the patients, anti-ds DNA detected in 33 cases (33%), anti-SSA and anti SSB in 10(20%), 6 (12%) cases respectively [Table 4].

Four (8%) patients died due to acute myocardial infarction, three (6%) patients died due to cerebrovascular accident, and two patients died due to severe bacterial pneumonia.

DISCUSSION

In this study, the presenting symptoms were nonspecific and mostly had a weakness (74%), myalgia (64%), fatigue (60%), low-grade fever (24%), and weight loss (42%) in various combinations. All these were the major constitutional symptoms, and a high index of suspicion was made in every case for the possibility of lupus, along with exclusion of other diseases that might have the same presentations (tuberculosis or HIV-AIDS and malignancies). Regarding the spectrum of organ involvement, musculoskeletal involvement was the major organ involved, of which polyarthralgia (50%), body ache (46%), and low back pain (44%) were prevalent. Cutaneous involvement was the second most organ involvement (58%), although not so common in this age as reported previously.[4] Oral ulcers (46%) and photosensitivity (40%) were seen in the majority of these patients. One important observation was that 24% of patients had pulmonary involvement in the form of pleural effusion in 20%, interstitial lung disease in 10%, and pulmonary arterial hypertension in 6% cases. Patients having interstitial lung disease and pulmonary arterial hypertension had a history of repeated hospitalization, resulting in increased morbidity, as also reported previously.[7] Neurological involvements observed were nonspecific headache in 20%, seizure in 12%, and cognitive impairment in 14% of cases, which were possibly related to lupus disease process (as a spectrum of neuropsychiatric involvement) and/or associated comorbidities. Another important observation was that cognitive impairment was one of the only neuro-psychiatric manifestations contributed maximal functional impairment in this group of patients. Renal lesions, although less commonly seen in elderly lupus, were observed in about 22% of patients here, some patients (10%) had nephrotic range proteinuria (>3.5 g/24 h), and the rest had subnephrotic range proteinuria, with active urinary sediments.[8] Regarding the comorbidities, the majority of the patients had type 2 diabetes mellitus (56%), hypertension (40%), and dyslipidemia (44%) in various combinations and had more accrual damage as a result of aging and associated comorbidities.[9] Death occurred in about 18% of lupus patients in this study and was due to acute myocardial infarction (8%), cerebrovascular accident (6%), and pneumonia (4%). The mortality was higher due to combined effects of associated comorbid conditions and increased disease activity as reported.[8] Although ANA positivity might be increased in the aging population, this autoantibody was detected in all these elderly lupus patients, along with other autoantibodies and associated clinical features suggestive of lupus.[10] As this was a cross-sectional observational study only, it has many limitations, such as the sample size was small, long-term follow-up was not done, and lots of coexisting comorbidities might influence disease outcomes.

CONCLUSIONS

Lupus in the elderly had more insidious disease onset with nonspecific constitutional symptoms, had overall low-disease activity, accompanied by several comorbidities in various combinations, and had increased morbidity (fatigue, weakness, skin changes, and repeated hospitalization) and also mortality.

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Conflicts of interest
There are no conflicts of interest.

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Original Article

Delineating caregiver distress and health condition of dementia sufferers during lockdown due to COVID-19 pandemic

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Abstract

Objectives: The COVID-19 pandemic led several countries to go under strict lockdown, including India. This was mainly done to limit the spread of the virus by ensuring social distancing and following the other COVID-19 protocols. Managing and caregiving of chronic disorders like dementia became challenging. The aim of the study was to delineate the health condition of demented patients and distress of their caregivers during the lockdown caused by the COVID-19 pandemic.

Methods: A telephonic survey was conducted to collect the data of 57 participants who had attended the cognitive clinic of our institute for a follow-up within 1 year preceding the lockdown. Demographic details of the patient and caregivers were noted followed by the questions related to the patients' health and their caregivers' distress during the lockdown. The questionnaire had two parts: (a) Patient Health Condition (PHC)'(b) Caregiver Distress-which consisted of preexisting caregiver distress before the lockdown and increase during the lockdown.

Results: During the lockdown, 89.5% of caregivers reported increase in caregiver distress and 61.4% reported deterioration in PHC, including worsening of memory and behavioral symptoms. Caregivers reported increased feelings of sadness and hopelessness (65%), physical exhaustion (60%), investment of energy (67%), and anxiety of getting sick with nowhere to turn for support (51%). The increase in caregivers' distress during the lockdown was higher with a decline in patients' health condition and in female caregivers and severe stages of dementia.

Conclusion: The lockdown situation was detrimental to both the patients' health condition and caregiver distress in dementia.

Keywords: Caregiver distress, COVID-19, dementia, lockdown, pandemic

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INTRODUCTION

The World Health Organization declared COVID-19 as the pandemic in the beginning of March 2020.[1] From of March 24, 2020, nationwide lockdown was announced in India,[2] which led to restrictions in normal activities and

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movements outside one's living areas. Public transport was ceased throughout the country to restrict the movement of people to stop the spread of the virus. This was done as social distancing, self-isolation, and private and public quarantine help to control the mass spreading of the virus.[3] However, these restrictions had some adverse effects on the conditions of people who are suffering from other disorders. The difficulty in visiting health-care setups for follow-ups during the lockdown caused difficulty in patients and their caregivers as well. It became incredibly challenging for the caregivers of dementia patients to provide the necessary care, increasing the caregiver burden during the lockdown period.[4] A pandemic causes fear and distress[5] and along with that lack of certain necessary supply of goods and facilities. An overall drop in the economy also due to the pandemic[6] increased the hardship of people.

In a developing country like India, it is already a strain on the caregivers of the patients with dementia.[7] With additional pressure of lockdown, the strain is ought to increase.

The aim of the study was to delineate the caregiver distress of patients with dementia during the lockdown caused by the COVID-19 pandemic and whether caregiver distress increased during the lockdown. The health condition of patients was also a research concern and if these two had any relation.

METHODS

The study was conducted on caregivers of patients with Dementia at Bangur Institute of Neurosciences and IPGME and R, Kolkata, India, between the months of June and July 2020. This was the part of the ongoing research work of the department and permission was obtained from the Institutional Ethics Committee.

Patient Health Condition (PHC) was considered as the current physical, psychological, and social state of the patient.

Preexisting Caregiver Distress (PeCD) was considered as the physical, psychological, and social stress (distress) perceived by the caregiver of the patient with dementia due to the care they provide before the pandemic and lockdown.

Lockdown Caregiver Distress (LCD) was considered as the increased distress perceived by the caregiver of the patient with dementia during the lockdown caused by the COVID-19 pandemic.

Present Caregiver Distress (PCD) was considered as the summation of PeCD and LCD.

Severity of PHC was determined with the help of their functional impairment in daily activities.

- Patients who were totally dependent on their caregivers and were unable to walk, eat, take bath, use toilet or groom themselves were categorized as *severe dementia*
- Patients who were partly dependent on their caregivers for eating, bathing, toilet, and grooming but are able to walk by themselves were categorized as moderate dementia
- Patients with some behavior and memory problems, but were not dependent on their caregivers for activities such as eating, taking bath, using toilet, and for grooming themselves were categorized as mild dementia.

Tools

The questionnaire contains two parts related to: (a) PHC and (b) caregiver distress. Behavioral symptoms part of the PHC questionnaire was modified as per the requirements pertaining to lockdown, from the Neuropsychiatry Inventory Questionnaire.[8] The Caregiver Distress Questionnaire was also modified as per the requirements pertaining to lockdown, from the Informal Caregiver Burden Assessment Questionnaire.[9] The final questionnaire was reviewed by experienced cognitive neurologists and clinical psychologists and consensus was reached about the same.

Tool description

Questionnaire on PHC consists of demographic details of the patient and caregiver followed by questions related to the patients' health during the COVID-19 pandemic. The questionnaire on caregiver distress consists of PeCD before lockdown as well as an increase in distress during the lockdown due to the COVID-19 pandemic (vide Supplementary Material) (Annex I).

- Scoring: PHC Questionnaire has a total score of 20. Questions 1,2,3,4, and 6 having 1 score each of the answer is "YES" and 0 if the answer is "NO." Question 5 has 10 symptoms listed for which score is 1 for each symptom if increased during the lockdown. Question 7 has 4 functions and has a reverse scoring-inability, i.e., "NO" as an answer has a score of 1 for each function (Annex II)
- The Caregiver Distress Questionnaire consists of 13 questions each carrying 1 mark for "YES" and 0 for "NO" as an answer. Increase of caregiver distress during the lockdown in each question also carries 1 mark. Therefore, total score of PeCD Questionnaire is 13 and total score for LCD is also 13. The final questionnaire was reviewed by experienced cognitive neurologists and clinical psychologists and consensus was reached about the same.

Sample

The study was conducted on 57 caregivers of demented patients who had attended the cognitive clinic for a follow-up within 1 year preceding the lockdown.

Procedure

A list of 115 patients were prepared from the database of the Cognitive Clinic of the Institution. Data were collected by a psychologist (RM) through the telephonic survey between the months of June and July 2020. First, the convenience of time and availability for the collection of data were enquired of the caregivers. Verbal approval of the participants was taken after explaining the purpose of the survey. Two to three attempts were made to contact them who did not receive the call at once.

Statistical analysis

Statistics were performed using the SPSS 21 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The mean and standard deviation of the continuous variables were calculated and compared across groups using the Mann–Whitney *U*-test/Kruskal–Wallis test. Spearman's rank correlation coefficient was used to analyze the significant relationship between PHC and LCD. Paired *t*-test was used to compare between PeCD and PCD. *P* value at the level of < 0.05 was considered statistically significant.

RESULTS

Out of 115 patients, 12 caregivers reported the death of their patients, 45 contact numbers were either invalid or unreachable, and 1 caregiver refused to take part. Thus, a total of 57 caregivers completed the telephonic questionnaire. Of these 57 patients, 30 (52.6%) were suffering from Alzheimer's disease, 9 (15.8%) from frontotemporal dementia, 6 (10.5%) from vascular dementia, 4 (7%) from mixed dementia, 6 (10.5%) from Parkinson's disease with dementia, and there was 1 (1.7%) patient each suffering from corticobasal degeneration and dementia with Lewy bodies. The details of characteristics of patients are given in Table 1.

Table 1: Characteristics of patients and primary caregivers

Characteristics	Patient, *n* (%)	Primary caregiver, *n* (%)
Gender		
Male	33 (57.9)	20 (35.1)
Female	24 (42.11)	37 (64.9)
Age		
Below 60	17 (29.82)	40 (70.2)
60 and above	40 (70.18)	17 (29.8)
Education		
Below graduation	40 (70.18)	25 (43.9)
Graduation and above	17 (29.82)	32 (56.1)
Occupation		
Working	8 (14.04)	20 (35.1)
Nonworking	49 (85.96)	37 (64.9)
Relation		
Spousal	-	37 (64.9)
Nonspousal (children)	-	20 (35.1)
Number of caregivers		
Sole	-	15 (26.3)
Multiple	-	42 (73.7)
Seveirty of dementia		
Mild	33 (57.9)	-
Moderate	12 (21.05)	-
Severe	12 (21.05)	-
Patient health condition during lockdown		
Change in memory	38 (66.67)	-
Change in behavior	42 (73.68)	-
Caregivers' difficulties in patient's care during lockdown (*n*=38; 66.7%)		
Cognitive/behavioral issues difficult to manage	-	20 (35.1)
No one to support in family	-	7 (12.3)
Professional caregiver not available	-	3 (5.3)
Patient cannot be taken out for a walk	-	13 (22.8)
Difficult to consult doctor	-	26 (45.6)
Stoppage of medicine	-	11 (19.3)

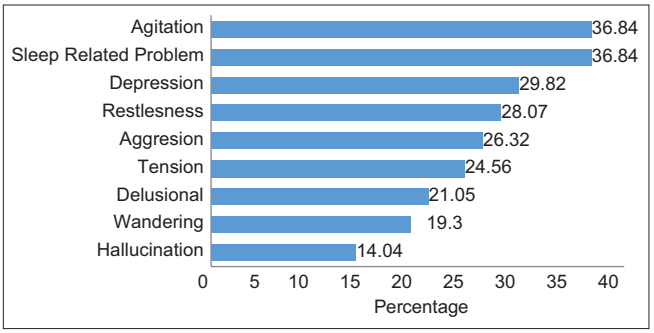

Figure 1: Increased behavioral symptoms of patients during the lockdown

In this study, during the lockdown due to the COVID-19 pandemic, 89.5% of caregivers reported increase in caregiver distress and 61.4% reported deterioration in the PHC, including worsening of several behavioral symptoms [Figure 1].

Overall, 67% of caregivers reported difficulties in patient's health care during the lockdown, 65% of caregivers reported increased feelings of sadness, helplessness, and hopelessness due to the care they provide, 60% reported increased physical exhaustion, 67% reported increased investment of considerable amount of energy, and 51% facing anxieties related to getting sick and having nowhere to turn for support [Figure 2].

The mean (± standard deviation) score was 6.09 (±4.19) for PHC, 7.39 (±3.31) for PeCD, 5.33 (±3.29) for LCD and 12.72 (±6.14) for PCD, respectively.

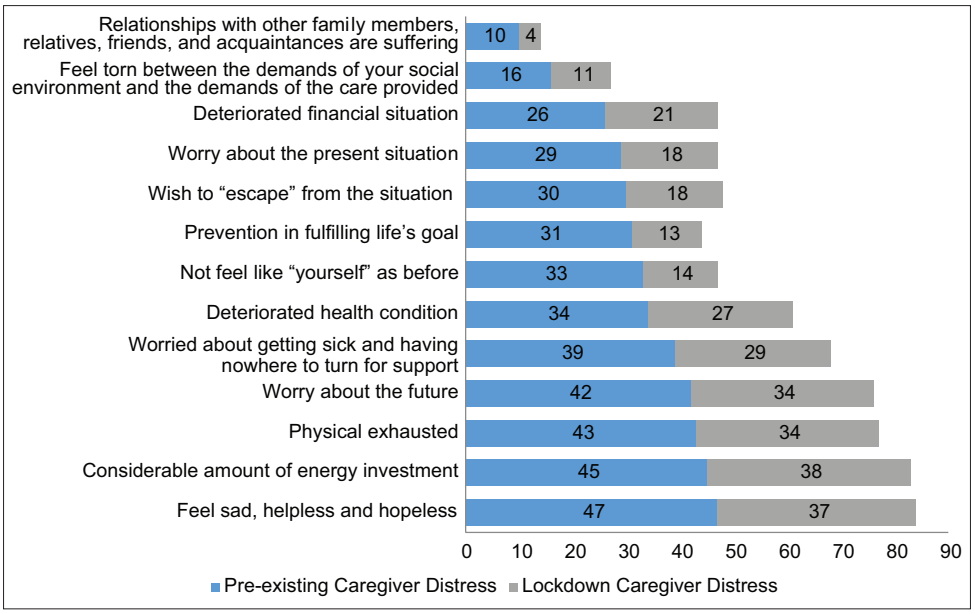

Figure 2: Preexisting and lockdown caregiver distress

The study shows a significant difference between PeCD and PCD during the lockdown due to the COVID-19 pandemic ($P = < 0.001$). A significant positive correlation was seen between PHC and LCD during the pandemic ($r_s = 0.357$, $P = 0.006$). It also shows a significant difference in LCD regarding gender of caregiver ($P = 0.009$) and severity of dementia ($P = 0.032$) [Table 2]. The increase of caregiver distress during the lockdown was higher in female caregivers and severe stages of dementia.

DISCUSSION

Patients with dementia are facing tremendous difficulties on the daily way of living during the lockdown caused by the COVID-19 pandemic. This study shows a significant increase in caregiver distress during the lockdown. Increase in caregiver burden and requirements in the number of caregivers for demented patients during the worldwide pandemic was seen in earlier studies.[4,10]

Deterioration of health condition of demented patients was reported by their caregivers. Increased disruptive behaviors such as agitation, sleep-related problems, depression, restlessness, and aggression along with delusional and hallucinatory behaviors were reported in patients during the lockdown. The contributing factors such as delay in access to health-care facilities, change in daily schedules, hindrance in social interactions along with prolonged period of social isolation may have challenged the health condition of the patients.

A positive correlation was observed between dementia patients' health condition and PCD during the lockdown.

Table 2: Attributes of increased caregiver distress during lockdown

Attributes	Mean±SD	*P*
Caregiver characteristics		
Gender		
Male	3.85±3.32	0.009*
Female	6.13±3.01	
Relation with patient		
Spouse	5.29±3.28	0.834
Children	5.4±3.37	
Education		
Graduate and above	5.38±3.24	0.904
Below graduation	5.26±3.4	
Number of caregivers		
Sole caregiver	5.46±3.44	0.806
Multiple caregivers	5.28±3.27	
Age (years)		
≥60	4.52±3.35	0.206
<60	5.87±3.12	
Occupation		
Working	4.55±3.01	0.130
Nonworking	5.75±3.38	
Severity of dementia		
Severe	7.5±2.54	0.032*
Moderate	5.16±2.85	
Mild	4.6±3.39	

*Significant at $P<0.05$ level. SD: Standard deviation

A higher level of caregiver distress is associated with lower quality of patient's health condition.[11]

In our study, 33 had mild dementia and 12 had moderate and severe dementia each. It is challenging for caregivers to provide proper care to the patients during the lockdown caused by the pandemic.[12] In our study, overall, 66.7% of caregivers have reported difficulties in providing care to patients during the lockdown due to unavailability of professional help, difficulty in availing health-care facilities,

stoppage of medicines, and financial crisis. 45% of them reported difficulties in availing health-care facilities. 35.1% of caregivers also reported difficulty in managing patients' behavior. It is also challenging to make patients understand about the crisis due to the COVID-19 pandemic and persuade them to follow the protocol of social distancing, self-isolation, sanitization, and wearing masks. Higher distress due to the lack of support was reported to be perceived by sole caregivers. Multiple caregivers and family support are particularly important for handling patients. This provides the primary caregivers with more confidence and competence to engage in the caregiving process along with their well-being.[13]

63.16% of caregivers reported increased feelings of sadness, helplessness, and hopelessness. Increased physical exhaustion and deterioration of their physical health due to the care they provide were also reported. Anxiety and worry related to PHC regarding the present situation and the future circumstances were also reported as one of the causes for increased caregiver distress. Feeling of being torn between the demands of their social environments and the demands of the care they provide also reportedly caused distress in them. Disengagement from relatives and friends along with the decline in social activities due to the practice of social distancing and isolation[14] escalated mental distress and loneliness.[15]

Financial hardships were also reported by nearly half of the caregivers as one of the causes of increased caregiver distress during the lockdown in our study.

LCD in female was significantly higher than male. According to Akpinar *et al*., female caregivers have significantly higher caregiver distress than male caregivers of patients with dementia.[16] Women are seen to carry out caregiving activities more regularly as compared to men. They experience a greater amount of physical and psychological strain and distress while providing care. This is because women are more vulnerable to caregiving stressors and possibly identify, report, and deal with it in a different way than men.[17] Variables such as patient-related factors, caregiver health problems, sociodemographic attributes, kinship status, and culture can also be contributing factors having the impact of gender on caregiver distress.[17] There was no significant difference of LCD regarding other caregiver attributes such as age, education, occupation, relationship of caregivers with their patients, and number of caregivers (sole or multiple).

The increased caregiver distress during the lockdown (LCD) was greater in patients with severe dementia in our study. In patients with dementia, severity and inability in functioning are directly associated with increase in caregivers' distress.[18] Alterations in cognition and behavior along with the diminishing capacity to perform activities of daily living are responsible for increased dependency and loss of autonomy in patients with advanced dementia.[19] Restriction in daily activities of patients with severe dementia might also lead to dependency on their caregivers. This increases the caregivers' physical as well as mental exhaustion and contributes to caregiver distress.

The prolonged stretch of the COVID-19-related lockdown, social distancing, and isolation not only created uncertainty but also constant distress among the caregivers.

Limitations

The main shortcoming of the study was that the tools used to assess the caregiver distress and condition of health of the dementia patients are not standardized tools. Since the tools have to be used over phone, it was not feasible to use any Likert scaling-based questionnaire like most of the existing scale. The questionnaire was so made that it can assess the distress and condition of health during the lockdown.

CONCLUSION

Daily functioning and routine of demented patients and their caregivers was disrupted during the lockdown due to the COVID-19 pandemic. The findings showed a significant increase in caregiver distress during the lockdown. Deterioration of PHC in terms of behavioral and psychological symptoms was seen. A positive correlation was observed between deterioration of PHC and LCD. Female caregivers and caregivers with severe dementia patients had higher lockdown caregiver distress. Thus, COVID-19 pandemic-associated lockdown situation was detrimental to both the patients' health condition and caregiver distress.

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Conflicts of interest

There are no conflicts of interest.

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ANNEX-I

Patient Health Condition Questionnaire

Patient's details:

Name _____Age _____Y, Gender: M/F, Education _____ Y, Duration _____Y, Dx _____

1. Has his/her health condition deteriorated during the lockdown due to COVID-19 pandemic? **Y/N**
2. Have you consulted any local physician during this period? **Y/N**
3. Has he/she needed hospitalization during this period? **Y/N**
4. Has his/her memory deteriorated during this period? **Y/N**
5. Is there any change in behavior of the patient during the lockdown? Y/N

Serial number	Question	Increased
1	Agitation	
2	Aggression	
3	Restlessness	
4	Anxiety	
5	Depression	
6	Wandering	
8	Sleep-related problem	
9	Delusional behavior	
10	Hallucinatory behavior	

6. Is there any change in weight in the patient? **Y/N**
   - Weight gain
   - Weight loss

7. Is he/she able to do the following functions himself/herself? **Y/N**
   - Walk **Y/N**
   - Eat **Y/N**
   - Groom **Y/N**
   - Bath/Toilet Y/N

Caregiver Questions

Caregiver's details:

Age _____Y, Gender: M/F, Education _____Y,

Relation with the patient_____

Do you have any knowledge about COVID 19? **Y/N**

Are you the sole caregiver in your family? **Y/N**

Who else resides with you at your home? **Y/N**

Are you working? **Y/N**

If yes, what changes has happened in your job/profession during this lockdown

- Working from home
- Need to go on some days
- Lost the job/wage

- Any other

During this lockdown period are you experiencing any difficulties in patient's care? **Y/N**

If yes, what is the cause for this?

- Behavioral issues difficult to manage
- No one to support in family
- Professional care giver not available
- He/she cannot be taken out for a walk
- Difficult to consult doctor
  - Cannot attend clinic
  - Not available over phone

- Stoppage of medicine
  - If yes, reason:
  - Non-availability at chemist
  - Not able to go out to fetch
  - Cannot procure (financial reason)
  - Others e.g., no valid prescription

ANNEX-II

Caregiver burden questionnaire

Ser	Questions	Prelockdown	Increase during lockdown
1	Do you think caring of your dear one is preventing to fulfill your life's goal?		
2	Do you feel sad, helpless, and hopeless due to the care you provide?		
3	Do you feel physically exhausted due to pressure of the care you provide?		
4	Do you wish to "escape" from the situation you are in?		
5	Do you sometime feel you are not like "yourself" as before?		
6	Is your financial situation deteriorated due to care giving?		
7	Is your health condition deteriorated due to care giving?		
8	Do you think the care you provide takes a lot of your energy?		
9	Do you feel torn between the demands of your social environment (such as family and friends) and the demands of the care you provide?		
10	Are you worried about your future because of the care you provide?		
11	Are you worried about the present situation due to the care you provide?		
12	Do you think your relationships with other family members, relatives, friends, and acquaintances are suffering because of the care you provide?		
13	Are you worried about getting sick and having nowhere to turn for support?		

Original Article

Socioeconomic paradigm and its impact on retinoblastoma – A study in Kolkata, India

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Abstract:

Introduction: The purpose of this study is to understand the impact of socioeconomic factors in West Bengal, as it could be pivotal in restricting the morbidity and mortality of this disease to a large extent.

Materials and Methods: The study has been carried out in a tertiary medical college in Kolkata, West Bengal. Fifty retinoblastoma patients attending the outpatients' department have been selected for the study. Scoring of the families was done using Kuppuswamy's Socioeconomic Status Scale. Data thus collected were analyzed using Microsoft Excel Worksheet for the generation of valid statistical results.

Results: Most of the cases occurred in the 1–2 years age group in the case of males and the 2–4 years age group in females. The average age of presentation of the bilateral cases is around the second birthday for unilateral cases around the third birthday. Eighty percent of the families belonged to the lower, upper-lower, or lower-middle strata of the society according to the Kuppuswamy Classification Scale. All the patients worse than Group D or E (the International Classification of Retinoblastoma 2005 by Murphree AL) at presentation belonged to lower, upper-lower, or lower-middle group. None of the cases with maternal education above or equivalent to the high-school level of education had reported at a stage worse than D, hence prognostically better.

Conclusion: In West Bengal retinoblastoma as elsewhere is most common in the 0–4 age group and most commonly affects the economically poor sections of the society. Retinoblastoma awareness programs if initiated with special emphasis on maternal awareness can be hugely beneficial in limiting the disease burden.

Keywords: Kuppuswamy scale, retinoblastoma, socioeconomic paradigm, West Bengal

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INTRODUCTION

Data pooled worldwide suggests that retinoblastoma happens to be the most common primary intraocular malignancy in children.[1] The age-standardized incidence rate of retinoblastoma is more common in the underprivileged part of the world as compared to the more developed Western countries.[2] The Indian picture is reflected to some extent in the National Cancer Registry Programme, but those data do not portray the panoramic picture. These data are more focal than uniform.[3,4] There is insufficient data about socioeconomic status and its effects in childhood cancer survival, and therefore, there

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is a growing necessity to understand factors influencing outcomes other than those related to treatment alone.[5]

The epidemiological status of this disease is somewhat hazy when we shift our focus to the Eastern part of India. At the same time, one very important aspect of retinoblastoma is often overlooked and that is its socioeconomic paradigm. Like any other cancer, retinoblastoma too puts huge pressure on the public exchequer, as its treatment entails more often than not a combination of surgery, radiotherapy, and chemotherapy. Prompt diagnosis and early treatment should be the mainstay of focus in the management of this menace. The purpose of this study is to throw some light on the socioeconomic perspective of retinoblastoma, as it is quite evident, that, this could be pivotal in restricting the morbidity and mortality of this disease to a large extent.

MATERIALS AND METHODS

An observational cross-sectional type of study was conducted. The study has been carried out at a tertiary medical college of kolkata, West Bengal. A retrospective cohort was constructed for the study using fifty (50) retinoblastoma patients attending the out patients' department (OPD) during 1 year extending between April 2018 and March 2019. This particular Medical College in Kolkata serves as the Government Apex institute of Ophthalmology in the state of West Bengal in the eastern part of India, which is a tertiary care center for adult and pediatric patients. Here, comprehensive actions for ophthalmic cancer control and prevention are developed and implemented as a national level center of excellence.

Study tools

Medical charts for all eligible patients were studied. A form was prepared to guide data extraction, which was performed by one of the authors (The first author). Socioeconomic and household data were extracted from a standard form completed by the second author at the beginning of the study.

West Bengal is having a population of 9.13 crore with a sex ratio of 950 and total child population (0–6 years) of 10,581,466 as per the 2011 census.[6]

Operational definition and diagnostic criteria for retinoblastoma were set as a white pupillary reflex with a notable intraocular mass seen under indirect ophthalmoscopy (performed by author 1) confirmed by ocular ultrasonography and orbital computed tomography (CT) scan. All the cases with features of focus of tumor calcification seen by ultrasonography and/or CT scan were included in the study. All the operated cases were later confirmed with histopathological diagnosis. Detailed family history pertaining to education and occupation of the head of the family and family income were collected from the parents and scoring of the families was done using Kuppuswamy's Socioeconomic Status Scale.[7] All community-based studies focus on socioeconomic stratification as this is one of the keys to understanding the affordability of various amenities including health care. When it is taken as an amalgamation of education, occupation, and income, it reflects the value system expected for that level of education and occupation. Income is parallel to the standard of living. Socioeconomic status is established determinant of health. Kuppuswamy's Socioeconomic Status is an important tool in hospital-and community-based research in India, which was originally proposed in 1976.[7] The Institutional Ethical Committee approval was taken before the initiation of the study. Formal informed consent was taken from the parents of all the patients in their vernacular. Data thus collected were analyzed using Microsoft Excel Worksheet in the Department of Anatomy of Another Tertiary Medical College of Kolkata, West Bengal, for the generation of valid statistical results.

RESULTS

At the said OPD, during the period between April 2018 and March 2019, the number of registered cases of ocular tumors in children was 50 of which all the cases were diagnosed to be retinoblastoma. Out of these 50 cases, 33 cases were males (66%) and remaining 17 cases (34%) were females [Table 1]. From Table 1, it was found, in the study population, most of the cases occurred in the 1–2 years age group in the case of males (48.5%) and the 2–4 years age group in females (47.1%). Overall incidence was mostly noted in the 1–2 years age group (40%). In our study, one case was noted to be of 10 years of age and another one was of 8 years and both were of female sex. The overall incidence rate drastically reduced after age four. The overall incidence rate after 4 years is merely 6%. Males are affected more (66%) than females (34%).

Of all the cases of retinoblastoma in this study, 68% were unilateral and 32% were bilateral. The average age of

Table 1: Number and age-specific incidence of retinoblastoma in the reference population (*n*=50)

Age group (years)	Male, *n* (%)	Female, *n* (%)	Total, *n* (%)
<1	6 (18.2)	3 (17.7)	9 (18)
1-2	16 (48.5)	4 (23.5)	20 (40)
2-4	10 (30.3)	8 (47.1)	18 (36)
>4	1 (3.03)	2 (11.8)	3 (6)

presentation of the bilateral cases is 23.5 months, i.e., around the second birthday. For unilateral cases, the average age of presentation is 36.22 months, i.e., around the third birthday.

In our study, we found that, at presentation 42% of cases presented at Stage E, 28% with Stage D, 8% with Stage C, 10% with Stage B, and the rest of the cases presented with Stage A [Figure 1]. Here, we have followed the International Classification of Retinoblastoma 2005 by Linn Murphree[8] Groups D and E are associated with worse prognosis.

This study tries to focus on the socioeconomic pattern of the patients suffering from Retinoblastoma. The Kuppuswamy scale was followed to categorize the status of the families involved. This categorization is based on three parameters, namely family income, educational qualification of the head of the family, and occupation of the head of the family. Based on this scale [Table 2], the average Kuppuswamy score of all the involved patients was 10.6 with a standard deviation of 6.73. It implies that most of the families belong to the lower or upper-lower strata of the society according to the Kuppuswamy Classification Scale. Twenty-four percent of the patients belong to the lower strata, 26% belong to the upper-lower group, 30% to the lower-middle, 10% to the upper-middle, and the rest 10% to the upper group of the Kuppuswamy scale.

From Figure 2, we can see that, all the patients worse than Group D or E at presentation (70% of the total patients) belonged to the lower, upper-lower, or lower-middle group. None of the patients in our study belonging to the upper-middle or upper group presented with a stage worse than C, with limited retinal seeding (treatable with plaques) which signifies a better prognosis.

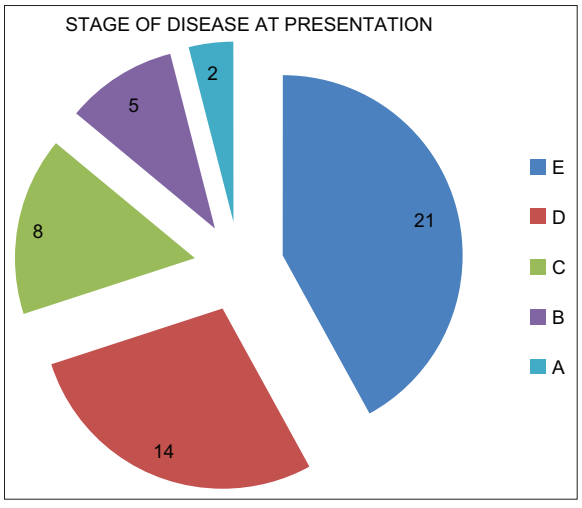

Figure 1: Pie diagram showing stage of retinoblastoma at presentation in the study population ($n = 50$)

Another parameter that we studied in our reference population was the level of maternal education and its relation to stage of disease at presentation. Quite interestingly, it is noted that when the level of maternal education is relatively high, patients usually present at an early stage. In our study group, 30% of the mothers were illiterate, 36% were having primary education, 10% were middle school dropouts, 12% were having high school education, and merely 12% were having graduate or postgraduate qualifications.

We sought to find any association between maternal education and the stage of presentation of retinoblastoma [Figure 3]. Higher the level of maternal education earlier is the stage of presentation. In 40% of the patients presenting at a stage of D or worse, mothers had no introduction to formal schools, 28.6% had primary education and 14.3% of them had completed middle school. About 17.1% of the patients presenting with a diagnosis of worse than Stage D disease had mothers having high school level of education. None of the prognostically poor patients (Stage D or worse) had mothers who had completed their graduation or higher level of study.

DISCUSSION

Retinoblastoma is an embryonal tumor arising from the retinal cells. It is supposedly the most common intraocular malignancy in children. Most of the cases occur before

Table 2: Socioeconomic classification of the patients under the study

Kuppuswamy socioeconomic scale	Number of subjects	Percentage
Lower	12	24
Upper-lower	13	26
Lower-middle	15	30
Upper-middle	5	10
Upper	5	10

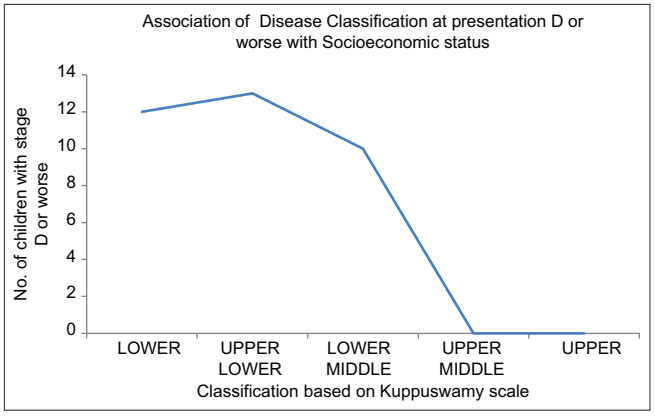

Figure 2: Association between Kuppuswamy scale and presentation with Stage D disease or worse ($n = 50$)

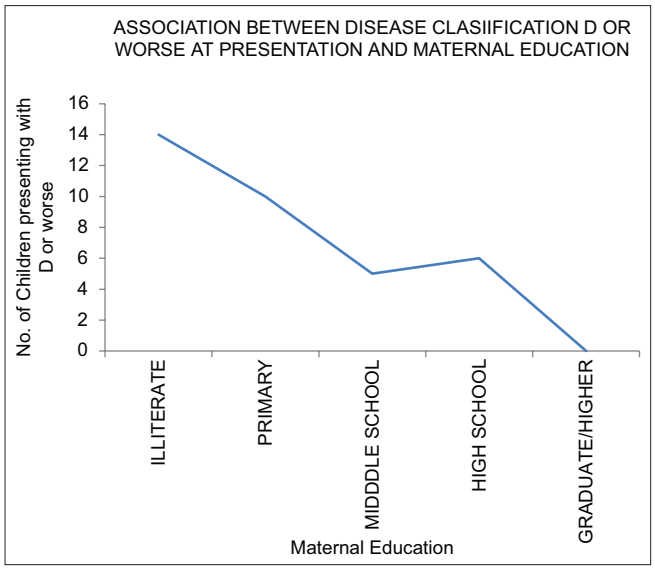

Figure 3: Association between maternal education and presentation with Stage D disease or worse (n = 50)

5 years of age. So far only 24 cases have been reported between 20 and 74 years age group.[9] Knudson first proposed the molecular mechanism responsible for the disease, the presence of 13q abnormalities that led the path to discovery of the retinoblastoma 1 (RB1) gene. Tumors develop when both alleles of the RB1 tumor suppressor gene undergo loss-of-function.[10,11] Several studies have been conducted worldwide regarding the epidemiological pattern of this disease; however, extensive data for an Eastern Indian population is lacking. This study does not primarily aim to find out the age-specific incidence rate of the disease in this region as it entails a much more extensive period of study. We aimed to show the epidemiological trends of Retinoblastoma in West Bengal. Similar to other reference studies,[12] we also found that the incidence markedly gets reduced with increasing age, getting markedly reduced after 4 years, a mere 6% in our case.

There is a great deal of variation in the incidence rate of retinoblastoma between developed and developing nations.[13,14] There is also a notable variation in the age of presentation of the unilateral versus the bilateral cases. In our study, the bilateral cases presented a year earlier, around 2 years of age as compared to the unilateral cases which presented around 3 years. In Great Britain[15] the peak age of presentation of the bilateral cases are before the first birthday and that for the unilateral cases is 2 years. In South Africa[16] the unilateral cases presented at 3.5 years whereas the bilateral cases presented at 3 years of age. This difference in the age of presentation may be explained by the lack of awareness in parents regarding this disease and its impact. Unilateral cases are often missed by parents as the visual disturbance in the affected eye is masked by the seeing eye and unless there is a gross white pupillary reflex in the cancerous eye, uninitiated parents often fail to diagnose minor visual signs, or symptoms of the child. It shows that in this regard, this part of India is also quite lacking in terms of retinoblastoma awareness.

Late presentation although uncommon has been encountered in two of our cases, which presented at 10 and 8 years of age, respectively, and hence the family physician should be having a high index of suspicion while managing a white pupillary reflex in this age group.

With reference to the socioeconomic status of the patients suffering from this rare disease, it has been observed to be more prevalent in the economically poorer parts of the world, being as high as 42.5 per million (incidence rate of retinoblastoma for children aged 0–4 years) in Mali, Africa (Bunin GR, 2007), as compared to 3.5/million in Bulgaria, and Europe, (Parkin DM, 1998). Interestingly, a similar observation has been made in our study. We categorized the families of our subjects according to the Kuppuswamy Scale of Socioeconomic Classification, which takes into account, the total family income, education of the head of the family, and occupation of the head of the family while attributing these groups. We noted that, 80% of our study population belonged to either lower or upper-lower, or the lower-middle strata of the society. This observation is having grave realizations in itself because treatment for retinoblastoma is quite costly. Only respite can be obtained if an early diagnosis can be made. In this regard also, we found that 70% of the patients presented at Stage D or E and all of them belonged to the lower, upper-lower, or lower-middle strata of society. A Stage D or E is prognostically very poor and requires extensive radio and/or chemotherapy for palliation. Although lack of awareness in this section of society can be made a culprit in this regard, but the socioeconomic parameters may be suggestive of some environmental factors which may be acting coherently with genetic factors or independently in the causation of retinoblastoma. However, the role of viruses[17] or parental dietary factors[18] have been studied in the past and results have been inconclusive.

One unique feature of our study is the focus on maternal education. Since mothers are the primary caregivers in our society, they are often the first to report about the ailments of the child. As expected we noted that the higher the level of maternal education earlier is the stage of disease presentation. In most of the epidemiological studies, paternal education is given more importance, but our study refutes this practice and our study strongly

recommends that the level of maternal education is of prime importance while ascertaining the epidemiological paradigm of a disease in society.

CONCLUSION

Retinoblastoma is a rare disease affecting primarily children of the 0–4 age group. Even though it is rare it is a huge burden on public health, especially in economically backward regions. The notable conclusions that can be drawn from this study are that, as observed in several parts of the world, retinoblastoma is seen to be more prevalent in the lower economic groups. Presentation at a much-advanced stage in the same groups makes matters worse and maternal education has a direct bearing with the stage of presentation. Hence, it can be concluded that awareness programs in this regard can be hugely beneficial in limiting the disease burden.

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Conflicts of interest
There are no conflicts of interest.

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Case Report

A case of systemic lupus erythematosus presenting with bilateral malignant proptosis

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Abstract

A young girl, who developed sudden-onset reddening and swelling of both the eyes with rapidly deteriorating vision, got admitted in the critical care unit. She had a history of skin rashes, photosensitivity, and oral ulceration. Immunologically, antinuclear antibody and anti-dsDNA were detected in high titer, and she was diagnosed as suffering from lupus with bilateral proptosis. She was treated aggressively with intravenous pulse methylprednisolone, but unfortunately, she lost her vision in her both eyes.

Keywords: Eye involvement, lupus, proptosis

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INTRODUCTION

Systemic lupus erythematosus is a chronic autoimmune disease with variable clinical presentation. It may affect any organ system and cause damage if not identified early and treated properly. Eye involvement is one of the most serious organ involvements and causes permanent vision loss. Orbital proptosis in lupus is basically a nongranulomatous inflammatory disorder that may severely affect any orbital structure leading to total vision loss. Here we are reporting a lupus patient who presented with acute onset bilateral proptosis in severe form , and treated aggressively but lost vision in both the eyes.

CASE REPORT

A 22-year-old female was admitted with a history of sudden-onset swelling and reddening of both the eyes along with severely diminished vision in both the eyes [Figure 1]. She had a history of photosensitivity, skin rashes, oral ulceration, and eye pain in both her eyes but did not have any features suggestive of cranial nerve involvement. She also had a history of occasional low-grade fever, multiple joint pain, loss of appetite, and moderate weight loss but did not seek any medical attention. Laboratory reports revealed leukopenia (2500/cmm), thrombocytopenia (platelets – 80,000/cmm), high erythrocyte sedimentation rate (60 mm 1st h), normal renal and thyroid functions, negative thyroid-stimulating hormone receptor antibody, and normal urine analysis. Immunological tests done were anti-nuclear antibody(ANA) detected at high titer and was homogenous pattern, anti ds- DNA was also detected at low to moderate titer but anti-SSA or anti-SSB antibodies were not detected and serum complement (C3 and C4) level were also normal. Magnetic resonance imaging (MRI) of the orbit showed marked soft tissue swelling and involvement of ocular muscles along its tendinous insertion causing compression effects over the optic nerve bilaterally. Thus, a clinical diagnosis of lupus with bilateral proptosis in severe form

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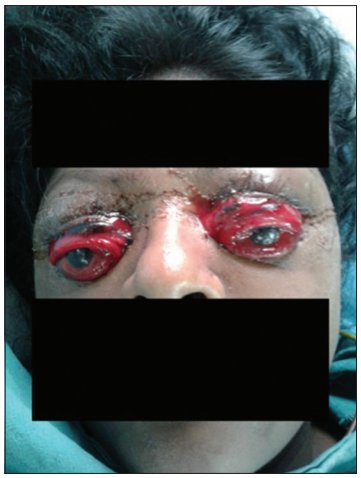

Figure 1: At presentation – bilateral orbital proptosis in severe form

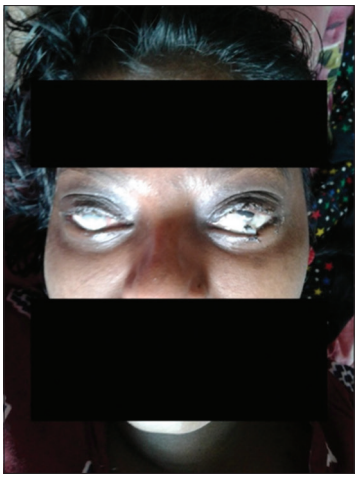

Figure 2: Bilateral loss of vision after recovery

was made. She was treated aggressively with intravenous pulse methylprednisolone (1 g daily for 3 days) along with hydroxychloroquine (400 mg/day), but unfortunately, she did not respond and lost her vision in both the eyes permanently [Figure 2].

DISCUSSION

Lupus patients can have eye involvement in various forms, and keratoconjunctivitis sicca is the most common one. Involvement of retinal vessels is seen in <10% of cases and is one of the very important disease manifestations as it reflects systemic disease activity.[1] In this case, orbital pseudotumor was a part of spectrum of idiopathic orbital inflammation and due to nongranulomatous inflammatory disorders that may involve any structure in the orbit.[2] Patients might present acutely with marked orbital swelling and loss of vision due to severe inflammation and compression effects if not treated timely and aggressively. This condition must be differentiated from orbital cellulitis, which is usually unilateral and associated with fever.[3] Diagnosis is usually made by clinical and radiological imaging (computed tomography/MRI), which also avoids the need for direct tissue diagnosis.

This type of presentation in lupus is very unusual, and diagnosis in such cases is often delayed because of less systemic manifestation, moreover, this may lead to permanent vision loss if not identified early and also treated aggressively.[3] Hence, lupus should be considered in the differential diagnosis in cases of orbital pseudotumor-like presentation with excluding other eye swelling, and clinical clues in favor of lupus must be searched thoroughly so that early aggressive therapy could be started to prevent vision loss.[4]

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

Rickets due to renal tubular acidosis: A case report and our perspective

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Abstract

Renal tubular acidosis (RTA) is a diverse group of tubular disorders characterized by failure of urinary acidification in the presence of metabolic acidosis with variable electrolyte abnormalities. RTA can present with a variety of manifestations to the nephrologist, orthopedist, pediatrician, and endocrinologist. Short stature, rickets, renal stones, and failure to thrive are the presentations that the endocrinologist can encounter. Here, we present one such case of rickets caused by distal RTA with secondary proximal tubular dysfunction.

Keywords: Renal tubular acidosis, rickets, short stature

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INTRODUCTION

Rickets is a metabolic bone disorder caused by defective mineralization and widening of growth plates at the ends of long bones.[1] Rickets can be classified as calcipenic – caused by Vitamin D deficiency, defective metabolism and resistance, or calcium deficiency; phoshopenic – caused by acquired or congenital causes of urinary phosphate loss, dietary deficiency, or malabsorption; direct inhibition of mineralization – hypophosphatasia, fluorosis, excess aluminum, chronic kidney disease (CKD), and renal tubular acidosis (RTA).[2-4]

Knowledge about more common forms of rickets, especially nutritional is widespread and physicians and pediatricians are well equipped to deal with these entities. Rickets associated with CKD is difficult to miss due to the associated history and uremia. Rickets due to renal tubular defects such as RTA and phosphate wasting disorders are an area with inadequate physician expertise and can be easily missed.

The following case presentation describes our approach to diagnosing this not so common entity which can be easily missed for other forms of rickets. A step-wise approach if adopted will ensure correct diagnosis and timely treatment.

CASE REPORT

This 15-year-old boy presented with progressive knee bending since the age of 8 years [Figure 1]. The boy was born out of a second degree consanguineous marriage and had normal birth, perinatal and developmental history till the age of 8 years when he started developing pain, swelling, and progressive bending of both his knee joints. Painful swelling of both wrists was also noted at

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Figure 1: Patient at presentation showing genu valgum deformity with widening of wrists

the same time, and he also started faltering on his statural growth. There was no history of seizures, tetany, fractures, hematuria, renal stones, excessive thirst, delayed dentition, dental abscess, or chronic diarrhea. He was exclusively breastfed till more than 1 year of age and his diet consisted primarily of carbohydrates and inadequate portions of milk and milk products. He had been treated in the past with multiple doses of Vitamin D and calcium which failed to improve his symptoms.

On examination, he was short and malnourished with a height of 118 cm (−6 SDS for age and sex) and weighed 11 kg (−3 SDS for age and sex). His upper segment:lower segment ratio was 1.2 and his bone age was 11 years. He had genu valgum with an intermalleolar distance of 17 cm. There was widening of the wrist joints. There were no features of hypocalcemia or other bony or skeletal deformities.

Given the long-standing nature of the disease, a history of consanguinity, severe short stature, and failure to respond to multiple doses of Vitamin D, our differentials were Vitamin D resistant rickets, phosphopenic rickets, or renal rickets.

The initial set of investigations obtained showed a normal hemogram with raised alkaline phosphatase (962 IU/l), normal renal function, and euthyroidism. X-ray of the wrist and knee joints showed characteristic cupping, fraying, and splaying seen in rickets along with thinning of the cortex [Figure 2]. The serum electrolyte report showed normal sodium, low potassium (2.3 meq/l), normal corrected calcium (8.6 mg/dl), and phosphopenia (2.2 mg/dl). Blood gas analysis revealed normal anion gap hyperchloremic metabolic acidosis and urine pH performed simultaneously

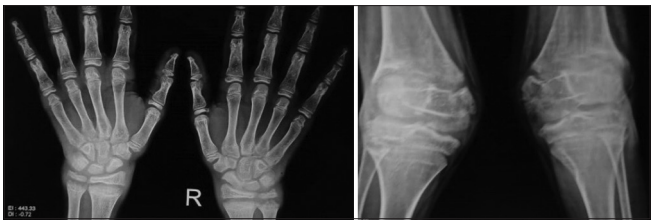

Figure 2: X-ray at presentation showing rachitic changes

was 6.9. The serum 25 (OH) Vitamin D3 was 20 ng/ml and the iPTH was 4.6 pg/ml.

Our case of suspected rickets due to RTA was thereby subjected to further investigations to prove the diagnosis. Since the patient had overt metabolic acidosis with a failure of acidification of the urine, tests to induce acidosis such as the ammonium chloride loading test were unnecessary. The analysis of urinary electrolytes in a 1.2 Lcollection over 24 h showed: potassium-32.2 mmol, Na – 98 mmol, calcium –109 mg, creatinine – 260 mg, Cl-86.5 mg, citrate – 22.4 mg, and uric acid – 1160 mg. The spot urine b2 microglobulin was >20,000 ng/ml (N:0-300) and glucose was absent in urine. The ultrasonography kidney showed bilateral medullary nephrocalcinosis [Figure 3].

A diagnosis of distal renal tubular acidosis (dRTA) with secondary proximal tubular dysfunction (PTD) was established. ANA and Anti-TPO antibody were negative and hearing assessment was normal.

He was started on alkali therapy with 3 mEq HCO_3/Kg/day and followed up for improvement. At 6 months of follow-up, bone pain and muscle weakness have subsided. Blood pH, serum HCO3, and K levels have increased. Serum phosphate normalized and beta-2 microglobulin, marker of proximal tubular dysfunction also decreased significantly.

X-ray features of rickets have resolved [Figure 4] and the height velocity has improved.

DISCUSSION

RTA is a heterogeneous group of disorders characterized by hyperchloremic metabolic acidosis due to failure of urinary acidification. This failure of acidification can be due to impaired bicarbonate absorption at the proximal tubules or impaired H^+ secretion by the intercalated cells of the distal tubule.[5]

Common presentations of RTA in children are growth failure, failure to thrive, and refractory rickets. All of these are evident in the index case. Rickets in RTA is mainly

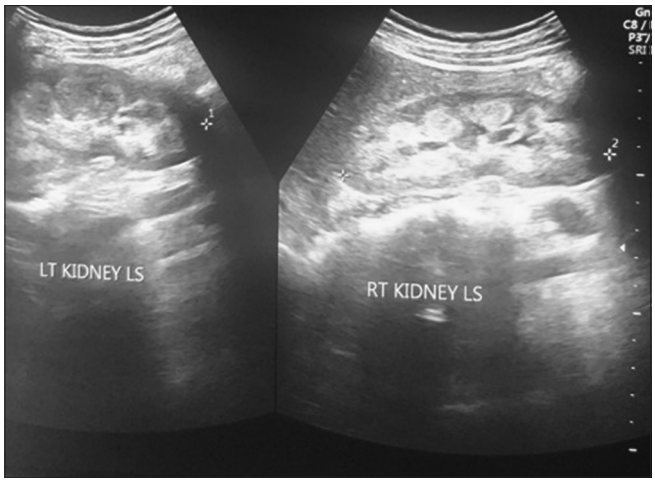

Figure 3: USG KUB showing bilateral medullary nephrocalcinosis. USG: Ultrasonography, KUB: Kidney, ureter, and bladder

caused by bone acting as a buffer for acidosis, leading to leaching of the mineral matrix from the bone and growth plate. Renal loss of phosphate and impaired synthesis of 1,25 dihydroxy D3 are also contributors.

Although secondary causes are to be sought in dRTA in adults, dRTA in children is generally primary.[6] Sjogren's syndrome is a commonly encountered etiology of secondary dRTA in adults, and the prevalence varies between 23% and 35%.[7]

The risk of nephrocalcinosis or nephrolithiasis is much more common in dRTA compared to other forms of RTA and is almost diagnostic of dRTA in the appropriate clinical setting.

PTD secondary to dRTA has been previously documented in case studies. Studies from India have reported almost 100% PTD in a setting of dRTA, especially in children.[8] Glucosuria is usually absent as part of PTD, which is an important clue to differentiate dRTA with consequent PTD from the classical Type 3 RTA. Although the precise mechanisms underlying PTD in patients with dRTA remain incompletely understood, there are two potential explanations, namely endosomal dysfunction in the proximal renal tubular cells secondary to intracellular acidosis and hypokalemic nephropathy. This abnormality is reversible, once systemic acidosis is abated with alkali therapy, as seen in the follow-up data for our case.[9]

The aim of distal RTA treatment in children is not only to correct biochemical abnormalities but also to improve growth and prevent kidney stones and skeletal abnormalities. The basis of treatment is alkali replacement. Potassium citrate or sodium citrate is preferable to

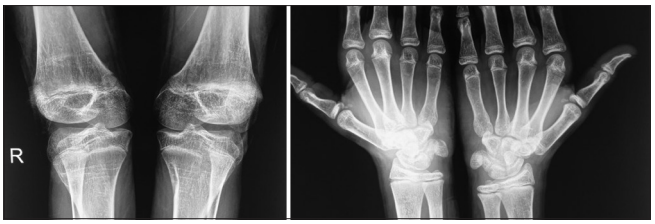

Figure 4: Post-treatment X-ray showing resolution of rachitic changes

bicarbonate because citrate salt can correct hypocitraturia and prevent nephrolithiasis. Potassium supplementation and K^+-sparing diuretics, such as spironolactone or amiloride, may be necessary to manage hypokalemia. Once acidosis has been corrected, potassium supplements are seldom required.

CONCLUSION

Refractory rickets can be an enigma for the physician. Widely believed to be uncommon, RTA is a potential cause of rickets not responding to Vitamin D and calcium therapy. RTA can present not only with rickets but also with short stature, failure to thrive, growth retardation, and nephrocalcinosis. A properly curated step-wise algorithm can lead to an accurate diagnosis of RTA with these presentations. Treatment is rewarding, as inexpensive alkali therapy can cause dramatic improvement in all these manifestations and prevent or delay permanent renal damage.

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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Case Report

Systemic lupus erythematosus presenting as Guillain–Barre syndrome

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Abstract

A 37-year-old male patient presented with acute symmetrical ascending areflexic flaccid quadriparesis progressive in nature for the past 6 days before admission preceded by tingling sensation in both hands and feet with the right-sided lower motor type of facial nerve palsy for 2 days. Clinically, this was consistent with Guillain–Barre (GB) syndrome and was given intravenous immunoglobulin (IVIG). Cerebrospinal fluid study and nerve conduction study also supported the clinical diagnosis of GB syndrome. He developed Type 2 respiratory failure on the 4th day of admission for which he was intubated. After successful extubation, his weakness even worsened markedly despite IVIG therapy and was subjected to plasmapheresis following which the weakness improved remarkably. On further investigation for the associated fever, arthralgia, pallor, nephritis, antinuclear antibody (3+ coarse speckled pattern), anti-smith antibody, and anti-dsDNA antibody positivity were detected with low serum complement levels, and renal biopsy revealing class III lupus nephritis. He was put on oral corticosteroids and cyclophosphamide which resulted in further clinical improvement. The initial presentation of GB syndrome of systemic lupus erythematosus is uncommon and makes this case interesting.

Keywords: Guillain–Barre syndrome, lupus, neuropsychiatric systemic lupus erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with diverse multisystem involvement and the production of an array of autoantibodies. Neuropsychiatric lupus (NPSLE) encompasses a wide range of neurologic and psychiatric manifestations involving any aspect of the central nervous system or peripheral nervous system (PNS). Association of peripheral neuropathy in SLE is not so uncommon. The most common type of neuropathy encountered in SLE is sensory or sensorimotor axonal polyneuropathy, whereas mononeuritis multiplex and cranial neuropathies, as well as autonomic neuropathies, have also been documented.[1] However, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) or another variant of Guillain–Barré syndrome (GBS) is rarely reported in lupus, perhaps in 0.1% of cases.[2] Here, we report a case of lupus nephritis initially presenting as GBS (AIDP variant with secondary axonal changes), a rare neurological manifestation of lupus that initially did not respond to intravenous immunoglobulin (IVIG) therapy but responded well to plasmapheresis.

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CASE REPORT

A 37-year-old male presented with a 6-day history of progressive bilateral symmetrical ascending weakness,

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involving proximal muscles more pronounced than the distal muscles following tingling sensation in hands and feet. There were also features of right-sided facial weakness for the past 4 days. There was no associated bowel/bladder incontinence, low back pain, girdle-like sensation, preceding history of trauma, vaccination, diarrhea, or lower respiratory tract infection. On examination, no cranial neuropathy except right-sided lower motor neuron type of seventh cranial nerve palsy, hypotonia in all four limbs, and diminished power more pronounced in proximal muscle than in the distal group of muscles. There was associated weakness in the neck flexor and truncal muscles. All deep tendon reflexes were absent with bilateral flexor plantar responses. Sensory examination revealed impaired vibration and joint position senses, and his single breath count was 22. The patient was clinically diagnosed with GBS and was given IVIG (2 gm/Kg) over 5 days. Cerebrospinal fluid revealed albuminocytological dissociation (protein-106 mg/dl, cell count-10/c. mm, and all lymphocytes). The nerve conduction study was suggestive of acute demyelinating sensorimotor polyradiculoneuropathy with secondary axonal changes with prolonged latencies, decreased amplitude of compound muscle action potential, slowed nerve conduction velocities, and absence of F-waves. Despite IVIG therapy, the patient deteriorated further and developed Type 2 respiratory failure which necessitated intubation. He also developed bulbar palsy and retention of urine. On extubation after 3 weeks, his clinical condition deteriorated due to progressive muscle weakness which demanded urgent initiation of plasmapheresis following which his weakness improved remarkably, and autonomic dysfunction was almost resolved.

On further questioning, he complained of low-grade intermittent fever and arthralgia in small and large joints for some duration. In this background, a persistently high serum globulin level, with subnephrotic range of proteinuria (884 mg/24 h) and the presence of RBC (4–6/HPF) in urine led us to think of underlying autoimmune etiology. His serological markers revealed: a positive antinuclear antibody (3+) with coarse speckled pattern, positive anti-smith antibody and positive anti-dsDNA, low serum complement levels with negative Antineutrophil Cytoplasmic Antibody (ANCA), and anti-SSA and anti-SSB antibodies making the diagnosis of primary disease lupus. The renal biopsy specimen showed focal mesangiocapillary and sclerosing glomerulonephritis without tubulointerstitial chronicity which was consistent with the diagnosis pf lupus nephritis classIII. (A/C), modified NIH score: Activity index: 1/24, chronicity index 1/12. Thereafter, he was put on oral corticosteroids (1 mg/kg body weight) and pulse cyclophosphamide therapy. Two months following this, he made an almost complete clinical recovery with traces of albuminuria.

DISCUSSION

SLE is an immune-mediated disease that can affect any organ in the body. Although peripheral neuropathy is a well-recognized manifestation of NPSLE, GB syndrome as an initial presentation of lupus is quite rare. There are only 17 previous case reports of GBS as the initial presentation of SLE, almost all of these cases were young women.[3,4] In our case, SLE in a middle-aged male initially presenting as GBS made this case even rarer as there were no preceding SLE manifestations except fever and arthralgia, and he was diagnosed with concurrent lupus nephritis. The pathogenesis of GBS in SLE is still not well explained. There are several consensuses that cell-mediated and humoral immune processes or immunological cross-reactivity between autoantibodies in SLE and autoantibodies against neural tissue antigen or the presence of autoreactive antibodies cause damage to the PNS.[5,6] Four treatment options have been used in the previously reported cases of GBS in lupus-corticosteroids, cyclophosphamide, IVIG, and plasmapheresis.[2] Our patient did not improve with the initial IVIG therapy, who further responded remarkably well to plasmapheresis and responded well to oral corticosteroid and cyclophosphamide after the diagnosis of lupus nephritis. Both disease activity and organ involvement should be addressed for achieving remission and most cases completely recover after remission.[2] Here, our case also had almost complete clinical recovery after plasmapheresis and 2 months of corticosteroid and two cycles of cyclophosphamide therapy.

CONCLUSION

Although GBS is a rarely documented initial presentation in patients of lupus, the possibility of lupus should still be considered even if there was no antecedent clinical clue, especially when GBS was not responding to or even worsening despite initial IVIG therapy and when there are associated features of nephritis.

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

Endourological Management of a Case of Rectourethral Fistula in Post Bullhorn Injury

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Abstract

Bull horn injuries are common in rural India. We hereby report one such case causing urethrorectal fistula and managed endourologically. The patient presented with a history of bull horn injury in the perineum with the inability to pass urine. On examination, under anesthesia, induration in the anus and anterior wall of the rectum was found with passage of urine per rectum. Initially, sigmoid colostomy and suprapubic cystostomy were done. Later, cystoscopy-guided endodilatation, followed by per urethral catheterization was done. The patient was catheterized for 3 weeks and the fistula healed completely.

Keywords: Bull horn, endourological management, rectourethral fistula

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INTRODUCTION

Bull horn injuries are common accidents in rural India. These domestic animals can cause serious injuries by their various appendages, especially horns. There are only a few reports of bull horn injuries in literature. Unfortunately, these injuries are infrequently reported and evidence-based practice is lacking in this area.[1] We hereby report a rare case of bull horn injury-causing rectourethral fistula and its management

CASE REPORT

We present a case of a 56-year-old male patient who was presented to our emergency after being tacked by a domesticated bull in his ranch property while he was engaged in farming. The patient started passing a huge amount of urine while defecation and only a little amount of urine per urethra. He attended the primary health-care service, from where he was referred to our hospital. On examination, blood at the urethral meatus was seen. Perianal area and external genitalia were perfectly normal with no sign of any injury. On digital rectal examination, an induration was felt in the anterior wall of the rectum about 4 cm above the anal verge and the induration was felt on the posterior wall of the prostate. Proctoscopy findings also revealed the same. A small size per urethral catheter was tried to pass into the bladder with a gentle attempt but failed. After proper resuscitation, the patient was planned for diversion surgery. Before any operative intervention, we had taken proper written consent from the patient and the patient's party. The patient and the patient party had been explained in their own language about the procedure of the treatment. After 4 days of injury, SPC and diversion loop sigmoid colostomy were done. The patient revealed that the amount of urine passing through the anus had drastically diminished. Cystoscopy was done at 1 week following surgery which revealed normal anterior urethra with the

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inability to pass the scope beyond membranous urethra due to narrowing. The patient had undergone computed tomography (CT) urography with CT cystogram 15 days following surgery which revealed a urethrorectal fistula with extravasation of the dye from the posterior urethra to the rectum [Figure 1]. Conservative management was continued for 3 months. Retrograde urethrography and micturating cystourethrography were done which showed trabeculated bladder outline with SPC *in situ* [Figure 2a and b]. There was no evidence of rectovesical/rectourethral fistula and there was a narrowing in the prostatic urethra with an adjoining small diverticulum formation. Distal cologram was done which revealed no leak and no fistulous opening [Figure 2c]. After 3 months following conservative management, cystoscopy was done again, guidewire could be passed through the narrowing in the membranous urethra into the urinary bladder. Endodilatation with filiform dilators up to 28 fr was done over guidewire, followed by per urethral catheterization. Cystoscopy done again after 3 weeks revealed normal urethra. Perurethral catheter was removed and uroflometry was done [Figure 2d] which showed a normal pattern afterward suprapubic catheter was removed. Loop colostomy closure was done after 4 weeks of plasmacytoid urothelial carcinoma (PUC) removal. The patient was kept on NPM for 3 days and when the bowel sound appeared, liquid diet was started. Slowly, the patient was put on a solid diet. The patient could hold stool and his anal tone was normal on DRE. There was no postoperative fecal incontinence. Patient was doing well at 1 month of follow-up.

DISCUSSION

The ox, cow, and buffalo are docile as compared to the bull, which can easily become raged. The pattern of injury at different places seems to vary. In India, perineal followed by abdominal injuries predominate in contradistinction to those in the Latin countries, where lower extremity injuries are more common.[1]

Our patient did not have any major vascular injury. A perineal bleeding in trauma is notoriously difficult at times, to control by packing alone. Bladder neck ruptures and prostatic urethra injuries with pelvic fractures are also reported.[2]

A through and through bladder perforation, sparing the sphincters and urethra, with a pneumoperitoneum, is very unusual. The presentations of urinary peritonitis are diverse. Dramatic presentations like shock may be absent unless they are complicated by urinary sepsis, pelvic fractures, or visceral bleeding.[3]

Our patient was directly taken to the operating room for exploration, as there was an obvious bladder injury, and an anticipated bowel injury and contamination. A retrograde urethrocystography which is considered the gold standard for the identification of bladder and urethral ruptures, should be done.[4] The grave nature of the injury prompted us to have an SPC *in situ* for prolonged drainage of urine. A diversion colostomy helps in better wound management in patients with perineal wounds, after trauma or burns. We have done diversion sigmoid loop colostomy. This helped the perineal wound to heal faster without any secondary fecal sepsis.[5]

Initial management of incomplete urethral injuries remains controversial, but options include suprapubic urinary diversion with delayed urethral management, primary

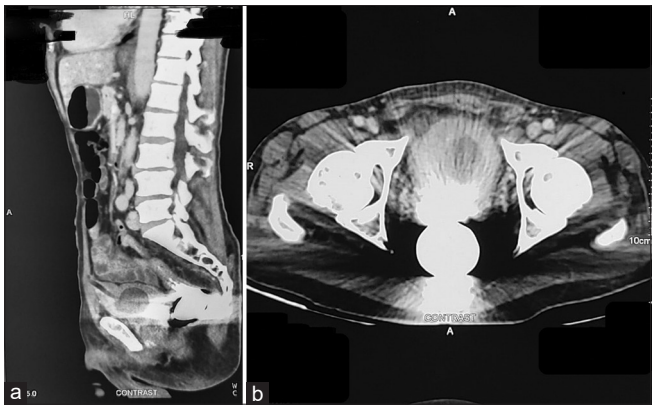

Figure 1: (a) Transverse section. (b) Sagittal section showed rectourethral fistula

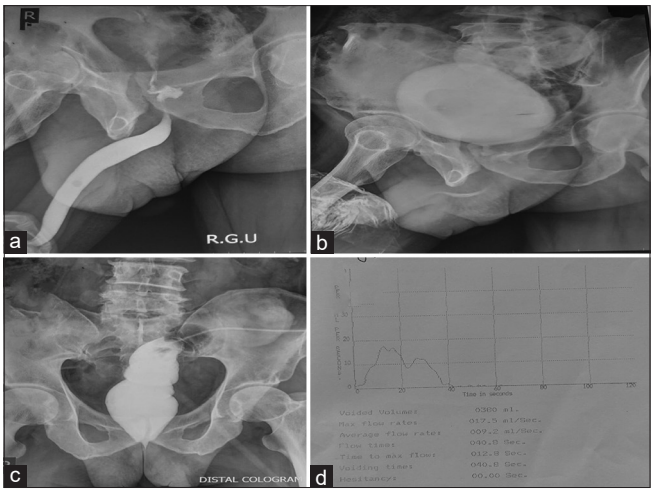

Figure 2: (a and b) RGU and MCU after 3 months of follow-up showing no contrast extravasation into the rectum, (c) Distal cologram after 3 months of follow-up showing no contrast extravasation into the prostatic urethra, (d) Uroflometry after PUC removal showing normal pattern. RGU: Retrograde urethrogram, PUC: Perurethral catheter

open repair, and primary endoscopic realignment over a catheter.[6]

There are four standard approaches for open rectourethral fistula repair.[7]

There are few cases of isolated urethral traumas and only one identified as a result of an animal attack. In this case, there was a urethrorectal fistula after a bull horn injury, in which the urethral injury was initially managed with suprapubic urinary diversion and subsequent endoscopic management.[8]

Sometimes, endourological management is feasible like in, our case where we did an SPC and a loop sigmoidostomy to keep the injured area dry and was given adequate time to heal. Delayed endourological management has helped us to manage the patient in a minimally invasive way.

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.

CONCLUSION

Bull horn injuries to the rectum which perforate the posterior urethra, sparing the anal sphincter are unusual and rare. Prompt exploration and diversion, keeping in mind the mechanics and the nature of bull horns, helps the surgeon to adequately deal with such atypical injuries, for optimal outcomes. Endourological management is feasible in some selected cases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Salt and pepper pot skull

A 20-year-old female presented with a 3-year history of progressive hip and leg pain at rest and on walking. X-ray showed multiple lytic lesions in the long bones of the lower and upper limb. Investigations revealed a high serum calcium 12 mg/dl (N - 8.6–10.3), alkaline phosphatase 4396 IU/L (N - 44–147), and intact parathyroid hormone (iPTH) 974 pg/ml (N - 10–55) with low serum inorganic phosphate of 2.5 mg/dl (N - 3.0–4.5).

X-ray skull showed the characteristic salt and pepper pot skull [Figure 1a]. It is characterized by numerous tiny lucencies in the calvarium along with a loss of definition between the inner and outer tables of the skull giving the skull a granular appearance.[1,2] Dual-energy X-ray absorptiometry scan for bone mineral density revealed a low Z-score of − 5.7 at distal radius, −3.8 at femoral neck, and − 4.3 at lumbar spine. A diagnosis of primary hyperparathyroidism was made. Ultrasound of the neck was suggestive of a right parathyroid adenoma. 99m Tc sestamibi single-photon emission computed tomography SPECT-CT confirmed the location of the adenoma posterior to the right lobe of the thyroid.

She underwent excision of the parathyroid adenoma with intra-operative iPTH estimation which showed more than 50% reduction at 10 min. Postoperatively, she suffered from a hungry bone syndrome which was appropriately managed. The histopathology of the excised adenoma showing abundant chief cells [Figure 1b, arrow] was reported as parathyroid adenoma.[3] On follow-up, her serum calcium normalized and her bone pains have subsided. A thorough skeletal survey and imaging can be useful in diagnosing metabolic bone disorders. The expanded differential diagnosis of skull demineralization includes osteoporosis associated with aging and also sickle cell anemia, thalassemia, metastatic bone disease, multiple myeloma, and the lytic phase of Paget disease, but the salt and pepper appearance due to resorption of trabecular bone of the calvaria is classically described for hyperparathyroidism.[4]

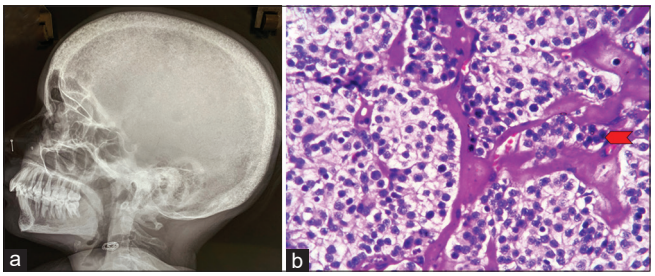

Figure 1: (a) Salt and pepper pot skull (b) Photomicrograph of parathyroid adenoma showing chief cell hyperplasia (arrow) H and E stain 400X

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.

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There are no conflicts of interest.

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Review Article

The noble mission of Nobel Laureate Sir Ronald Ross

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INTRODUCTION

July 25 is a Historic Day. On that day in the year 1603, James VI of Scotland was crowned by James of England Uniting Kingdom of England and Scotland. Malaria and Yellow fever, The deadly Mosquito borne diseases, compelled England and Scotland to form the Kingdom of Great Britain through Union Act 1707, to conquer these diseases to set up and spread their Colonies' business.

MALARIA HUNTERS

Two legendary Scots, Sir Ronald Ross [Figure 1] (13.05.1857-16.09.1932), inspired and guided by his mentor Sir Patrick Manson (03.10.1894-09.04.1922), made the breakthrough to combat Malaria and Mosquito-borne diseases and thus saving the humanity from this veritable scourge. A French Army Physician and Scientist (Father of Protozoa) Charles Louis Alphonse Laveran (18.06.1845-18.05.1924) discovered "oscillaria Malariae" (Plasmodium) on November 6, 1880 responsible for Malaria at Constantine, Algeria proving the "Germ Theory" of disease propounded by Louis Pasteur (27.12.1822-28.09.1885), in 1870. Thus, it was proved that Malaria (mal aria-bad air in Italian) or Paludism ("means Marshy" in French) is due to parasite, not due to bad air or marshy, i.e., Miasmatic origin. Sir Patrick Manson (Father of Tropical medicine) was the author of "Mosquito Malaria theory."

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EPIC STUDY

Sir Ronald Ross made the landmark discovery that female Anopheles mosquito is the Vector of Malarial Parasite in Secundrabad (August 20, 1897, calling MOSQUITO DAY) and the lifecycle of Malarial Parasite (Bird to mosquito to the bird cycle of malaria) at the Presidency General Hospital, Calcutta (established on April 22, 1770) now, known as SSKM Hospital, Kolkata, at the present Sir Ronald Ross Laboratory on July 4, 1898 (MALARIA DAY). Calcutta (Once Mecca of Medicine in India) is the BIRTH PLACE OF MALARIA LOGY (Covell, 1932). Sir Ronald Ross is revered as FATHER OF MALARIALOGY for his "Great and Epoch making Discovery."

Sir Ronald Ross was awarded the Nobel Prize in physiology and Medicine on December 10, 1902 and he was recognized as "One of Greatest benefactors of mankind."

In Nobel Citation, it was mentioned "for his work on Malaria by which he has shown how it enters the organism and thereby he laid the foundation for successful research on this disease and methods of combating it."

BIOGRAPHY

Sir Ronald Ross was born at Almora, India. He was the eldest son of the ten children of Sir Campbell Claye Grant

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Figure 1: Sir Ronald Ross (1857–1932)

Ross, a General in British Indian Army (Bengal Staff Corps) and Matilda Charlotte Elderton.

At the age of 8 years, he was sent to England to study. He completed primary school and secondary education. During school life, he developed intense interest in poetry, literature, music, painting and mathematics and devoted to pursue his passion. He was not very much attentive to his academic study or playing. His father was very tough to his son to be a medical doctor. Hence, he was enrolled at St. Bartholomew's Hospital Medical Collage in London on October 29, 1874 and passed in 1881. As a Medical Student, he did not show any brightness and also failed in examinations because he devoted to his Passions-not to be a Medical Doctor.

INDIA - HIS DREAM

Ronald Ross joined Indian Medical Service (IMS) on April 2, 1881, and worked from 25 years at different places such as Madras, Burma, Baluchistan, Andaman Islands, Bangalore, Secunderabad, Calcutta, and Assam. Wherever he went, two things – one iron frame upright Piano and one microscope – always were essential items of his luggage.

STUDY ON MALARIA

Ronald Ross used to suffer as a child seeing the malaria attack of his grandfather Lt. Col. Hugh Ross. Ross was determined to find a cure of the disease. During course of his Medical School, he saw a female patient presenting with muscle ache and high fever with chill and headache. That lady came from Essex marshes. Ronald Ross thoroughly examined her and provisionally diagnosed as a case of Malaria. However, malaria was very common in south America and India. The patient became frightened to see the exhaustive examination of Ronald Ross. She was lost to follow-up. Hence, Ross could not prove the diagnosis.

Ronald Ross's interest in Malaria began in 1892. He got a Laveran's masterpiece on Malaria (translated from French to English). It was a great inspiration to him. From 1892 to 1894, he could not find Laveran's "Oscillaria malariae" (Malarial Parasite). He met Sir Patrick Manson on April 10, 1894, at Cavendish Square, London, who taught him how to see the malarial parasite under microscope. During his leave from June 1888 to May 1889, he obtained D.P.H. (Diploma in Public Health) in London. He was first recipient of D.P.H. in the world. He was trained by Prof. Emanuel Edward Klein (Father of British Microbiology) on Bacteriology for 2 months. He married to Rosa Bessi Bloxam on 1889.

From 1894 to 1898, Ronald Ross was under the constant guidance of his mentor Sir Patrick Manson. 173 letters were exchanged between them from 1895 to 1899.

Ross observed early stages of Malarial Parasite in the stomach of a mosquito in May 1895. His total devotion was focused on mosquito and Malarial Parasite.

It was interrupted when he was deputed to Bangalore as a Sanitary Officer to investigate the outbreak of Cholera. At Bangalore, there was no mosquito. Hence, Ronald Ross was very unhappy, but he worked hard to check cholera through proper massive sanitization (Drainages, Cleanliness, etc). Ross was an adroit environmentalist. Between 1895 and 1897, he made Bangalore in a clean and healthy city by dint of his meticulous planning and leadership.

At Sigur Ghat, near Ooty, he saw "dappled winged" brown mosquitoes with peculiar posture. These dappled winged mosquitoes were species of the genus Anopheles. On August 20, 1897, he discovered that female anopheles mosquitoes were the vectors of Malarial Parasite at Secunderabad. He declared August 20, as Mosquito Day. He wrote a poem and sent to his wife Rosa Bessi Bloxam and Sir Patrick Manson On August 22:

"This day relenting God

Hath Placed Within My Hand A Wondrous thing, and God

Be praised. At His command Seeking his secret deeds

With tears and toiling breath, I find Thy cunning seeds

0 Million – murdering Death I know this little thing

A myriad men will save

0 Death, where is Thy sting?

Thy Victory, 0 Grave?

This discovery was published in the Indian Medical Gazette on August 27, 1897, and subsequently on the December 18, 1897, Issue of British Medical Journal titled – "on some peculiar pigmented cells found in two Mosquitoes fed on Malarial blood."

AGAIN INTERRUPTION IN RESEARCH WORK

In September 1897, Ross was transferred to Malaria-free Kherwara in Rajputana (Rajasthan). He became angry and deeply frustrated. He threatened to resign from service, but due to Patrick Manson's (Medical Advisor to Colonial Office) intervention, the Government arranged for his continued service and transferred to Calcutta "On a special duty" for 6 months under the Director General of IMS to investigate Malaria and Kala-azar (Visceral leishmaniasis). He joined the Presidency General Hospital (now SSKM Hospital) Calcutta on February 17, 1898. He was transferred to Calcutta on January 29, 1898.

DISCOVERY OF LIFE CYCLE OF MALARIAL PARASITE

At Presidency General Hospital, Calcutta Ross did his research on bird (purchased at his own cost) by grey Mosquitoes (Infected Culex Pipiens). His very obedient servant Mohammad Bux helped him a lot. His Laboratory Assistant was Dr. Kishori Mohan Bandhopadhyay. Due to plague in Calcutta at that time, human volunteers were not available; female Anopheles stephensi Mosquitoes do not cause Malaria in birds. Ross knew Danielewski's studies on bird Malaria. Ross used birds as experimental model.

ON July 4, 1898, he made the landmark discovery at D.D. Cunnigham's Laboratory (at present Sir Ronald Ross Laboratory) of life cycle of Malarial Parasite proving the hypothesis of Laveran and Manson.

RETIREMENT FROM INDIAN MEDICAL SERVICE

Ronald Ross left Calcutta on August 13, 1898, to get rid of "Administrative Barbarism." He submitted a report to the Government giving details of "Anti-Malarial weapons" including rational interventional strategies, as he thought to prevent, control, and eradicate malaria.

WORK ON KALA-AZAR (VISCERAL LEISHMANIASIS)

Ronald Ross submitted his report on the nature Kala-azar on January 30,1899, to the Director General of IMS.

Ross named "Leishman-donovan bodies" as parasite of Kalaazar discovered by W. B. Leishman (06.11.1865-02.06.1926) and Charles Donovan (September 19, 1863–October, 29, 1951). Leishman discovered in 1903 but could not definitely identify; Donovan in 1903 in his research found the same but called it a parasite. Ronald Ross solved this dispute and named this parasite as "Leishman-Donovan Bodies."

ROSS JOINED LIVERPOOL SCHOOL OF TROPICAL MEDICINE, UK

Returning from Calcutta, Ronald Ross joined as Lecturer with a very poor pay. He worked from 1899 to 1926 at different positions. He retired as Alfred Jones' Professor and Director of Tropical Medicine.

HEROIC EXPEDITIONS

During his service at LSTM, he made expedition to Freetown, capital of Sierra Leona (1899 and 1901), Mian mir Lahore (1901), Lagos (1901), Ismailia at Egypt (1902), Panama (1904), Greece (1906), Mauritius (1907–1908), Alexandria (1914–18) to control, prevent, and eradicate Malaria.

AWARDED NOBEL PRIZE IN PHYSIOLOGY AND MEDICINE (DECEMBER 10, 1902)

Ronald Ross was the First Indian to get the Nobel Prize in Physiology and Medicine. Malaria known as Modern Plague or Deadly Fever (Mrityujwar by Sushruta, 800 BC-700 BCE) is now defeated by Ronald Ross.

Sir Ronald Ross was a man of immense versatility; even within malaria, at least three streams of subsequent work flow from his original contribution; in parasitology-work on the life cycle, best known but perhaps not his greatest work, although crucial to all the rest; in epidemiological models which was 20 years ahead of his time and in sanitation or hygiene, in promoting the prevention of Malaria and other diseases by Environmental means.

-David J Bradley

Director, Ross Institute, London

ROSS INSTITUTE AND HOSPITAL FOR TROPICAL DISEASES

This institute was inaugurated in 1926 in Putney Heath by the Prince of Wales as a memorial to and in recognition of Ronald Ross's work. It was dedicated to study of the nature and treatment, propagation and prevention of tropical diseases.

In 1926, Ronald Ross became the Director-in-Chief of this institute till his death in 1932. After his death, it was incorporated by the London School of Hygiene and Tropical Medicine.

HONOR TO SIR RONALD ROSS

After his death on September 16, 1932, The Times, London, paid tribute to him "He slew the Dragon and delivered mankind from immortal bondage."

Dr. W. C. Gorgas said "Dr. Ronald Ross had dug the Panama canal with the help of microscope." Calcutta honors Sir Ronald Ross.

- Barkley Bronze Medal by the Asiatic society of Calcutta on May 20, 1903
    - Gate of Commemoration unveiled by Lord Lytton, in the presence of Sir Ronald Ross at PG Hospital Campus on January 7, 1927.
- Ronald Ross Building was established at PG (SSKM) Hospital Kolkata in 1954.
- Ronald Ross oration (yearly) was established at IPGM and R (Institute of Post Graduate Medical Education and Research) in 1956.
    - PG (SSKM) hospital was declared as a Heritage precinct and Sir Ronald Ross Laboratory Building as a Heritage Building by Calcutta Municipal Corporation on January 6,1991 due to appeal of Dr. Ranen Dasgupta.
- Sir Ronald Ross Sarani (Erstwhile Hospital Road) was declared by the Calcutta Municipal Corporation on the 09.01.2001, in response to appeal of Dr. Ranen Dasgupta
- Sir Ronald Ross Memorial Malaria Clinic (24 h) at Sir Ronald Ross Laboratory at SSKM Hospital was sanctioned by Government of West Bengal and Kolkata Municipal Corporation in response to appeal of Dr. Ranen Dasgupta, which was inaugurated on February 05, 2004.
- Sir Ronald Ross Park was established at SSKM Hospital on January 16, 2006. due to my endeavor.

CONCLUSION

Sir Ronald Ross was a remarkable man who contributed immensely not only in Malaria Research but also as a Mathematician, Epidemiologist, Sanitarian, Editor of Science Progress, Dramatist, Poet, Musician, Composer, Artist, and Author. He was a Polymath. Above all, he was a Medical Missionary.

Earnest appeal

To Commemorate his glorious attachment to PG SSKM Hospital Calcutta, The IPGME and R (Institute of Post Graduate Medical Education and Research) should be renamed as SIR RONALD ROSS INSTITUTE OF POST GRADUATE MEDICAL EDUCATION and RESEARCH. A MEDICAL MUSEUM should be established at the allotted land for the second campus of PG (SSKM) HOSPITAL at New Town, Kolkata, where foundation stone was laid on 11th November, 2010, to Showcase Calcutta, as MECCA OF MEDICINE and PG HOSPITAL AS PRIDE and GLORY OF BENGAL.

The History of Malaria contains a good lesson for humanity. We should be more scientific in our habits of thought and more practical in our habits of Government.

-Sir Ronald Ross

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