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GOVERNING BODY

ORIGINAL ARTICLE

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Infection Transmission Factors and their Perception amongst Healthcare Workers infected with SARS-CoV-2 in a Tertiary Care Hospital

Pooja Sethi, Desh Deepak**, Mala Chhabra***, Sampada SJ Ahagirdar****, Nandini Duggal******

Abstract:

Purpose: It is important to take stock and learn from previous pandemic experiences to make informed organisational strategies to improve the wellness of frontline workers. This study generates primary data on the incidence and contributing factors of SARS-CoV-2 infection and their perception amongst Healthcare Workers (HCWs) in India.

Methods: A structured questionnaire to assess the demographics and course of COVID-19 infection was sent out to 800 HCWs (19 - 65 years) who tested positive between March 2020 and June 2021. Descriptive statistics were used to analyse the data.

Results: A total of 453 participants aged 36.11 ± 11.12 years responded to the questionnaire. Out of these, 11% reported reinfection. Ninety-two per cent of participants had a symptomatic presentation with an average loss of 10 - 17 work-days. Factors associated with higher rate of hospitalisation were the presence of Type 2 Diabetes (25%) and the lack of use of any prophylactic agent (16%), compared to an overall rate of 11%. Only 40% of the infected HCWs were on COVID-19 duties. Nearly half (49%) perceived that they got their first COVID-19 infection from a contact with a patient while 68% of those who were infected the second time reported transmission from a social contact. Around 54% of them did not feel that they transmitted the disease to others.

Conclusion: Most HCWs missed work for 10 - 17 days. No co-morbidities, other than Type 2 Diabetes, seemed to have impacted the severity of infection in this relatively young population. Use of any prophylactic measure was associated with a lower rate of hospitalisation compared to no prophylaxis. Most of the HCWs did not perceive themselves as a source of SARS-CoV-2 transmission to the community.

Key words: Infection, transmission, perception, healthcare workers, SARS- CoV-2.

Introduction

Coronavirus pandemic, caused by the novel coronavirus (SARS-CoV-2), wreaked havoc across the world snuffing out millions of lives[1]. The Coronavirus was originally identified from Wuhan, Hubei province, China in December 2019 following Pneumonia cases of unknown aetiology[2]. The first case of SARS-CoV-2 in India was detected on January 30, 2020 in Kerala, in a student who had travelled from Wuhan with symptoms of respiratory discomfort[3,4]. The first death in India was reported on March 12, 2020. Infections with COVID-19 accelerated quickly, reaching 1,000 cases on March 28, 2020[5]. As of January 31, 2022, a total of 4,14,69,499 cases were reported with 4,97,975 deaths spread across 28 states and 8 union territories of India[6,7].

As seen across the globe, the novel coronavirus (SARS-CoV-2) has infected a large number of HCWs in India also[8]. Recent studies have concluded that HCWs who were SARS-CoV-2 positive constituted a significant proportion of all COVID-19 patients but the severity and mortality were lower amongst them compared to the general population[9]. HCWs are at increased risk of contracting COVID-19 due to direct or indirect exposure to COVID-19 patients and thereby require special attention. Though direct transmission in hospitals cannot be ruled-out, currently available data does not support widespread nosocomial transmission as a source of infection among patients or HCWs[10]. Also, secondary transmission from HCWs is a possibility among patients, family members and the community. Therefore, it is important to investigate the infection risk of HCWs, the clinical characteristics of the affected cases and the possible source of infection[11]. In India, there is lack of data regarding prevalence of COVID-19 amongst HCWs due to the absence of routine screening programmes within the hospital settings[12]. Many doctors, nurses, allied HCWs and support staff contracted COVID-19 at our hospital, a tertiary

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care government hospital catering to both COVID-19 and non-COVID patients since February 2020. Some HCWs also had reinfection during this period. Therefore, we studied the factors associated with SARS-CoV-2 infection and reinfection amongst HCWs and its impact. The objectives of the study were:-

1. Assessment of the association between demographics, co-morbidities, and exposure to COVID-19 patients with incidence of SARS-CoV-2 infection among HCWs.
2. To determine the efficacy of prophylactic measures for COVID-19 among HCWs.
3. To assess the impact of COVID-19 on HCWs in terms of loss of work days.
4. To identify the perceived source of SARS-CoV-2 infection in HCWs and to study the probability of community transmission of SARS-CoV-2 from HCWs.

Methodology

Ethical approval was obtained from The Institutional Ethics Committee, ABVIMS, Dr RML Hospital, New Delhi (500{36/2021}/IEC/ABVIMS/RMLH/627). Eight hundred HCWs who tested positive by RT-PCR testing between March 1, 2020 and June 30, 2021 were included in the study. A questionnaire in the form of a Google form was sent to all the participants by email. Those who had difficulty in filling the form were asked to answer the questions telephonically. This form included three sections; the first section covered the demographic details while the second section had questions regarding relevant medical history, level of baseline physical activity, use of any prophylactic measures, course of the disease and its severity, perception of the source of infection and onward transmission and absence from work. The third section was to be filled by only those HCWs who had contracted COVID-19 infection twice during the study period.

Responses were obtained from 453 participants. Among the non-responders some had left their job, some were not posted in the hospital during the study period while others did not want to participate in the study. For classification of our participants into those suffering from mild, moderate, or severe disease, we used lowest recorded SpO_2 as our criterion. Patients with a $SpO_2 \geq 94\%$ were classified as mild, 90 - 93% as moderate while patients having SpO_2 <90% were categorised as having severe disease, in accordance with the national guidelines for India issued by the Ministry of Health and Family Welfare[13].

All the demographic, clinical and other parameters were analysed using appropriate statistical tests. All data was entered in MS Excel. After cleaning, analysis was done in SPSS version 16.0 for statistical analysis. Descriptive tabulations were drawn and categorical data was mentioned as percentage and proportions.

Results

Demographics

A total of 453 healthcare workers who tested positive by RT-PCR during the study period, of which 273 (60%) were males and 180 (40%) were females. Their age ranged from 19 - 65 years with mean age of 36.11 ± 11.12 years. Among the participants 181 (40%) were doctors, 98 (21.6%) were support staff, 85 (18.7%) were nurses, 21 (4.6%) were sanitation workers, 36 (8%) were administrative staff and 32 (7.1%) allied HCWs as listed in Table I.

Table I: Demographics and detailed description of the study population.

Characteristics	1st COVID-19 Infection N = 453	2nd COVID-19 Infection N = 50
Age in years [Mean ± SD (Range)]	36.11 ± 11.12 (19 - 65)	31.36 ± 7.95 (23 - 57)
Gender - No. (%)		
Males	273 (60.26)	35 (70)
Females	180 (39.74)	15 (30)
BMI [Mean ± SD (Range)] (Kg/m^2)	25.42 ± 4.42 (15.57 - 44.43)	26.12 ± 6.09 (15.78 - 43.21)
> 30 Kg/m^2 (Obese) - no.(%)	58 (12.80)	10 (20)
Work Profile - no. (%)		
Doctor	181 (39.96)	19 (38)
Support Staff	98 (21.63)	14 (28)
Nurse	85 (18.76)	7 (14)
Administrative Staff	36 (7.95)	3 (6)
Allied Health Professional	32 (7.06)	3 (6)
Sanitation Worker	21 (4.64)	4 (8)
Onset of COVID-19 illness with respect to time of Vaccination- no. (%)		
Prior to vaccination	323 (71.30)	31 (62)
After first dose of vaccination	65 (14.35)	13 (26)
15 days or more days after second dose of vaccination	65 (14.35)	6 (12)
Presence of Co-morbidities - no. (%)		
None	300 (66.23)	35 (70)
Obesity	58 (12.8)	10 (20)
Hypertension	53 (11.7)	3 (6)
Diabetes Mellitus	32 (7.06)	1 (2)
Hypothyroidism	22 (4.86)	1 (2)
Others	31 (6.84)	4 (8)
Multiple	38 (8.39)	3 (6)
Level of Physical Activity as per WHO Criteria (> 150 min/week) - no. (%)		
Inadequate	339 (74.83)	37 (74)
Adequate	114 (25.17)	13 (26)
COVID-19 duty status 15 days prior to testing positive - no. (%)		
Not involved	269 (59.58)	27 (54)
Involved	184 (40.62)	23 (46)

Clinical profile

Only 35 (7.7%) participants were asymptomatic. The majority of participants experienced fever, followed by bodyache, cough, loss of smell, loss of taste and other symptoms; the details of the same are shown in Table II.

Table II: Distribution of symptoms during 1st and 2nd episodes of COVID-19 infection amongst HCWs.

Symptoms	1st COVID-19 infection (%) n = 453	2nd COVID-19 infection (%) n = 50
Asymptomatic	35 (7.73%)	2 (4%)
Fever	350 (77.26%)	34 (68%)
Bodyache	263 (58.06%)	29 (58%)
Cough	228 (50.33%)	25 (50%)
Loss of smell	213 (47.02%)	21 (42%)
Loss of taste sensation	193 (42.6%)	21 (42%)
Sore throat	184 (40.62%)	21 (42%)
Running nose/cold	110 (24.28%)	11 (22%)
Breathlessness	77 (17%)	9 (18%)
Diarrhoea, vomiting	60 (13.25%)	7 (14%)
Headache	6 (1.32%)	1 (2%)
Weakness/fatigue	4 (0.88%)	1 (2%)
Backpain	4 (0.88%)	0
Restlessness, depression, anxiety	2 (0.44%)	1 (2%)
Loss of appetite	2 (0.44%)	1 (2%)
Vertigo	1 (0.22%)	0

Out of 453, 50 (11%) required hospitalisation for an average duration of 10.5 days (1 - 45 days). Among those admitted 21 (42%) required oxygen support while 1 (2%) required ICU care. A total of 291 participants recorded SpO_2. 222 (76%) were categorised as mild, 43(15%) moderate and 26 (9%) as severe SARS CoV-2 infection, based on the SpO_2 criterion.

Among the participants, 300 (66.2%) did not have any co-morbidity while 38 (8.3%) had multiple comorbidities. The common co-morbidities noted among infected HCWs are detailed in Table I.

Only 27 (9%) of those who did not have any associated co-morbidity required hospitalisation. Among the co-morbidities, hypothyroidism did not have any significant effect on the severity of the disease and was not associated with an increased incidence of hospitalisation, but hypertension and obesity marginally increased hospitalisation rate. However, 11 (34%) of those suffering from diabetes alone or along with other co-morbidities suffered moderate-to-severe disease and 8 (25%) of those diabetics required hospitalisation.

Three hundred and thirty-nine (75%) participants had inadequate levels of physical activity (i.e., less than 150 minutes/week as per WHO criteria) but it was not associated with the severity of illness or hospitalisation requirement.

No significant relationship was found between the severity of disease and gender, blood group or job profile of the participants. However, it is noteworthy that among different professionals, most nurses 87.5% had mild illness and only 4.7% of them required hospitalisation.

Factors related to COVID-19 infection

269 (60%) HCWs who contracted SARS CoV-2 were not posted in COVID-19 areas of the hospital. However, the other 184 (40%) of these workers were posted for COVID-19 duty within 15 days prior to testing positive, of which 30 (6.6%) reported not following hand hygiene properly, 17 (3.8%) reported breach in PPE, 15 (3.3%) reported use of insufficient PPE as the probable reason for contracting infection. Half of the participants felt that contact with COVID-19 positive patients in-hospital was the source of infection. The perceived sources of infection for the other HCWs are detailed in Table III.

Table III: Perceived source of infection amongst HCWs.

Possible source of COVID-19 infection	1st COVID-19 infection (%) n = 453	2nd COVID-19 infection (%) n = 50
Contact with COVID-19 positive patient in hospital	223 (49.23%)	7 (14%)
Contact with COVID-19 positive colleague in the hospital	162 (35.76%)	0
Contact with COVID-19 positive friend/relative/social contact	55 (12.14%)	34 (68%)
Contact with COVID-19 positive family member	37 (8.17%)	1 (2%)
Visit to crowded place market/social gathering etc	21 (4.64%)	1 (2%)
Travel outside city	1 (0.22%)	0
Not sure	105 (23.18%)	7 (14%)

It was observed that 323 (71%) HCWs were infected prior to vaccination and 130 (29%) were infected after partial or full vaccination. Among those hospitalised, 42 (84%) were unvaccinated and only 8 (16%) were partially or fully vaccinated.

Majority of the participants, i.e., 244 (54%) HCWs felt that they did not transmit the disease to the community, while 126 (28%) felt that they were the source of infection for family members, 76 (16.8%) for colleagues, 98 (10.6%) for patients and 30 (6.6%) for social contacts and neighbours.

Prophylactic measures

Even though the majority (79%) of participants were taking multiple prophylactic medications in the form of Allopathic, Ayurvedic or Homeopathic preparations or home remedies they still contracted infection. Hospitalisation rate was 16.2%

in participants not taking any prophylaxis but was markedly reduced in those taking different preparations alone or in combination, as listed in Table IV.

Table IV: Hospitalisation rate among HCWs taking different types of prophylaxis.

Prophylaxis	Number of participants who took prophylaxis	Hospitalisation Rate
Ivermectin	125	12 (9.6%)
HCQS	98	10 (10.2%)
Ayurvedic medication/kadha	187	12 (6.41%)
Homeopathic	18	3 (16.66%)
Home remedies	174	17 (9.77%)
None	86	14 (16.2%)

Absence from work

Majority of the participants, i.e., 314 (70%) were absent from work for 10 - 17 days, 97 (21%) were absent for 17 - 29 days, 29 (6%) were absent for more than a month and only 13 (3%) were absent for less than 10 days.

Presentation of COVID-19 re-infection

Out of 453 participants, 50 acquired COVID-19 infection for a second time during the study duration. Of these 35 (70%) were males and 15 (30%) were females with a mean age of 31.36 ± 7.95 years (23 - 57 years). Among the re-infected participants 19 (38%) were doctors, 14 (28%) were support staff, 7 (14%) were nurses and other professionals 10 (20%) as listed in Table I. Similar to the trends in first infection, only 2 (4%) were asymptomatic; while the majority experienced fever, followed by bodyache, cough and other symptoms as detailed in Table II. Only 6 (12%) participants required hospitalisation for an average duration of 13.7 days (8 - 30 days). Among those admitted, only 4 patients required oxygen support and 1 patient required ICU care. During reinfection, the trend for mild illness remained similar at 26 (79%), while it reduced to 3 (9%) for moderate and increased to 4 (12%) for severe disease. 35 (70%) HCWs who had COVID-19 infection for the second time did not have any co-morbidities while 3 (6%) had multiple co-morbidities.

As during the first infection, most of HCWs, 27 (54%) who contracted COVID-19 the second time, were not posted in COVID-19 areas of the hospital. Twenty-three (46%) were posted for COVID-19 duty within 15 days prior to testing positive, of which 6 (12%) reported not following hand hygiene properly, 5 (10%) reported breach in PPE, 1 (2%) reported use of insufficient PPE as a probable cause for contracting infection. Unlike the first infection, majority of participants (34, i.e., 68%) felt that interaction with a COVID-19 positive social contact was the source of infection. The other perceived sources are detailed in Table III.

It was observed that 31 (62%) of the 50 re-infected individuals were not vaccinated, 13 (26%) were partially vaccinated and only 6 (12%) were fully vaccinated. The rate of hospitalisation was significantly lower among fully vaccinated (16.5%) and partially vaccinated (16.5%) as compared to unvaccinated 4 (67%) during the second episode of COVID-19 illness.

Majority of participants 20 (40%) felt that they did not transmit the disease to the community, 14 (28%) felt they were a source of infection for family members, 12 (24%) for colleagues, 9 (18%) for patients and 5 (10%) for social contacts and neighbours. Though most of the participants were taking prophylactic medications, yet they contracted infection, though the hospitalisation rate was significantly reduced among them.

Discussion

This study included 453 HCWs who were infected with SARS-CoV-2 over a period of one year and three months and included 50 participants who were reinfected during this period.

Thirty-three percent of the participants had co-morbidities[9,10]. Among the co-morbidities, Diabetes Mellitus was associated with a higher hospitalisation rate and severity of disease, as was found in many preceding studies. It is will known that both the innate and adaptive arms of the immune system are compromised in diabetes mellitus[14].

There was no significant difference between demographic profiles of participants who were infected once or twice during the course of study in terms of gender, age or nature of work. Most of the participants suffered from mild illness and symptoms present during the first and second infection were very similar.

Previous studies have concluded that consistently meeting physical activity guidelines was strongly associated with a reduced risk for severe COVID-19 outcomes[15] but in our study we did not find a correlation between physical activity and severity of the disease. However, it was observed that inadequate physical activity was associated with high-risk of infection and reinfection.

Posting of HCWs in high-risk areas was on a rotation basis, followed by quarantine and RT-PCR testing. It was observed that the risk of both first and repeat infection among people posted on COVID-19 duty was not higher compared to those who were posted in the other areas. This was likely as most HCWs working in high-risk zones were aware of exposure risk and hence followed infection control practices. Previous studies have reiterated that though

SARS-CoV-2 is a burden on HCWs, nonetheless, the use of PPE and infection control training are associated with decreased risk[8].

During the first infection, most HCWs attributed the source of infection as contact with a positive patient/ colleague in the hospital while during the second episode most HCWs attributed social contacts as a source of infection. This can possibly be explained as most HCWs who contracted SARS-CoV-2 twice were first infected between March 2020 to September 2020. During this period there was a lockdown imposed in the country for a long duration and HCWs were not intermingling with the society. However, most HCWs, were reinfected during February 15, 2021 to April 15, 2021. During this time period there were fewer COVID-19 related restrictions and lockdown had not been imposed, so HCWs were intermingling in the community[11]. In both the COVID-19 infections, majority of participants reported not infecting their family members, colleagues or social contacts. This indicates that HCWs were cautious and followed COVID-19 protocols to prevent community spread.

Unvaccinated individuals were more likely to get infected and re-infected. Previous studies have also indicated that vaccination after SARS-CoV-2 infection increased T-cell immunity, antibody-secreting memory B-cell response to the spike protein, and neutralising antibodies are present even after the first dose of vaccination[16].

Most HCWs perceived that they were at a higher risk of exposure and thus the majority of them were taking prophylactic preparations to reduce the chances of infection. As there were no proven measures, various approaches were adopted. In our study, the hospitalisation rate was much lower among participants taking Ivermectin, Hydroxychloroquine and Ayurvedic preparations. The doses and duration varied. Most had taken more than one prophylactic preparation. So, it cannot be decisively concluded that the low hospitalisation rate was the result of any particular prophylactic preparation. This could also have resulted because these HCWs were more cautious to take extra precautions making them more compliant tocovid-appropriate behaviour.

The MOHFW guidelines recommended isolation for 17 days for Covid positive cases which was later reduced to 10 days. As most of the HCWs suffered mild illness, the average days of absenteeism was 10 - 17 days in line with government guidelines for quarantine[12].

Limitations of the study

Only 64% of the participants recorded SpO_2 because of which, all the participants could not be classified into mild, moderate or severe categories. It is likely that the remaining 36% suffered from a milder form of illness. In addition to this, the clinical presentation of HCWs who had very severe disease and died because of COVID-19 could not be accounted for in this study[13], hence there could be a bias in the study, including a greater number of HCWs with milder disease.

Conclusion

It was seen that the majority of participants had mild illness, symptomatology of which was similar in character during the first and the second infection.

Amongst the HCWs, the presence of Type 2 Diabetes was associated with an increased severity and hospitalisation, while other comorbidities were not found to be related to the disease severity, either during the first or second episode of infection. Inadequate physical activity levels were associated with a high-risk of infection and reinfection but not with the severity of disease.

The use of Allopathic and Ayurvedic formulation as prophylactic measures may contribute to a reduction in the hospitalisation rate. However, larger studies are required for a definite conclusion.

The average loss of work days due to COVID-19 illness was 10 - 17 days.

Majority of the participants felt that they contracted the first infection from a COVID-19 positive patient and the second infection from a social contact. Both the infections were seen, mostly, before complete vaccination. Vaccination was also associated with a reduced rate of hospitalisation.

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ORIGINAL ARTICLE

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Testing the Tormenting TRIO: A Study of Thyroid Autoimmunity, Iron Deficiency and Thyroid Diseases in the First Trimester of Pregnancy

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Abstract

***Introduction:** Anaemia is a worldwide leading health problem affecting women, which is still more common during pregnancy as the demand for iron increases. A review of the most recent literature reveals that the link between Iron deficiency and thyroid diseases is controversial. A few studies have shown that Iron deficiency anaemia can cause thyroid hypofunction by reducing Thyroid peroxidase (TPO) enzyme activity[1]. Hence this study was taken up with the objectives of 1) To evaluate the association between Iron deficiency and thyroid disorders in the first trimester of pregnancy, and 2) to evaluate the association between thyroid autoimmunity and Iron deficiency in early pregnancy.*

***Material and methods:** This was a cross-sectional study conducted between Jan 2017 and June 2019 at JSS Hospital, Mysuru. 500 pregnant women were recruited. Under aseptic precautions, venous blood was sent for analysis of Hb, TSH, T3, T4, Anti-TPO antibody and Serum Ferritin. Chi-square analysis was done to analyse any association between Iron deficiency and Hypothyroidism.*

***Results:** Out of 500 women, 9 were excluded because of preanalytical error, hence there were 491 pregnant women in the first trimester of pregnancy. Among 491 pregnant women, 156 (31.77%) were hypothyroid and 7 (1.42%) had thyrotoxicosis. Among 156 Hypothyroid women, 9 (5.76%) had overt hypothyroidism and 147 (94.23%) had subclinical hypothyroidism. Among 491 pregnant women, 128 (29.22%) had iron deficiency, 82 (18.72%) had iron deficiency anaemia, 228 (52.05%) had normal Hb and ferritin. 53 (10.79%) women were excluded as they had low Hb but normal ferritin, hence three groups were made for analysis. TSH was higher in the iron deficiency anaemia group compared to the other 2 groups but it was not statistically significant. There was no difference in the rates of thyroid dysfunction among different groups.*

***Conclusion:** The prevalence of hypothyroidism was very high (31%) in our setting compared to that seen in earlier published reports. There was no association found between hypothyroidism and iron deficiency in this study contrary to previous studies. There was no association found between thyroid autoimmunity and iron deficiency in this study.*

***Key words:** Subclinical hypothyroidism, anaemia, thyroid antibodies, gestation.*

Introduction

Anaemia is a worldwide health problem affecting 33% of non-pregnant women and 38% of pregnant women[2]. As pregnancy progresses, the prevalence of anaemia also increases. Iron deficiency anaemia (IDA) accounts for 75% of anaemia during pregnancy[3,4]. The prevalence of anaemia in pregnant women is 50.3% and in non-pregnant women is 52.2%, in India (NFHS-4)[5]. Pregnant women are highly susceptible to iron deficiency anaemia as there is increased demand for iron during pregnancy[6]. Recently the prevalence of hypothyroidism is seen to be increasing among women. The causes are unknown, when thyroid antibodies are negative in them. Some studies have noted that iron deficiency anaemia can cause thyroid hypofunction by reducing Thyroid peroxidase (TPO) enzyme activity[1]. Iron deficiency was linked to a twofold rise in hypothyroidism[7,8]. Women with thyroid dysfunction were more likely to have anaemia compared with euthyroid women[9]. Iron deficiency (ID) is related to a high prevalence of thyroid autoimmune disease (TAI), higher serum thyroid-stimulating hormone (TSH), and lower free thyroxine (FT4) levels during the first trimester of pregnancy[10]. A clinical study that involved 15,000 Chinese pregnant women showed that subclinical hypothyroidism was not related to anaemia, whether treated or not[11]. Sahu *et al*[12] and Wang *et al*[13] also drew the same conclusion. There were only a few studies in India regarding this issue, hence this study was taken up.

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Aims and objectives

1. To evaluate the association between iron deficiency and thyroid disorders in the first trimester of pregnancy.
2. To evaluate the association between iron deficiency and thyroid autoimmunity in the first trimester of pregnancy.

Methodology

This was a cross-sectional study conducted between January 2017 and June 2019 at JSS Hospital, a tertiary care teaching and research hospital attached to JSS Medical College in Mysuru city, South India. 500 consecutive pregnant women aged 18 - 45 years in the first trimester of pregnancy were recruited. Informed written consent was taken from all women. Ethical Clearance was obtained from JSS Medical College Institutional Ethics Committee. (JSSMC/IEC/14/6047/2016-17).

Pregnant women who had any past or present history of thyroid dysfunction/disease, family history of thyroid disease, previous head or neck irradiation, usage of drugs such as levothyroxine, methimazole, iodide, lithium, amiodarone and corticosteroids, patients diagnosed with autoimmune and connective tissue diseases were excluded from the study. Detailed history and clinical examination were recorded in clinical proforma. Under all aseptic precautions, venous blood of about 5 ml was drawn and sent for analysis of Hb, TSH, T3, T4, Anti-TPO antibody and serum ferritin. T3, T4, TSH, Anti-TPO antibody and serum ferritin were measured by chemiluminescence method for all pregnant women. TSH value >2.5 μIU/ml but less than or equal to 10 with normal T4 were considered to have subclinical hypothyroidism (SCH), TSH value >10 μIU/ml irrespective of T4 values and TSH value >2.5 μIU/ml with low T4 values were considered to have overt hypothyroidism[14] (American Thyroid Association and National Guidelines). Serum ferritin less than 20 was considered as iron deficiency and pregnant women having both Hb < 11g/dl and serum ferritin < 20 ng/ml were considered to have iron deficiency anaemia. All parameters were compared and statistically evaluated for significant association between groups.

Statistical analysis

Data collected were entered in Microsoft Excel and analysed using SPSS version 22.

Descriptive statistical measures like percentage, mean and standard deviation were calculated. Inferential statistical tests like the Chi-square test, two-way ANOVA were used wherever relevant and statistical significance was considered at a p-value of < 0.05.

Results

Out of 500 subjects in the study, 9 were excluded because of preanalytical error, hence data of the remaining 491 pregnant women were analysed. Most of them, 403 (82%) were in the age group 21 - 30 years, the majority - 363 (74.75%) belonged to the urban category, most, i.e., 481 (98%) were literate and 466 (95%) were homemakers. 412 (84%) had married when aged between 18 - 25 years age, 407 (83%) had a non-consanguineous marriage, 228 (46%) were primigravida and 263 (53%) were multigravida, only 4 (0.8%) had previous caesarean section and 51 (10%) had a previous history of irregular menstrual cycles. 370 (75%) were non-vegetarians, 418 (85%) had an intake of cauliflower and cabbage weekly once. 227 (46%) had normal BMI, 107 (21%) were overweight, 65 (12%) were obese and 92 (18%) were underweight.

Among 491 pregnant women, 128 (29.22%) had iron deficiency, 82 (18.72%) had iron deficiency anaemia, 228 (52.05%) had normal Hb and ferritin and 53 (10.79%) were excluded as they had low Hb but normal ferritin, hence three groups were made for analysis as shown in Table I. Age, weeks of pregnancy and BMI were similar among the three groups. There was variation in SBP between groups with a significant p-value - 0.02, SBP was less in the iron deficiency anaemia group.

The predominant symptom of the iron deficiency anaemia group was fatigue (26.82%) followed by hair loss (24.39%) (Table II).

Table I: Comparison of clinicodemographic variables among different groups according to iron status.

Groups	n	Age (years)	Weeks of Pregnancy	BMI (Kg/m^2)	Pulse (bpm)	SBP (mm Hg)	DBP (mm Hg)	Hb (g/dl)	Serum Ferritin (ng/ml)
ID	128 (29.22%)	23.00 ± 3.60	8.26 ± 2.35	21.67 ± 3.39	80.41 ± 6.87	112.43 ± 10.53	78.56 ± 7.17	12 ± 0.84	13.05 ± 4.87
IDA	82 (18.72%)	22.93 ± 3.00	8.54 ± 2.10	21.77 ± 3.46	83.06 ± 9.73	106.95 ± 11.62	69.75 ± 7.19	9.62 ± 1.07	9.41 ± 5.39
Normal	228 (52.05%)	23.90 ± 4.05	8.66 ± 2.14	22.10 ± 3.67	81.98 ± 9.00	111.16 ± 11.38	71.68 ± 7.96	12.23 ± 0.75	47.19 ± 33.88
p-value		0.125	0.258	0.512	0.077	0.02	0.189	< 0.0001	< 0.0001

Table II: Comparison of symptoms among different groups according to iron status.

Symptoms	Iron deficiency anaemia	Iron deficiency	Normal	p value
Tiredness	22 (26.82%)	49 (38.28%)	84 (36.84%)	0.19
Feeling Cold	5 (6.09%)	27 (21.09%)	44 (19.29%)	0.01
Dry Skin	5 (6.09%)	8 (6.25%)	17 (7.45%)	0.87
Hair Loss	20 (24.39%)	55 (42.96%)	69 (30.26%)	0.009
Poor Memory	1 (1.21%)	2 (1.56%)	4 (1.75%)	0.94
Constipation	0 (0%)	6 (4.68%)	6 (2.63%)	0.12
Weight Gain	1 (1.21%)	3 (2.34%)	4 (1.75%)	0.83

Among 491 pregnant women, 156 (31.77%) were hypothyroid and 7 (1.42%) had thyrotoxicosis. Among 156 hypothyroid women, 9 (5.76%) had overt hypothyroidism and 147 (94.23%) had subclinical hypothyroidism. The prevalence of hypothyroidism was very high in this study due to the low TSH cut-off value used according to recent ATA guidelines whereas previous studies have used TSH >4 μIU/ml.

Predominant symptom in hypothyroid women was fatigue (35.6%) followed by hair loss (31.7%), cold intolerance (16.9%), dry skin (6.72%), constipation (2.65%), weight gain (2.24%) and poor memory (2.04%). Goitre was present in 10 women.

The thyroid function indices are compared in Table III. TSH was higher in the iron deficiency anaemia group compared to the other 2 groups but it was not statistically significant. T3.T4 and Anti-TPO antibody were similar in all groups with no statistical significance.

Table III: Comparison of thyroid status among different groups according to iron status

Groups	n	TSH (μIU/ml)	T3 (ng/ml)	T4 (μg/dl)	Anti-TPO Ab (IU/ml)
ID	128	1.63 ± 1.60	1.41 ± 0.34	8.87 ± 2.55	16.70 (9.91, 24.60)
IDA	82	2.01 ± 1.50	1.41 ± 0.39	9.33 ± 3.04	14.75 (10.22, 21.85)
Normal	228	1.77 ± 1.70	1.45 ± 0.76	9.39 ± 2.39	16.87 (12.19, 22.27)
p-value		0.536	0.791	0.173	0.793

2.34% of pregnant women had overt hypothyroidism and 26.56% had SCH in the ID group. 29.26% of women had SCH in the IDA group. Overt hypothyroidism was not found in the IDA group. There was no difference in the rates of thyroid dysfunction and thyroid autoimmunity among different groups as in Table IV.

Subgroup analysis was done, as depicted in Table V, and it did not show any association between iron deficiency and SCH.

Table IV: Comparison of thyroid dysfunction among different groups according to iron status.

Groups	Overt Hypothyroidism	SCH	Hyperthyroidism	TPO Ab Positivity
ID	3 (2.34%)	34 (26.56%)	3 (2.34%)	6 (4.68%)
IDA	0 (0%)	24 (29.26%)	1 (1.21%)	5 (6.09%)
Normal	6 (2.63%)	66 (28.94%)	2 (0.87%)	13 (5.70%)
p value	0.34	0.91	0.54	0.88

Table V: Subgroup analysis.

Groups	SCH 1 TSH >4 but < 10	SCH 2 TSH >4.5 but < 10
ID (128)	13 (10.1%)	9 (7.03%)
IDA (82)	11 (13.41%)	9 (10.9%)
Normal (228)	16 (0.07%)	11 (8.59%)
p value	0.26	0.201

Discussion

Iron is a very essential micronutrient and a major component of haemoglobin, myoglobin and various enzymes such as thyroid peroxidase and myeloperoxidase. Iron also has a role in the regulation of immune and thyroid function. Iron deficiency results in impairment of cognitive performance and behaviour, immune function, thermoregulation and exercise/work capacity. Iron deficiency (ID) remains a worldwide problem, affecting about 20% of the world's population. In industrialised countries, the prevalence of iron deficiency in pregnancy ranges from 24 - 44%[3,15]. The prevalence of anaemia in India is above 40% and in Karnataka, it is 75.9%[3]. The prevalence of anaemia in pregnant women is 50.3% and in non-pregnant women is 52.2% according to NFHS-4[5]. Pregnant women are highly susceptible to IDA as there is increased demand for iron. Iron deficiency anaemia in pregnancy can lead to various complications like preterm birth, low birth weight, post-partum haemorrhage and unhealthy neurodevelopment in the foetus.

Recent research suggests that iron deficiency with or without anaemia impairs thyroid function[17]. It decreases plasma T4 and T3 concentrations by impairing two initial steps catalysed by heme-dependent thyroid peroxidase (TPO) enzyme in thyroid hormone synthesis and ID appears to decrease TSH response to TRH, reduce the peripheral conversion of T4 to T3 and increase circulating TSH[17]. However, in all these studies, there was no association found between ID and subclinical hypothyroidism[16,17]. ID can adversely influence thyroid hormone metabolism by altering control of the central nervous system (CNS)[21] and decreasing the binding of T3 to hepatic nuclear receptors[22]. ID could also impair thyroid metabolism through lowered

oxygen transport[23]. It is likely that these mechanisms jointly contribute to the impairment of thyroid function in iron deficiency anaemia[17].

There are a few published articles which have studied the association between iron deficiency and hypothyroidism in pregnant women; a few have positive association and a few have shown no association, which are discussed below.

ID was found in 35% of the women in the study by Veltri *et al*, which included 1,900 pregnant women. Thyroid autoimmunity (TAI) and SCH were substantially more common in the ID group than in the non-iron deficiency group (10% vs 6% and 20% vs 16%; P = 0.011 and 0.049, respectively). After controlling for confounding factors, ID remained linked with TAI in the logistic regression model (P = 0.017). During the first trimester of pregnancy, ID was more common, and it was linked to a higher incidence of TAI, higher serum TSH, and lower FT4 levels[10].

In a study done in China by Li *et al*, ID could lead to hypothyroidism during early pregnancy which could be explained by TAI. 2,654 pregnant women were enrolled, the positive rate of TPO antibody was higher in the IDA group rather than mild ID and controls with $p < 0.05$. They also observed that pregnant women in mild ID and IDA groups have higher TSH and lower FT4 levels than in the control group, the rate of hypothyroidism or SCH in the IDA group was significantly higher than in mild ID and controls group ($p < 0.01$)[17].

In both pregnant and non-pregnant women, the prevalence of mild and severe hypothyroxinaemia was considerably higher in women with ID than in women without ID, according to Yu *et al* study (p 0.01). Logistic regression analysis demonstrated that ID was an independent risk factor for both mild and severe hypothyroxinemia in pregnancy, independent of the effects of iodine and TAI. ID might be a causal factor for hypothyroxinaemia in pregnant women during the first trimester[18].

In research by Zhang *et al*, 7,463 first-trimester pregnant women were included which showed that the ID group had lower serum FT4 levels than the control group ($p < 0.01$), while the ID group's median TSH level was similar to the control group's[19].

In a study done by Sahu *et al*, 633 women in the second trimester from India were enrolled and found that the percentage of anaemia was more in SCH, but it was statistically insignificant[12].

In a study by Wang *et al*, which enrolled 756 first-trimester pregnant women, no link was found between SCH and other obstetrical issues such as gestational hypertension, premature delivery, anaemia, post-partum haemorrhage, low newborn Apgar scores, or low birth weight[13].

Yang *et al* (2015) observed no statistically significant difference in the incidence of placental abruption, anaemia or foetal distress between the SCH-treated and untreated groups in a trial of 2,042 women in early pregnancy with SCH[11].

In the present study, the prevalence of hypothyroidism was very high due to the low TSH cut-off value used (TSH > 2.5 μIU/ml) in the study according to recent ATA and National Guidelines[14] contrary to previous studies which used TSH > 4 μIU/ml.

In the present study, 128 (29.22%) women had ID and 82 (18.72%) had IDA. 2.34% of pregnant women had overt hypothyroidism and 26.56% had SCH in the ID group, 29.26% of women had SCH in the IDA group. Overt hypothyroidism was not found in the IDA group. None had severe IDA. There was no difference in rates of thyroid dysfunction among different groups in the current study, hence no association was found between ID and thyroid dysfunction in this study. There was no difference in Anti-TPO antibody levels among different groups, hence no association was found between ID and TAI in this study.

Overt hypothyroidism and TPO antibody-positive status were found to be risk factors for gestational anaemia in a meta-analysis published in 2020, however SCH and hyperthyroidism were not[20]. In the current study, the prevalence of SCH (94.23%) was more compared to overt hypothyroidism (5.76%) this might be the cause that the present study could not find any association between ID and hypothyroidism.

The strength of the study is that a large number of pregnant women were recruited; this was a larger study compared to previous studies and the association between TAI and ID was also studied.

Limitations of the study: The results of the study are limited by the fact that it was a single-centre cross-sectional study.

Conclusion

The prevalence of hypothyroidism was very high in our setting compared to that seen in earlier published reports. There was no association found between hypothyroidism and ID in this study contrary to previous studies. There was no association found between TAI and ID in this study.

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FORM IV (See Rule 8)

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Assessment of Menstrual Pattern in Women Post-COVID-19 Vaccination: An Observational Study

Sandhya Jain, Rinkal Goyal***

Abstract

Purpose: Women all over the world are receiving COVID-19 vaccines. Commonly reported side-effects include sore arm, fever, fatigue, and myalgia. Recent literature has suggested about possible menstrual abnormalities due to these vaccines. This study aims to assess the incidence of heavy bleeding and menstrual irregularity in the month subsequent to COVID-19 vaccination.

Methods: An online questionnaire was distributed to reproductive-age women (18 - 45 years) who had received at least one dose of COVID-19 vaccine. They were asked to fill out a questionnaire after attaining informed consent. After exclusion of 96 responses, a final sample of 100 was obtained. Descriptive tables were generated and scoring and categorisation were done.

Results: Mean age of the participants was 22 years, majority of them being students (74%). Participants were vaccinated with Covishield (73%), Covaxin (26%), or Sputnik-V (1%). 5%described their bleeding as heavy, 31% reported blood clots during menstruation and 3 women had periods that lasted for more than one week. Moderate to severe dysmenorrhoea was present in 36%. Six per cent individuals could not predict the start date of their period at all, suggesting menstrual irregularity. Dose of vaccine whether first or second and type of vaccine did not have any association with heavy bleeding (P = 0.587 and P = 0.158 respectively) or menstrual irregularity (P = 0.133 and P = 0.336 respectively).

Conclusion: Heavy bleeding and menstrual irregularity were commonly present following COVID-19 vaccination. Participants reported blood clots very commonly. Larger studies with extended follow-up are needed to fully understand post-vaccination menstrual changes.

Key words: Heavy menstrual bleeding, COVID-19 vaccination, menstrual irregularity, covishield, covaxin.

Introduction

COVID-19 infection struck India during the month of February, 2020. More than 40 million people have been affected as of now[1]. Occurrence of the pandemic led to rapid development of different vaccine types. Vaccination drive started in India in January, 2021 and presently adults are offered Astra Zeneca's Covishield, Bharat Biotech's Covaxin, or Sputnik-V. In contrast to Covaxin, which is an inactivated vaccine, Covishield and Sputnik-V are adenoviral vector vaccines. Covishield and Covaxin are available in two doses, separated by 12 - 16 weeks and 4 weeks, respectively, whilst sputnik-V is available in two doses separated by 21 days. Some commonly reported side-effects that women might experience after receiving the COVID-19 vaccine are injection site tenderness/pain, headache, fatigue, fever, myalgia, nausea, and vomiting, etc.[2]. At the end of December 2021, the UK's Medicines and Healthcare Products Related Agency (MHRA) recorded more than 40,000 incidents of menstruation disturbances across all COVID-19 vaccination brands available in the UK, including Covishield[3]. These reported menstrual changes were transient in nature[3]. COVID-19 infection itself can cause menstrual cycle changes, possibly due to an immune-mediated mechanism and inflammation of the endometrial lining[4-6].

In a published case-control study in the UK, menstrual cycle changes were found in 20% of women up to 4 months after receiving their first vaccine dose. The odds of reporting any menstrual changes were increased for smokers and individuals with positive COVID-19 status[6]. In a study from the Middle East and North Africa region, 66.3% of women experienced menstrual abnormalities after vaccination, and the majority of them had symptoms after the first dose[10]. A study among Japanese women found that age-adjusted odds of attending hospital were increased for abnormal amount of menstrual bleeding; irregular menstruation, and persistent occurrence of abnormal amounts of menstrual bleeding following HPV vaccine administration[11]. So far, the Indian government has not listed menstrual cycle changes or unexpected vaginal bleeding[12]. No study, done in India, is yet available in the literature.

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The objectives of this study were: 1) to assess the incidence of heavy bleeding and menstrual irregularity post-COVID-19 vaccination, and 2) to investigate the factors associated with menstrual abnormalities post-COVID-19 vaccination.

As per CDC, heavy menstrual bleeding is defined as menstrual bleeding that is heavy or lasting for more than 7 days or passing blood clots of the size of a quarter coin or larger[13].

Material and Methods

This descriptive, cross-sectional study was conducted among Indian women aged 18 - 45 years who were menstruating after attaining informed consent. It involved an anonymous questionnaire distributed online using a convenient sampling method. The research proposal was approved by The Institutional Ethics Committee for Human Research (IEC-HR), University College of Medical Sciences, Delhi (Proposal no. IECHR-2021-51-5-R2). Women who received at least one dose of the COVID-19 vaccine between July, 2021 and December, 2021 were included in the study. We excluded those women who refused participation, had any changes to periods in terms of pattern or flow in 3 months prior to vaccination, had a recently diagnosed medical/inflammatory disorder, had pregnancy or abortion prior to vaccination, and had recent changes in contraception.

Since at the time of sample size calculation, no study was available to find out the prevalence of heavy menstrual bleeding post-COVID-19 vaccination, prevalence was assumed to be 50%, with a 10% margin of error. On calculation initial sample size came out to be 96. Therefore, 100 women were recruited to study. Fig. 1 shows a flowchart of the study population selection.

Recruitment was done by the principal investigator, strict confidentiality was maintained and data was kept completely anonymised. An online questionnaire containing a semi-structured proforma was used to collect:-

1. Socio-demographic details such as age, occupation, income, religion, and marital status;
2. Clinical details such as parity, abortion, substance abuse, height and weight for calculation of BMI (based on revised consensus guidelines for Asian Indians and World Health Organisation (WHO) criteria)[14].
3. Details about the COVID-19 received and dates of 1st and 2nd doses.

Categorisation of the socio-economic class was based on the BG Prasad scale updated for the year 2021, calculated using the total number of family members and total monthly income of the family in rupees[15]. The menstrual bleeding questionnaire was used to assess heavy bleeding, passage

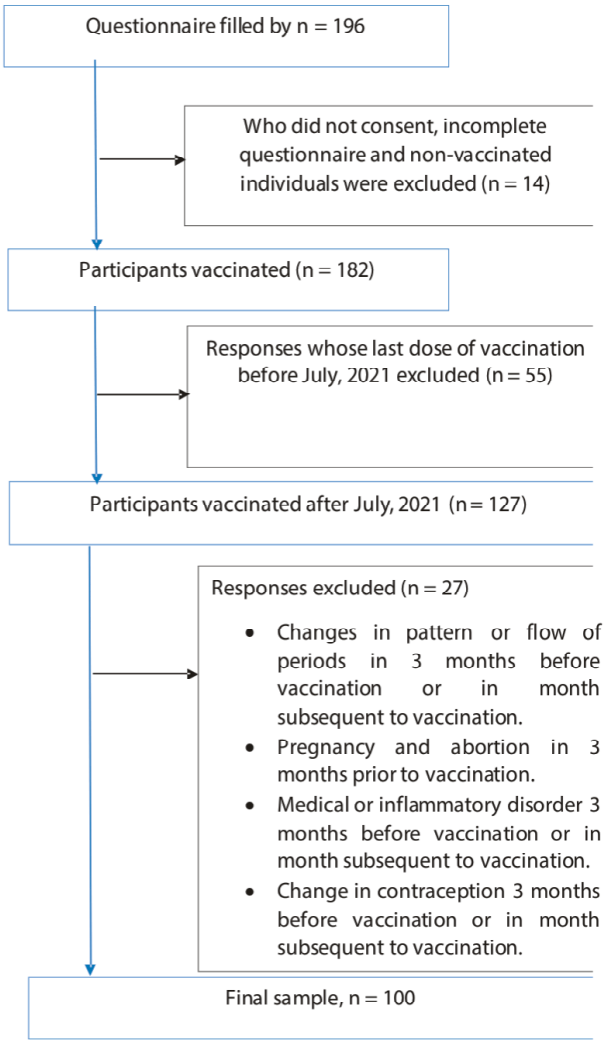

Fig. 1: *Flowchart of study population selection.*

of blood clots, menstrual pain, and irregularity in the one month post-vaccination[16].

Statistical analysis was performed using SPSS 22.0 (IBM, Armonk, NY, USA). Descriptive analysis was done to calculate the frequencies. Pearson's Chi-square or Fisher's exact test was used to compare qualitative variables. Quantitative variables such as BMI was compared by independent t-test. An exact 95% confidence interval was calculated for reported heavy bleeding and irregularity. Statistical significance was assumed at $p < 0.05$.

Results

The final sample size of vaccinated individuals was 100, of which the majority (73%) received Covishield, 26% received Covaxin, and the remaining (1%) received Sputnik-V. The majority received both doses of vaccine (77%). Among the participants, ages ranged from 18 - 45

years with a mean of 22 years. Most respondents were students (74%) and belonged to the upper socio-economic class (89%). Table I shows the baseline characteristics of the study population. The vast majority of participants were disease-free, although 4% of them had a chronic skin condition, and 2% each had thyroid disease, PCOS, and tuberculosis. 13% of the participants used the barrier method of contraception. Participants who were smokers were only 1%.

Table I: Baseline characteristics of study population.

Characteristics	Study population (n = 100)	
	Number	%
AGE (years)		
< 20	24	(24)
20 - 30	61	(61)
> 30	15	(15)
Religion		
Hindu	95	(95)
Muslim	2	(2)
Others	3	(3)
Occupation		
Housewife	14	(14)
Student	74	(74)
Professional	11	(11)
None	1	(1)
Marital status		
Unmarried	82	(82)
Married	18	(18)
Socio-economic status		
Upper class	73	(73)
Upper middle class	16	(16)
Middle class	9	(9)
Lower middle class	1	(1)
Lower class	1	(1)
Parity		
0	89	(89)
1	4	(4)
> = 2	7	(7)
Name of vaccine		
Covishield	73	(73)
Covaxin	26	(26)
Sputnik-V	1	(1)
Status		
Partially vaccinated (single dose)	23	(23)
Fully Vaccinated (double dose)	77	(77)

Five per cent of women experienced heavy bleeding (95% CI 1.6 - 11.2), 31% of women (95% CI 22.1 - 41) reported blood clots during menstruation and, 3 women had periods lasting for more than 1 week. Additionally, moderate-to-severe menstrual pain was experienced by 36% of women. The questionnaire also contained a question concerning the predictability of the start date of the period, which was used to assess menstrual irregularity. Six per cent of participants (95% CI 2.2 to 12.6) could not predict the start date of the periods at all; in 57%, it was somewhat predictable, and in the remaining 37%, it was completely predictable (Fig. 2).

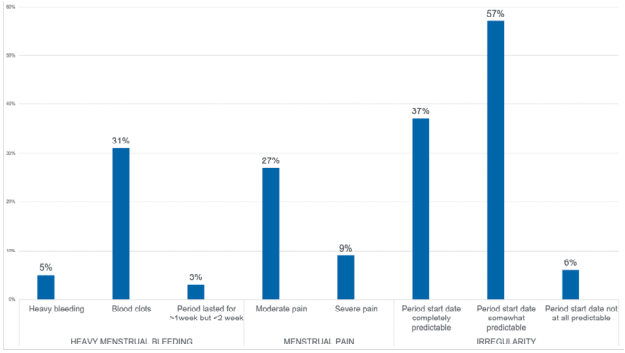

Fig. 2: *Percentages of heavy menstrual bleeding, menstrual pain, and irregularity post-COVID-19 vaccination.*

The univariable analysis showed that heavy bleeding and menstrual irregularity were reported after both the first and second dose of vaccination but it was not statistically associated with any particular dose. (p = 0.587 for reported heavy bleeding, p = 0.217 for blood clots, and p = 0.133 for irregularity) (Fig. 3). Heavy bleeding, the passage of blood clots, or menstrual irregularity did not have any association with the brand of vaccine administered, i.e., Covishield or Covaxin (p = 0.158 for heavy bleeding, p = 0.575 for blood clots, and p = 0.336 for menstrual irregularity). Both vaccine brands were associated with menstrual abnormalities, indicating that neither adenovirus vector nor inactivated virus strategy is specifically linked to these changes. For this analysis, a respondent who received Sputnik-V (n = 1) was excluded (Fig. 4).

Participants who had a diagnosis of a medical disorder did not differ in experiencing menstrual abnormalities from those who were medically healthy. No association was found between reported blood clots in periods (p = 0.678) or irregularity (p = 0.441) and long-standing history of medical disorders such as Tuberculosis, thyroid disorder, chronic skin condition, or PCOS. BMI was not associated with heavy bleeding or menstrual irregularity. On an independent t-test, it was found that BMI values of women with heavy bleeding or menstrual irregularity and those who did not have heavy bleeding or menstrual irregularity

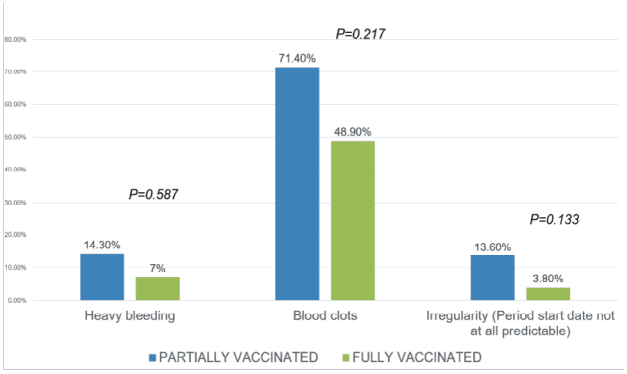

Fig. 3: *Comparison of menstrual pattern (heavy bleeding, blood clots and irregularity) in single dose and doubled dose vaccinated individuals.*

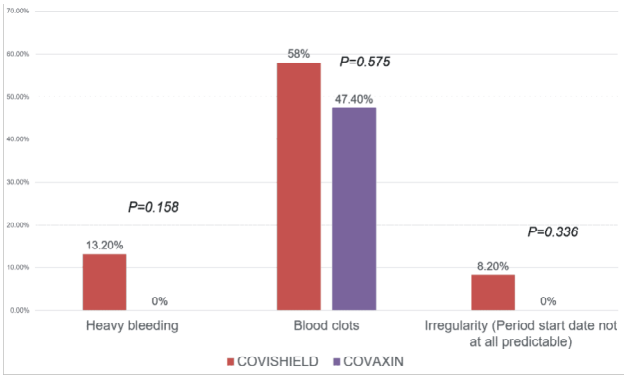

Fig. 4: *Comparison of menstrual pattern (heavy bleeding, blood clots and irregularity) in Covishield and Covaxin.*

were not statistically different (p = 0.398 for heavy bleeding and p = 0.136 for menstrual irregularity).

In response to a question concerning whether or not they would refrain from advising other women to get the vaccine in light of any menstrual abnormalities (if observed), we discovered that 4% of respondents had done so. This showed that there was some amount of vaccine hesitancy in the general population.

Discussion

This study, done among 100 women in India, found that among vaccinated women of reproductive age who had no change in the pattern or flow of their periods prior to vaccination, 5% reported heavy bleeding, one in 3 women passed blood clots during menses, and 6% were unable to predict the start of their periods one month after their last dose of vaccination.

We found that heavy bleeding and menstrual irregularity were reported after both the first and second dose of the vaccine. Here, menstruation was assessed for one month after the last dose of the vaccine. There is a possibility that findings reported after the second dose might be a result of the first dose of the vaccine as seen in a UK-based case-control study where 20% reported any changes to their menstrual cycle up to 4 months after receiving their first injection[6]. In this sample, we did not find any association of heavy bleeding or menstrual irregularity with any particular brand of vaccine. A similar finding was observed in a study done in the UK by Male where the brand of vaccine was not associated with differences in timing or flow of the next period[19]. A study done in the Middle East and North Africa also showed similar results[10].

In the present study, people who had a diagnosis of medical disorder (Tuberculosis, thyroid disorder, PCOS, or chronic skin condition) did not differ in experiencing menstrual abnormalities from those who were medically healthy. Our findings are consistent with a recent study done in the MENA region where thyroid disorders, PCOS, and symptoms of menstrual abnormalities were not associated[10]. Though, it is difficult to propose this considering the small number of participants who had been diagnosed with medical disorders. The mechanism behind these post-vaccination menstrual changes is still unknown. However, it has been proposed that endocrine abnormalities and immune-mediated mechanisms are responsible for this[4,17]. Participants who had previously contracted SARS-CoV-2 infection were excluded from our study, therefore the results that are reported cannot possibly be the consequence of an immune response to the disease, as was the case in a study where odds of reporting any changes in the menstrual cycle were increased due to prior COVID-19 infection[6].

The strength of this study is that it is a pioneer study, done in India, assessing menstrual pattern post-COVID-19 vaccination. An online questionnaire was used instead of face-to-face interview, in light of the ongoing pandemic situation, to limit transmission of the virus. The limitations are that it is retrospective in nature, with recall and selection bias, and small sample size. A control group could have been taken to compare the findings that were observed. Assessment of menstrual pattern was only done for one-month post-vaccination although further follow-up is desirable. Prospective studies recruiting a large sample and longer follow-up are needed.

Conclusion

In our study, heavy bleeding and menstrual irregularity were commonly present following COVID-19 vaccination. It opens a new domain of counselling women prior to vaccination about menstrual disturbances so that they can be more receptive and prepared for the same. The

mechanism underlying the potential effects of the COVID-19 vaccine on menstruation needs to be studied. Larger prospective studies with extended follow-up are required to fully understand the problem.

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ORIGINAL ARTICLE

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Enlarged Perivascular Spaces in Basal Ganglia: A Potential Early Imaging Marker of Hypertension induced Cerebral Small Vessel Disease

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Abstract

Background: Cerebral Small vessel disease (cSVD) is a common cause of cognitive decline. In this study we aimed to ascertain if enlarged Perivascular spaces (ePVS) in basal ganglia are a potential independent biomarker of hypertension induced cSVD.

Methods: The study participants comprised of patients between 40 and 70 years of age referred for Brain MRI. Patients with hypertension ≥ eight years formed the case group. Non-hypertensive patients were selected as controls. Subjects with (i) carotid artery plaques, more than 50% stenosis of carotid artery on either side (ii) micro/macro haemorrhage and intra cranial atherosclerosis were excluded. 2D FLAIR sequence was used for rating of white matter hyperintesities (WMH) and differentiating lacunar infarcts from enlarged PVS. A 3D FIESTA C was acquired to clearly delineate PVS. Sensitivity, specificity, PPV, NPV and AUC of PVS and WMH for predicting lacunar infarct was calculated in overall study subjects.

Results: 61 hypertensives and 59 non-hypertensives, fulfilled the eligibility criteria. Lacunar infarct was present in 22 (36.07%) hypertensives. WMH was present in 13 (21.31%) cases and six (10.17%) controls. ePVS was seen in 56 (91.80%) cases and 13 (22.03%) controls. There was 100% sensitivity of ePVS in predicting lacunar infarct among hypertensives. The AUC of ePVS in predicting lacunar infarct was significantly more than that of WMH. In overall study subjects maximum AUC was seen in the 41 to 50 years age group.

Conclusion: Enlarged Peri vascular spaces should not simply be overlooked as an inevitable consequence of aging. ePVS in basal ganglia could be an early and independent marker of hypertension induced Cerebral Small Vessel Disease.

Key words: Enlarged Perivascular spaces, White Matter Hyperintensity, Cerebral Small Vessel Disease, Lacunar infarct.

Introduction

Due to mild clinical symptoms at the onset, cerebral small vessel disease (cSVD) is frequently a neglected cause of stroke. However, it remains one of the leading causes of cognitive decline in the elderly population[1,2]. As there is no consensus on clinical criteria for cSVD, neuroimaging has become an important diagnostic tool for both symptomatic and silent cSVD. Hypertension remains the commonest and most important risk factor for cSVD[1,4-6]. Peri vascular spaces (PVS) are interstitial fluid-filled spaces surrounding the penetrating vessels in the brain. Long-term hypertension can cause endothelial damage with altered blood brain barrier leading to leakage of plasma components into the vessel wall resulting in enlarged PVS (ePVS)[3,7]. Studies have shown that ePVS often co-exist with white matter hyper intensities (WMH) and lacunes, which are themselves associated with hypertension[2]. ePVS have only recently been recognised as a marker of cSVD. Lacunar infarcts have long been established as a clinical and imaging prototype of cSVD due to hypertension[8]. WMH of presumed vascular origin, have been considered the most widely accepted MRI marker of cSVD in our set up and hardly any data is available on PVS. In this study we aimed to ascertain if ePVS in basal ganglia could be a potential independent imaging marker of hypertension induced cSVD.

Material and Methods

Study design and eligibility

The study population comprised of patients between forty and seventy years of age, referred to the Radiology Department at our hospital for Brain MRI between August 2019 and Mar 2021. The study participants comprised of patients with a history of hypertension for eight or more years selected as cases, and patients in the same age group with no history of hypertension, selected as controls for this comparative cross sectional study. Relevant clinical and imaging data was obtained and recorded from all recruited

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participants. Hypertension was defined as repeated BP ≥ 140/90 mmHg or on antihypertensive medication[9].

Presence of other risk factors

Presence of diabetes, defined as Fasting Plasma Glucose ≥ 126 mg/dl or 2 hours Post-Prandial Plasma glucose ≥ 200 mg/dl or HbA1c ≥ 6.5%, was recorded[10].

Presence of dyslipidaemia was defined as per European Society of Cardiology and European Atherosclerosis Society guidelines[11].

Presence of history of smoking, elicited or volunteered, both current and past, irrespective of the form and frequency of smoking as was recorded.

Pre-imaging exclusion

Study participants with more than 50% carotid artery stenosis or carotid wall plaques on any side detected on Sono-Colour Doppler study/CT Angiography and ii) those with Atrial Fibrillation/valve prosthesis, which could be a likely source of cardiac emboli, were excluded.

Imaging procedure

After obtaining informed consent, brain image acquisition of all study participants was carried-out on 3 Tesla MR imaging scanner (Discovery 750; GE Healthcare, Milwaukee, Wisconsin) using a 32 channel phased array head coil. The essential sequences for all study participants included: 2D Axial T1W, 2D Axial T2W, 2D Axial T2 FLAIR, 2D Axial DWI, 2D Axial SWI and 3D TOF Angiography of Brain.

Post-imaging exclusion

Study participants showing previous or current macro/micro haemorrhages on SWI, more likely due to amyloidopathy were not included.

Study participants with atherosclerotic changes in MCA, seen as narrowing or stenosis on 3D TOF MR angiography were excluded[12].

MRI acquisition for WMH

FLAIR images were acquired using the same parameters for all study participants: T R 12,000 ms, TE 140 ms, TI 2,500 ms; flip angle 150 degree; slice thickness 4 mm; interslice gap 1 mm; FOV 210 x 210 mm; matrix 352 x 352; acquisition time 2 min 36 secs.

Lacunar infarcts were defined as infarcts ≥ 20 mm on axial section the territory of a single perforating artery. Number and location of lacunar infarcts was recorded. Recent lacunar infarcts were differentiated from previous infarcts on DWI imaging. Previous lacunar infarcts ≥ 15 mm, with CSF signal intensity on T1W and T2 W sequence and hyperintense rim on FLAIR sequence were defined as lacunes[13].

WMH scoring

Deep white matter hyperintensity, 13 mm or more from ventricular surface and within 4 mm from corticomedullary junction was recorded[14].

We used a simple modified Fazekas rating scale for grading WMH[15].

- Grade 0: WMH not visualised in the deep white matter.
- Grade 1: punctate lesions in the deep white matter with a maximum diameter of 9 mm for a single lesion and of 20 mm for grouped lesions.
- Grade 2: early confluent lesions of 10 - 20 mm single lesions and >20 mm grouped lesions in any diameter, and no more than connecting bridges between the individual lesions.
- Grade 3: single lesions or confluent areas of hyperintensity of ≥ 20 mm in any diameter.

WMH contiguous to the ventricular surface resulting from CSF leakage and irregular periventricular WMH likely due to haemodynamic insufficiency was excluded from the scoring.

MRI acquisition for peri-vascular spaces

For study participants with visualised PVS in Basal Ganglia seen on T2 W sequence an additional 3D Fast Imaging Employing Steady State Acquisition with Cycled Phases (Fiesta C) sequence was acquired using the following parameters: TR 8 ms; TE 2.4 ms; matrix 300 x 300, NEX 87, flip angle 55 degree, slice thickness 6 mm, inter slice gap. 2 mm. Slice per SLAB 120, Bandwidth 62.5 Khz, slice oversampling: 6.7, FOV 230 mm matrix 384 × 384, voxel size: 0.5 × 0.5 × 0.6 mm. Acquisition time 4 min 10 secs. To reduce scan time and motion artefacts, sections were limited to region of Basal ganglia.

PVS scoring

Peri vascular spaces was defined as round or linear fluid filled spaces with CSF signal intensity, that followed the typical course of the lateral striate arteries[13]. Number of ePVS was recorded at substantia innominata at the infraputaminal level, section of ventral putamen, and the dorsal putamen at level of caudate on the basis of scoring by Patankar *et al*[7], ePVS was rated as grade 0 to 3.

- Grade 0: five or less than five ePVS on either side in infraputaminal section.

- Grade 1: five or more than five ePVS on either side in infraputaminal section.
- Grade 2: five or more ePVS on either side in ventral putamen.
- Grade 3: five or more ePVS in either caudate.

Two raters (MKM and CP with ten and eight years experience in neuroimaging independently performed the scoring for lacunar infarcts,WMH and ePVS. Both raters repeated the scoring sessions with order of subjects changed to ensure reliability and reduce bias.

Statistical analysis

The following statistical tests were applied for the results:

1. The association of the variables which were quantitative in nature were analysed using Mann-Whitney Test.
2. The comparison of the variables which were qualitative in nature was analysed using Chi-Square test/Fisher's Exact test.
3. Sensitivity, specificity, positive predictive value and negative predictive value of PVS and WMH for predicting lacunar infarct was calculated.
4. Univariate logistic regression was used to find predictors of lacunar infarct. For statistical significance, p value of less than 0.05 was considered as significant.A weighted Cohen test was used to quantify the level of inter rater and intra rater agreement for lacunar infarcts, WMH and PVS. The values more than > .81 defined excellent agreement.

The study was conducted in accordance with guidelines of our hospital ethics committee.

Results

Sixty one hypertensive and 59 non-hypertensive patients (control group) fulfilled the inclusion criteria. The distribution of clinico-demographic characteristics of study subjects by age groups, gender and other risk factors is shown in Table I.

Score of Lacunar Infarcts, WMH and ePVS

Cohens' kappa value demonstrated excellent intra-rater agreement between the two scoring sessions for each rater for lacunar infarcts,WMH and ePVS.

Lacunar infarcts were noted in 22 (36.07%) hypertensive patients (p < .0001, Fisher Exact test). Most lacunar infarcts were noted in the thalamus and periventricular white matter. Cohens' kappa value for inter-rater agreement was .93 for lacunar infarct indicating excellent agreement between raters.

Table I: Comparison of Socio-demographic characteristics between cases and controls.

Socio-demographic characteristics	Case (n = 61)	Control (n = 59)	Total	p value	Test performed
Age (years)					
41 - 50	21 (34.43%)	19 (32.20%)	40 (33.33%)	0.943	Chi square test, 0.117
51 - 60	20 (32.79%)	21 (35.59%)	41 (34.17%)		
61 - 70	20 (32.79%)	19 (32.20%)	39 (32.50%)		
Mean ± SD	55.18 ± 8.49	55.95 ± 7.78	55.56 ± 8.12	0.667	Mann Whitney test; 1717.50
Median (IQR)	54 (48 - 63)	58 (48.5 - 62.5)	56 (48 - 63)		
Range	41 - 70	42 - 68	41 - 70		
Gender					
Female	12 (19.67%)	11 (18.64%)	23 (19.17%)	0.886	Chi square test, 0.02
Male	49 (80.33%)	48 (81.36%)	97 (80.83%)		

WMH was present in 13 (21.31%) cases and six (10.17%) controls (p = 0.095, chi square test). Among cases the WMH emerged and progressed in higher age groups. It was not seen in the 41 to 50 years age group. WMH was noted in two (10%) cases in the 51 to 60 years age group and 11 (55%) in the 61 to 70 years age group. (p < .0001, Fisher's Exact test). Grade 1 WMH was seen in two (10%) cases in the 51 to 60 years age group and four (20%) cases in the 61 to 70 years age group. Grade 2 WMH was seen in one (5%) case in the 51 to 60 years age group, three (15%) cases in the 61 to 70 years age group. Grade 3 WMH was seen in five (25%) cases in 60 to 70 years age group. Cohens' kappa value for inter-rater agreement was .89 for WMH, indicating excellent agreement.

Imaging characteristics of PVS on FIESTA-C

PVS in basal ganglia were clearly seen on 3D-FIESTA C (Fig. 1b, Fig. 2b). In the coronal plane, PVS were semi-curved tubular structures oriented upward initially and then curved medially to the floor of the lateral ventricle, following the course of the lateral striate arteries (Fig.1b). Striate arteries were noted within the larger PVS (Fig. 3a, 3b). Some PVS were irregular in shape and size with pencil-tip like configuration of tubules (Fig. 4a, 4c). Lacunar infarcts were clearly seen separate from the ePVS (Fig. 4b). The PVS were more prominent in the infra-putaminal section (Fig. 2c). Cohens' kappa value for interrater agreement was .87 for scoring of ePVS, indicating excellent agreement.

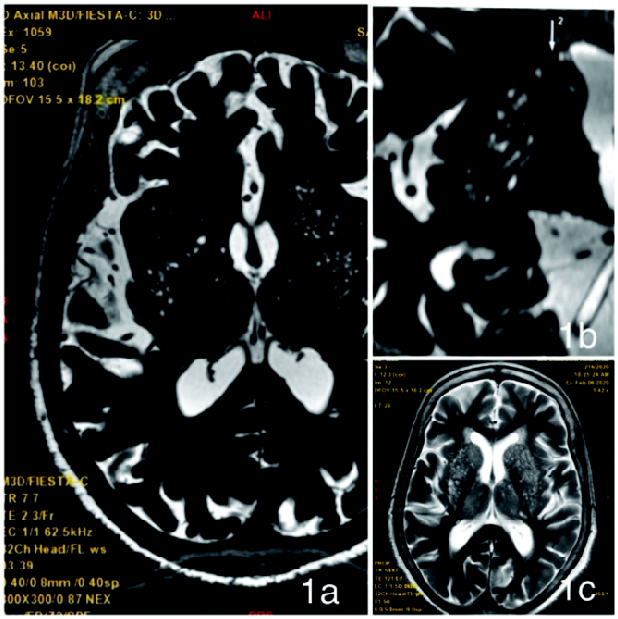

Fig. 1: *69-year-old male with hypertension, A. 3D Axial FIESTA-C image shows multiple ePVS in bilateral basal ganglia. (more than 5 spaces seen in right caudate scored as grade 3), B. 3D coronal FIESTA-C image shows multiple curvilinear spaces following the trajectory of lenticulostriate arteries. C. 3D axial image shows multiple ePVS in bilateral infraputaminal section.*

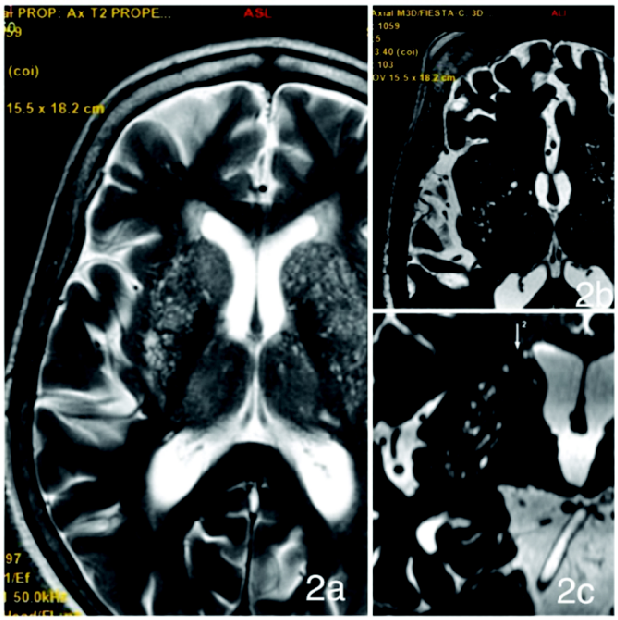

Fig. 2: *70-year-old female with history of hypertension, A. Axial T2 image shows multiple enlarged Perivascular spaces (ePVS) in basal ganglia with Swiss cheese striatum. The margins of PVS are blurred B. 3D Axial FIESTA-C image shows sharply delineated PVS C. 3D Coronal FIESTA-C image shows PVS following curvilinear path reaching up to right caudate (less than five ePVS in caudate scored as grade 2).*

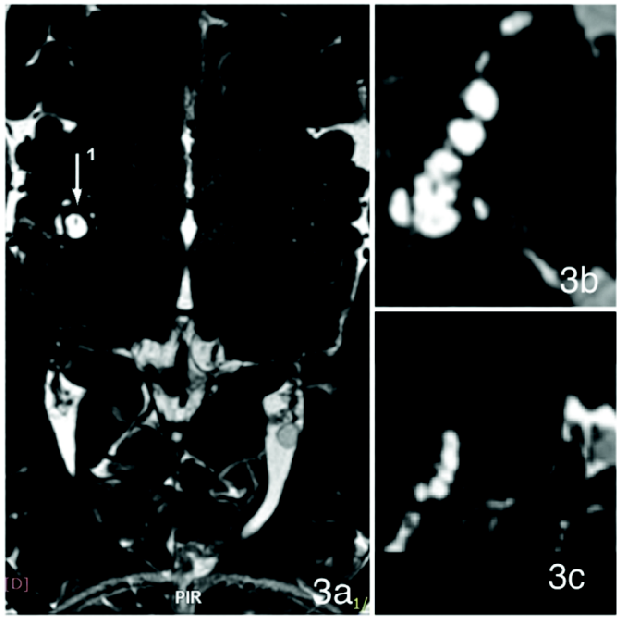

Fig. 3: *45-year-old male with hypertension, A. 3D Axial FIESTA-C image shows enlarged round ePVS with central dot (lenticulostriate artery) in right substantia innominata, B. 3D Coronal FIESTA-C image shows dilated beeded ePVS on the right surrounding the lenticulostriate artery, seen reaching just short of the caudate. C. 3D Saggital FIESTA-C image shows corrugated tube appearance of ePVS.*

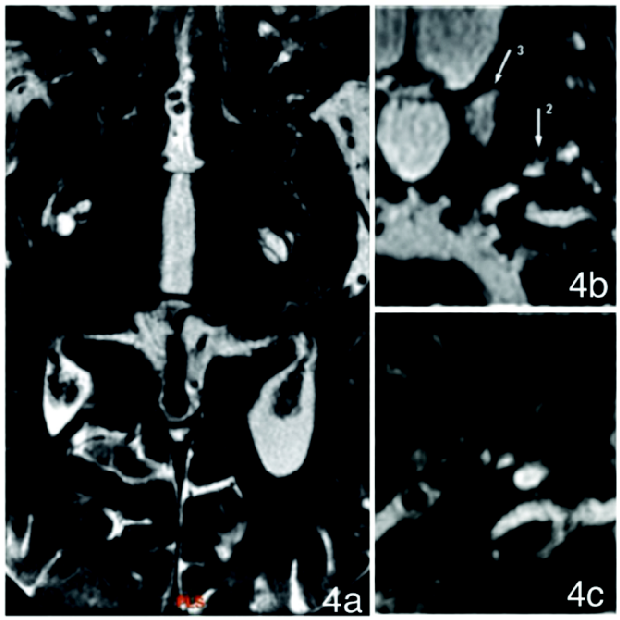

Fig. 4: *65-year-old male hypertensive, A. 3D Axial FIESTA-C image shows Irregular ePVS seen in bilateral infraputaminal section B. typical pencil tip end seen on left side. Image shows tubular CSF intensity C. 3D coronal FIESTA-C image shows wedge shaped Lacunar infarct in left thalamus, separate from the PVS.*

Comparison of WMH and ePVS in study subjects

ePVS was seen in 56 (91.8%) cases and 13 (22.03%) controls ($p < .0001$, Chi square test).

Grade 0 ePVS was seen in three (4.92%) cases and 44 (74.58%) controls ($p < .0001$, Chi square test).

In all age groups among hypertensives, the number of cases with ePVS were significantly more than number of cases showing WMH ($p < .0001$, Fisher's Exact test).

Results of data analysis

Table 2:- Sensitivity, specificity, positive predictive value and negative predictive value of PVS and WMH for predicting lacunar infarct in total study subjects.

Lacunar infarct	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
PVS	100% (84.56% to 100.00%)	52.04% (41.71% 62.24%)	0.76 (0.67 to to 0.83)	31.88% (21.17% to 44.21%)	100% (93.02% to 100.00%
White matter hyperintensity	31.82% (13.86% to 54.87%)	87.76% (79.59% to 93.51%)	0.6 (0.50 to 0.69)	36.84% (16.29% to 61.64%)	85.15% (76.69% to 91.44%)
p value	**0.016**	**< 0.0001**	–	–	–

There was 100% sensitivity of PVS in predicting lacunar infarct in hypertensives across all age groups, with maximum diagnostic accuracy seen in the 41 to 50 years age group (Table III).

Table III: Sensitivity, specificity, positive predictive value and negative predictive value of PVS and WMH for predicting lacunar infarct in hypertensive in age group 41 - 50 years.

Lacunar infarct	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
PVS	100% (15.81% to 100.00%)	26.32% (9.15% to 51.20%)	0.63 (0.40 to 0.83)	12.5% (1.55% to 38.35%)	100% (47.82% to 100.00%)
White matter hyper intensity	0% (0.00% to 84.19%)	100% (82.35% to 100.00%)	0.5 (0.28 to 0.72)	–	90.48% (69.62% to 98.83%)
p value	–	**0.0001**	–	–	–

In the 51 to 60 years age group, the diagnostic accuracy (AUC .50, PPV 40%) of WMH to predict lacunar infarct was marginally better than that of ePVS (AUC .52, PPV 50 %).

In the 61 to 70 years age group diagnostic accuracy of WMH (AUC .44, PPV 54.55%) was less than that of PVS (AUC .05, PPV 60%). ePVS showed highest odds ratio among all the predictors of lacunar infarct (Table IV).

Table IV: Univariate logistic regression to find out predictors of lacunar infarct.

Variable	Beta co-efficient	Standard error	p value	Odds ratio	Odds ratio Lower bound (95%)	Odds ratio Upper bound (95%)
Age (years)	0.118	0.038	**0.002**	1.126	1.045	1.213
Gender						
Female				1.000		
Male	0.104	0.675	0.878	1.109	0.295	4.166
PVS	1.970	1.641	0.230	7.174	0.288	178.900
White matter hyperintensity	0.914	0.637	0.151	2.494	0.716	8.689
Smokers	0.119	0.780	0.879	1.126	0.244	5.189
Diabetes	0.627	0.864	0.468	1.872	0.344	10.182
Dyslipidaemia	0.348	0.813	0.669	1.416	0.288	6.971

Discussion

The vascular 'Centrencephalon', the phylogenetically primitive part in the basal region of the brain is perfused by short straight arteries that transmit high pressure over a short distance directly from the large arteries to end arterioles. The present study centres around this region where true lacunar infarcts occur due to hypertension induced small vessel disease[16]. Study participants with large artery atherosclerosis and cardiac conditions that were likely sources of embolism were excluded from the study. Study subjects with focal pathology in the parent MCA that can obstruct the orifices of the perforating arteries and those with macro/micro haemorrhages, more likely caused due to amyloidopathy were also left out from the study to include cases with true lacunar infarcts caused by hypertension induced small vessel disease[12]. The strict eligibility criteria for inclusion was a major strength of this study.

Lacunar infarct was present only in cases and absent in controls which confirmed the strong association of lacunar infarct with hypertension. Lacunar infarct being a prototypical and quantifiable imaging feature determined the presence of cSVD in our study[8]. This was another strong point of our study as most other studies have considered the highly subjective clinical manifestation of cognitive impairment for presence of cSVD[7,17,18]. Only Deep WMH present in the centrum semiovale, fed by arterioles prone to arteriosclerosis was included in the scoring of WMH, as the Juxta cortical white matter having a dual blood supply is unlikely to be susceptible to cSVD[13].

Late emergence and progression of WMH grade was noted in the 50 to 70 years age bracket. WMH was not seen exclusively in hypertensives. Other studies have also shown WMH to be multifactorial in aging individuals[17].

Lateral striate arteries are very thin calibre arteries, that arise from the horizontal segment of the MCA and enter the substantia innominata through the anterior perforated substance[16]. These then ascend and turn medially across

the putamen and internal capsule to reach the border zone of corona radiata via the caudate. Visualisation of PVS was clearly improved by use of FIESTA C, which remained a major strength of our study. Used in the 3D mode, it provided high spatial resolution and high signal from the PVS which were seen as CSF intensity tubular structures that followed the orientation of the lateral striate arteries on coronal and saggital images and could easily be distinguished from lacunes. Striate arteries seen within few of the perivascular spaces further helped in differentiating the larger spaces from lacunes.

The results of this study supported the notion that ePVS in basal ganglia are an early and independent MRI marker of cSVD. ePVS was seen in 56 (91.8%) cases and 13 (22.03%) controls ($p < .0001$, Chi square test). A strong association of ePVS with hypertensives was seen in our study ($p < .0001$).

Across all age groups, the number of cases with ePVS were significantly more than number of cases showing WMH ($p < .0001$, Fisher's Exact test). This difference was more significant in the 41 to 50 years age group. In the 60 to 70 years age group, the difference somewhat balanced out and became minimal. Hurford *et al* found a strong relationship between basal ganglia PVS severity and hypertensive arteriopathy of cSVD[18].

The abrupt change in caliber from large arteries and perpendicular orientation of perforating arteries renders them susceptible to the pulse pressure. A double meningeal wrapping of striate arteries compared to single coat in most other cerebral vessels which further affects their drainage with early visualisation of PVS in this region[19]. In our study, PVS were most prominent in the substantia innominata. The perforating end arteries in this region are susceptible even to the high impact of normal blood pressure as seen by presence of grade 0 (less than five) ePVS in significant number of controls.

Our study results showed that diagnostic accuracy of PVS in predicting lacunar infarct was significantly higher than that of WMH in overall study subjects confirming ePVS as a useful imaging marker of cSVD.

Hansen *et al*[17] also found PVS dilation to be a useful biomarker of SVD. PVS appeared more specific and retained greater discriminative power than WMH to distinguish patients with vascular dementia from healthy individuals.

In the Northern Manhattan study[20], stroke free participants were followed-up for an average of 9 ± 2 years. Those with higher ePVS scores on initial MRI had higher incidence of vascular complications especially if their pulse pressure or systolic blood pressure was elevated. Study performed by Loos *et al*[21] showed extensive Basal Ganglia PVS on MRI in 118 patients with lacunar stroke was associated with progression of WMH on follow-up MRI after two years. However, presence of WMH at baseline remained an important determinant of further progression of WMH in cSVD.

Yang *et al*[22] found 24 hour BP variability to be associated with lacunar infarctions and WMH. Ambulatory BP was also independently associated with the degree of ePVS in basal ganglia. In a study by Klarenbeek *et al*[23], higher day time ambulatory BP level was found to be associated with enlarged PVS in the basal ganglia. This association was independent of the presence of WMH and lacunar infarcts.

Our cases comprised of patients with history of long standing hypertension or hypertensives with non compliance to drug therapy. We did not correlate ePVS with the ambulatory BP of our study subjects as in studies by Yang *et al*[22] and Klarenbeek *et al*[23]. This was another limitation of our study.

We selected non-hypertensive patients in the same age range as the cases to form a non-hypertensive control group for comparative analysis which added statistical power to our study.

Age, gender, diabetes, dyslipidaemia and smoking which could be confounding variables were taken care of both in the design stage by matching and univariate logistic regression in the analysis stage of the study. A high odds ratio showed strong association between PVS and lacunar infarct in hypertensives in the present study without a wait for a long latency period needed in cohort studies[20,21]. However, true causal relationship between ePVS and and cSVD could not be established as in the follow-up studies which could be another limitation of our study.

Conclusion

Peri-vascular spaces in the brain should not simply be overlooked as an inevitable consequence of aging. Visual estimation of the number and distribution of PVS on MRI has the potential to be an early and independent imaging marker of Cerebral Small Vessel Disease, a prevalent but often unrecognised disorder. ePVS in basal ganglia could be utilised in clinical practise to slow down and if possible halt the progression of hypertension induced cSVD before it reaches the stage of cognitive decline.

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ORIGINAL ARTICLE

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Clinico-Laboratory Profile of Deaths in COVID-19 Positive Patients: A Retrospective Study from a Tertiary Care Hospital in India

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Abstract

Introduction: COVID-19 infections have caused millions of deaths around the world. This study gives a detailed insight into the demographic and clinico-laboratory profile of deaths among COVID-19 patients over a period of one year admitted in a tertiary care COVID hospital.

Methodology: In this retrospective observational study, medical records of admitted COVID-19 positive deaths in adult patients over a period of one year from 1st April 2020 to 31st March 2021 were retrieved. The data includes the co-morbidities present, symptoms, duration of symptoms to admission time, duration of hospital stay, clinical examination findings and laboratory reports.

Results: Medical records of 445 COVID-19 positive deaths were studied. The mean age was 55 ± 18.49 years and the majority were in the age group of 41 - 60 years. Around 61% were males and 39% were females. Diabetes and hypertension were the most common co-morbidities present. The average duration of symptoms before hospitalization was 5.26 ± 4.5 days. Breathlessness was the most common presenting symptom. The average duration of stay in the hospital was 6.73 ± 7.18 days. The serum ferritin, C-reactive protein (CRP), serum lactate dehydrogenase (LDH) and D-dimer were increased in the majority of patients.

Conclusion: An early admission and optimal management during the initial period of COVID-19 disease is critical and may help in decreasing the mortality. The raised CRP, high serum LDH and serum ferritin can be used as predictors of poor prognosis.

Key words: COVID-19, prognostic markers, clinical profile in COVID-19, laboratory profile in COVID-19, deaths in COVID.

Introduction

The novel corona virus 2019-nCoV or COVID-19 has infected people all over the world in a short span of time. On March 11, 2020, WHO declared COVID-19 as a pandemic. There have been about 609 million confirmed COVID-19 cases with over 6.5 million deaths globally[1]. Around 5.2 lakh deaths occurred due to this pandemic in India, and about 26,499 deaths have been reported in the capital city of New Delhi[2]. COVID-19 has a varied spectrum of presentation ranging from asymptomatic cases to severe pneumonia to acute respiratory distress syndrome (ARDS) with multiple organ failure and death. In a study from China by Wang K *et al*, the major cause of death in COVID-19 patients was found to be acute respiratory failure and sepsis[3]. On one hand, the case fatality ratio (CFR) has been quite high in some countries like Yemen (18%), Sudan (7.84%), Syria (5.53%), Somalia (5%), and Mexico (4.7%), on the other some countries have very low CFR such as Bhutan (0.03%), Singapore (0.09%), and New Zealand (0.11%). Among the countries with maximum confirmed cases, India has a CFR of about 1.1% compared to Russia (1.88%), Brazil (1.98%), USA (1.1%) and global CFR of 1%[1]. This variation in mortality rates has been postulated to be due to various factors such as racial differences, population age composition, health facilities availability, hospitalisation criteria and local administrative policies[4].

It has been observed that lymphopenia, high NLR (Neutrophil lymphocyte ratio), raised D-dimer and high C-reactive protein (CRP) are poor prognostic factors in COVID -19[5]. However, there is a relative lack of literature on demographic, clinical and other laboratory factors associated with the disease severity and mortality in COVID-19. Hence, the present study was conducted to identify the same.

Methodology

This retrospective observational study was conducted at Department of Medicine of a dedicated tertiary level COVID-19 care hospital of New Delhi, India. The medical records of COVID-19 positive deaths during the period of one year from 1st April 2020 to 31st March 2021 were retrieved after obtaining Institutional Ethics Committee approval. All adult patients (>18 years of age) who were admitted and died with confirmed COVID-19 infection [confirmed by

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positive reverse transcriptase polymerase chain reaction (RTPCR) or cartridge based nucleic acid amplification test (CBNAAT) or rapid antigen test (RAT) of nasopharyngeal/ oropharyngeal swab] were included in the study. The data including age, gender, co-morbidities, duration of symptoms, duration of hospital stay, clinical examination findings, laboratory reports and treatment given (as mentioned in case sheets) was recorded as per the study proforma.

Statistical Package for Social Sciences (SPSS) version 16 (Chicago, USA) software was used for statistical analysis. All quantitative variables were expressed as Mean ± Standard Deviation and Median. Qualitative variables were expressed as proportion. The Cox proportion analysis was applied to identify the significant risk factors.

Results

Over a period of one year, from 1st April 2020 to 31st March 2021, around 1,843 patients with COVID-19 positive report were admitted in COVID wards/Intensive care units (ICU)/ high dependency units (HDU) of our hospital. The medical records of 445 COVID-19 positive deaths during this period were retrieved from the medical records section, and data collected from case records was subsequently analysed.

Among the 445 COVID-19 positive deaths observed, 271 (60.9%) were males and 174 (39.1%) were females. The mean age of the study population was 55 ± 14.89 years, ranging from 18 - 94 years. The majority (47.41%) were in the age group of 41 - 60 years (Table I).

Table I: Age-wise distribution of patients.

AGE (in years)	Males	Females	Total
≤25	5	11	16 (3.59%)
26-40	41	19	60 (13.48%)
41-60	126	85	211 (47.41%)
61-80	89	57	146 (32.80%)
≥81	10	2	12 (2.69%)
TOTAL	271	174	445

About 76% of the patients had one or more co-morbidities. Diabetes and hypertension were the most common co-morbidities observed, followed by coronary artery diseases (CAD) and chronic kidney disease (CKD) (Table II). The routine blood investigations and examination findings are presented in Table III.

The average duration of symptoms before hospitalisation was 5.26 ± 4.53 days, with the median time being 4 days.

Breathlessness was the most common presenting symptom, seen in 80% (356 of 445) of patients, followed by fever in 270 patients (60.6%) and cough in 196 patients (44%). Other common symptoms observed were vomiting, diarrhoea, sore throat and chest pain.

Table II: Distribution of patients based on the co-morbidities.

Co-morbidity	N (%)
Diabetes	188 (42.24)
Hypertension	176 (39.55)
Coronary Artery Disease (CAD)	61 (13.70)
Chronic Kidney disease (CKD)	53 (11.91)
Chronic obstructive Pulmonary Disease (COPD)/ Bronchial Asthma	25 (5.61)
Chronic liver disease (CLD)	16 (3.59)
Thyroid disorders	16 (3.59)
Others (HIV, CNS disorders, Rheumatic heart Disease, Malignancy, Rheumatoid arthritis, depression, etc.)	31 (6.96)

Table III: Routine blood investigation and examination findings

Parameter	N	Mean±SD
Systolic Blood Pressure (mmHg)	423	116.98 ± 29.97
Diastolic Blood Pressure (mmHg)	408	74.29 ± 15.22
Respiratory rate (per minute)	263	25.92 ± 6.88
Oxygen saturation at room air SpO_2(%)	366	80.48 ± 15.69
Haemoglobin (gm/dl)	380	11.11 ± 2.63
Total Leucocyte Count (per mm^3)	379	12338 ± 9343.54
Neutrophils (per mm^3)	318	83.11 ± 8.90
Lymphocytes (per mm^3)	247	13.39 ± 8.64
Neutrophil lymphocyte Ratio (NLR)	247	9.21 ± 8.6
Platelet count (lacs/mm^3)	376	2.02 ± 0.98
Random Blood sugar (mg/dl)	69	223.52 ± 144.27
Blood Urea (mg/dl)	379	80.71 ± 71.31
Serum Creatinine (mg/dl)	379	2.51 ± 3.53
Total Bilirubin (mg/dl)	295	1.25 ± 2.84
Aspartate transaminase (AST)(U/L)	367	105.86 ± 304.04
Alanine Transaminase (ALT) (U/L)	367	73.79 ± 245.94
Alkaline Phosphatase (ALP) (U/L)	315	131.40 ± 105.77
Serum Sodium (mmol/l)	378	138.07 ± 7.91
Serum Potassium (mmol/l)	376	4.39 ± 1.06

The average duration of stay in the hospital, (i.e., the time from hospital admission to death) was 6.73 ± 7.18 days.

Around 25% deaths occurred within the first 24 hours of admission and another 12% in the next 24 hours, (i.e., more than one-third people died within the first 48 hrs of admission) (Table IV). It was observed that elderly patients had shorter hospital stay and died early (Table V).

Table IV: Distribution of patients based on duration of hospital stay.

Duration of hospital stay	N (%)
Less than 12 hours	45 (10.11%)
12 - 24 hours	63 (14.15%)
24 - 48 hours	53 (11.9%)
3 - 5 days	86 (19.32%)
5 - 10 days	102 (22.92%)
11 - 14 days	42 (9.43%)
≥ 15 days	54 (12.13%)

Table V: Mean duration of hospital stay according to age.

Age (in years)	Mean duration of hospital stay (in days)
≤ 25	7.81
26 - 40	7.45
41 - 60	6.64
61 - 80	6.71
≥ 81	3.25

The mean NLR ratio (N = 247) was 9.21 ± 8.6. Around 59% patients (146/247) had NLR > 5.9 at the time of admission. The cut-off of NLR > 5.9 was taken as it was found to be associated with high in-hospital mortality in patients hospitalised for COVID-19 pneumonia in a validation analysis by Yildiz *et al*[6]. The mean serum ferritin level (N = 107) was 639.09 ± 562 ng/ml. (Normal value in males:18 - 464 ng/ml and females < 50 years: 6 - 137 ng/ml and females > 50 years: 11 - 264 ng/ml). 66% (71 of 107) patients had raised serum ferritin levels. 30.8% patients (33 of 107) had very high levels (greater than 1,000 ng/ml) of serum ferritin.

CRP levels were available for 101 patients. CRP was elevated (> 6 mg/l) in 83.16% (84 of 101) of patients with mean CRP being 104.45 ± 99.85 mg/l.

Similarly, serum lactate dehydrogenase (LDH) was raised (> 450 U/L) in 94.4% (135 of 143) of patients with mean value of 1077.75 ± 704.88 U/L. Twelve patients had serum LDH levels greater than 2,000 U/L.

35 of 37 patients had increased D-dimer level of more than 250 ng/ml. Of this, 9 patients had d-dimer levels more than 2,500 ng/dl. Highest level observed was 10,000 ng/dl.

Almost 70 per cent of patients (272/391) had bilateral infiltrates on chest X-ray. 31 of 391 (8%) had unilateral infiltrates/consolidation on X-ray and around 22% (88 of 391) had normal X-ray findings.

Invasive ventilation was given to 36% (162) patients. Non-invasive ventilation in the form of BI-PAP and high flow nasal cannula (HFNC) were applied to 8.8% (39) and 4.3% (19) of total patients respectively.

Steroids were given to 284 patients (63.8%) and low molecular weight heparin (LMWH) was given to 285 patients (64%). 22 patients received Remdesivir.

The Cox-Proportional Analysis showed that those with breathlessness had (hazard risk HR - 1.15, 95% confidence interval CI - 1.02 - 1.29) (p = 0.021) indicating higher mortality in those who had dyspnoea. The CRP levels had a (HR 1.002, 95% CI 1.001 - 1.003) (p = 0.003) indicating higher CRP levels were associated with increased mortality. Use of steroids and LMWH showed hazard risk of 0.083 (p < 0.001) and 0.084 (p < 0.001), respectively suggesting that their use was associated with less mortality.

Discussion

This is one of the largest study of COVID-19 related mortality spread over a period of one year.

The mortality among hospitalised patients was found to be higher as compared to overall mortality in the country, as most of the patients who were admitted to the hospital had moderate-to-severe COVID-19. Patients with mild COVID-19 were managed at home or COVID-19 care centres.

A male predominance was seen, with about 61% males among the total deaths. Asirvatham *et al* also reported a higher proportion of deaths (71%) among men[7]. The gender disparity in morbidity and mortality associated with COVID-19 is attributed to increased expression of angiotensin converting enzyme-2 (ACE-2) in lungs which is regulated by male sex hormones[8]. ACE-2 enzymes have been postulated in the pathogenesis of COVID-19. Viral interaction with the ACE-2 receptor causes endothelial injury and thus, increased risk of thrombosis. Another reason for higher mortality among males is due to the increased presence of risk factors such as smoking and alcohol use which is not common in Indian females. In a study by Li Y *et al*, X chromosome and sex hormones were attributed in providing innate and adaptive immunity to females and thus, lower mortality in women with COVID-19[9].

The mean age was 55 ± 14.89 years with a median of 55 years. In a similar study from Mumbai, the median age was

64.8 years[10]. Higher mortality rates were observed with advancing age due to poor lung functions, presence of co-morbidities and reduced innate and adaptive immune response.

The most common co-morbidities observed were diabetes and hypertension. Around 70% of patients had one or more co-morbidities. Previous studies have also shown that there is higher mortality in COVID-19 patients with co-morbidities compared to patients without any co-morbidities[11,12].

The median time duration from symptom onset to hospitalisation was 4 days which was same as reported by Asirvatham *et al* in their study[7]. In a similar study from Italy, the reported mean interval between symptom onset and hospitalisation was 3.6 ± 3.2 days[13].

Breathlessness was the most common symptom observed (in about 80% of patients) followed by fever in about 60% of patients. Tambe *et al* reported that breathlessness was the most common symptom observed followed by cough and fever[14].

The average duration of hospital stay, (i.e., period from hospital admission to death) was 6.73 days (median time duration was 5 days). In a study from China during the initial phase of the pandemic, Chen *et al* reported a median time of 16 days from disease onset to death[15]. However, a study from India reported the median time interval of 4 days[7].

It was observed that the duration of hospital stay was shorter for elderly population. The average duration of hospital stay was just 3.25 days for patients greater than 81 years of age as compared to 7.81 days for patients less than 25 years of age. Londhey *et al* also observed around 27% (209/763) deaths in first 24 hours and 52% deaths between 24 - 72 hours[10]. Goel *et al* also reported 33% deaths within first 72 hours of hospital admission[16]. A study from Sudan reported around 63.64% of deaths within first 24 hours of admission[17]. The early deaths post-hospitalisation may be due to delay in seeking healthcare. The reasons for this delay include ignorance of severity of disease, fear of sealing of the residential area, quarantine of other family members and lack of transport facilities because of nationwide lockdown. Infact, in many of these patients there was rapid deterioration of the disease due to so called "Happy Hypoxaemia syndrome" - a syndrome in which there is pronounced arterial hypoxaemia but the patient does not have proportionate signs and symptoms of respiratory distress[18]. These patients present late to hospital as they do not have any severe respiratory distress or dyspnoea despite low blood oxygenation.

High serum LDH levels were observed in 95% of patients, raised CRP levels in 83% and high levels of serum ferritin in 66%. About 31% had very high level of serum ferritin (levels > 1,000 ng/ml). A study from Saudi Arabia noted that patients who died due to COVID-19 had high levels of ferritin, lactate dehydrogenase, D-dimer, and erythrocyte sedimentation rate at admission and 24 hours prior to death[19]. Thus, high LDH levels, D dimer, ferritin and CRP can be considered as poor prognostic markers.

Conclusion

The study concludes that maximum deaths were in first 24 - 72 hours of hospital admission. Thus, early admission and better management with ICU care during the initial period of disease is critical and may help in decreasing the mortality. There should be increased awareness about the need of early hospital care, as soon as there is fall in oxygen saturation. It may cause a rapid deterioration in clinical condition and a timely intervention can affect the course of disease. Raised CRP, high serum LDH and serum ferritin levels can be used as predictors of poor outcome.

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ORIGINAL ARTICLE

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Treatment Outcomes of Isoniazid Monoresistant Pulmonary Tuberculosis Patients Under RNTCP

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Abstract

Background: Monoresistance to isoniazid (INH) is emerging as one of the major causes of treatment failure and increasing the probability of multidrug resistant TB (MDR TB). With the revised treatment regimen, possibility of better outcomes alongwith factors influencing it need further evaluation.

Methods: An observational, prospective study was conducted from 1st September 2017 to 31st May 2019 among 85 newly diagnosed INH monoresistant pulmonary tuerculosis (PTB) patients at RBIPMT, Delhi, fulfilling inclusion criteria.

Result: Out of the total 85 patients enrolled, 8 were cured, 53 completed their treatment, 13 were lost to follow-up, 6 patients died and 5 had a treatment failure. 14 (77.8%) were current smokers, 14 (51.8%) had a current history of alcohol intake, 18 (78.3%) were contacts of a TB case, 17 (92.9%) were household contacts of MDR TB, 21 (55.3%) were of lower socio-economic class, 12 (80%) had increased TLC, 8 (80.0%) had deranged LFT, 4 (80.0%) had deranged KFT , 17 (73.9%) had BM1 < 17.5 Kg/m^2, 16 (94.1%) had far advanced disease, 16 (64.0%) had cavity, and 15 (88.2%) had extensive disease on chest X-ray were significantly associated with unsuccessful outcome. 47 (90.4%) had sputum smear status < 1+ and at follow-up, increased weight, sputum smear negative status, minimal lesion on chest X-ray and improved symptoms were significantly associated with successful outcome.

Conclusion: Early detection, identification of risk factors and adequate treatment of INH monoresistant TB, along with appropriate lifestyle modifications were associated with better treatment outcomes.

Keywords: Pulmonary tuberculosis, drug resistance, and risk factors.

Introduction

TB remains an important public health problem due to the long period of 6 months or more of treatment, the potential of infectivity, risks of mortality, and crippling economonic impact[1].

INH and rifampicin are the main drugs for successful treatment of drug sensitive (DS) TB in short duration regimen (6 months to less than a year). Inability to prescribe INH due to resistance complicates the outcome, probably due to amplification of drug resistance[2]. Approximately 25% of MDR-TB suspects were found to have first-line mono- and poly-drug resistance under the revised national tuberculosis control program (RNTCP)[2].

Presence of various forms of resistance to first-line anti-TB drugs is an important cause for unfavorable outcomes including failure of treatment, amplification of drug resistance and death. Early identification of patterns of drug resistance, either by culture followed by drug susceptibility or by genotypic methods is important for deciding treatment regimen[3].

In 2017, among all cases of TB, the average global frequency of INH resistance without concurrent rifampicin resistance was 7.6% (95% CI 6.3% - 8.5%). In new and previously treated cases, the global averages were 7.1% (95% CI: 6.2 - 8.0%) and 7.9% (95% CI: 5.9 - 10%), respectively[1].

In March 2016, the Revised Technical and Operational guideline for Tuberculosis declared a new regimen for INH mono-resistant tuberculosis that included kanamycin, levofloxacin, rifampicin, ethambutol and pyrazinamide in the intensive phase for 3 - 6 months and followed by continuation phase of levofloxacin, rifampicin, ethambutol and pyrazinamide for 6 months[3]. WHO came up with treatment recommendations for scrapping of the injectable drug kanamycin altogether, due to the unacceptably high incidence of adverse effects. These recommendations have been adopted by the Indian RNTCP too, w.e.f. January 2019[4]. However, as the start of this study was prior to this new update, every patient received kanamycin injection.

The purpose of this study was to ascertain the outcomes of this newly introduced regimen for INH mono-resistant TB and to see whether this regimen was associated with

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improved outcomes we also wanted to identify possible factors which may predict success or failure of the treatment among these patients.

Material and Methods

Study site: Kingsway Chest Centre (KCC) OPD and in-Patient Department of Rajan Babu Institute for Pulmonary Medicine and Tuberculosis (RBIPMT), North Delhi Municipal Corporation, GTB Nagar, Delhi-110009. The report of INH resistance was obtained via Line Probe Assay (LPA) testing from IRL situated at New Delhi TB centre, Delhi.

Study population: Newly diagnosed INH mono-drug resistant PTB patients attended at RBIPMT for initiation of treatment with newly introduced treatment regimen during the intake period who met the inclusion criteria were offered to participate in the study, irrespective of age and gender.

Study design: It was an observational, prospective longitudinal study.

Study duration: Intake was from 1st September 2017 to 31st May 2018, i.e., total of 9 months. Final date of follow-up was 31st May 2019.

Sample size: As per the National Drug Resistant Surveillance (NDRS) survey in 2015, the prevalence of INH resistance was 16%[2]. The formula used to calculate sample size in prospective studies was- N = 4 pq/d2. Sample size was calculated as 96 for 1 year of intake. Since this was a time bound study with intake of 9 months and accounting for dropouts and patients refusing consent, the sample size was determined to be 50.

Sampling technique: Every consecutive patient who fulfilled inclusion and exclusion criteria was included.

Inclusion criteria

1. Patient of PTB who tested INH mono-resistant by LPA or sputum culture followed by Drug Sensitivity Testing (DST) from IRL.
2. All patients who had given written consent and were willing for regular follow-up, diagnostic evaluation and if indicated, hospitalisation
3. Age above 14 years, irrespective of gender.

Exclusion criteria

1. Not willing to give consent.
2. Patients of rifampicin resistance, MDR, pre-XDR and XDRTB.
3. Extra pulmonary TB cases.
4. Patients not belonging to Delhi.
5. All patients below 14 years of age.

Consent and ethical consideraton

The study was carried-out after obtaining approval from the Institutional Human Ethics Committee. An informed written consent was obtained from all patients.

Flow chart of methodology

Study subjects enrolled after informed consent.

History and clinical examination was done. Investigation-Body weight (BMI[5]), haematology, biochemistry, sputum smear examination, chest X-ray[6].

Patients were started on regimen for INH resistant TB as per newly revised guidelines. Three monthly follow-up with symptoms, body weight, sputum smear examination and chest X-ray was carried out.

Assessment was based on successful or unsuccessful outcomes[3] and comparison with various factors for possible significance.

The radiological extent of the disease was based on the guidelines of National Tuberculosis Association of USA as:

1. Minimal: These lesions include those that are of slight-to-moderate density but do not contain demonstrable cavitation. They may involve a small part of one or both lungs, but the total extent, regardless of distribution, should not exceed the volume of lung on one side.
2. Moderately advanced: These lesions may be present in one or both lungs, but the total extent should not exceed the following limits: disseminated lesions of slight moderate density that may extend throughout the total volume of one lung or the equivalent in both lungs; dense and confluent lesions limited in extent to one-third of the volume of one lung; total diameter of cavitation, if present must be less than 4 cm.
3. Far advanced: Lesions more extent than moderately advanced[7].

Minimal and moderately advanced lesions were grouped into less extensive group and far advanced lesions were grouped into more extensive group.

Statistical analysis

Descriptive statistics was analysed with SPSS version 21.0 software. The various risk factors and predisposing conditions were expressed as frequencies and percentages.

Nominal categorical data between the groups was compared using Chi-square test. For all statistical tests, a p-value less than 0.05 was taken to indicate a significant difference.

Results

Out of the total 85 patients enrolled, 8 patients completed the RNTCP definition for cure, 53 patients completed their treatment and were grouped under successful outcomes (group A). 13 were lost to follow-up, 6 patients died and 5 had a treatment failure in the form of microbiological positivity or change of regimen, all of them were termed under unsuccessful outcome (group B).

As shown in Table I, out of 85 patients, 34 (82.9%) patients who were between 21 - 40 years of age had significantly successful outcome. Majority of patients were males 60 (70.6%). Cough and sputum production were most common symptoms presented by 83 (97.6%), and 80 (94.1%) patients, respectively. Breathlessness (p = 0.03), haemoptysis (p = 0.001), chest pain (p = 0.002) or loss of appetite (0.005) individually were significantly associated with unsuccessful outcome. Out of 67 never/former smokers 57 (85.1%) had successful outcome while out of 18 current smokers, 14 (77.8%) had unsuccessful outcome. Out of 60 patients with no history of alcohol intake, 48 (82.7%) patients had successful outcome, while out of 27 with current history of alcohol intake, 14 (51.8%) had unsuccessful outcome. 21 (55.3%) out of 37 patients of lower socio-economic class had unsuccessful outcome, while 44 (93.6%) who belonged to upper and middle class had successful outcome.

Table I: Comparison of treatment outcomes in various demographic characterstics.

Demographic characterstics		Group A	Group B	p-value
	No. (%)	No. (%)		
Age (Range in years)	≤ 20	9 (64.3)	5 (35.7)	0.49
	21 - 40	34 (82.9)	7 (17.1)	**0.02**
	41 - 60	15 (62.5)	9 (37.5)	0.23
	> 60	3 (50.0)	3 (50.0)	0.21
Gender	Male	41 (68.3)	19 (31.7)	0.27
	Female	20 (80.0)	5 (20.0)	
Symptoms	Fever	42 (67.7)	20 (32.3)	0.17
	Cough	59 (71.1)	24 (28.9)	0.36
	Sputum	58 (72.5)	22 (27.5)	0.54
	Breathlessness	10 (52.6)	9 (47.4)	**0.03**
	Hemoptysis	2 (18.2)	9 (81.8)	**0.001**
	Chest pain	2 (25.0)	6 (75.0)	**0.002**
	Loss of appetite	12 (50.0)	12 (50.0)	**0.005**
	Loss of weight	28 (66.7)	14 (33.3)	0.30
Smoking Status	Never and former smokers	57 (85.1)	10 (14.9)	**0.00001**
	Current smokers	4 (22.2)	14 (77.8)	
Alcohol Intake	Never	48 (82.7)	10 (17.2)	**0.0009**
	Current or stopped one year ago	13 (48.1)	14 (51.8)	
Socio-Economic Class	Lower	17 (44.7)	21 (55.3)	**0.001**
	Upper and middle	44 (93.6)	3 (6.4)	

18 (78.3%) patients out of 23 who had contact with TB case and 17 (92.9%) out of 20 who were household contact of MDR-TB case were significantly associated (p = 0.0001 and 0.001 respectively) with unsuccessful outcome while 38 (92.7%) out of 41 who took full course of ATT treatment were significantly associated (0.001) with successful outcome as shown in Table II. 36 (97.3%) out of 37 patients with normal haemoglobin levels, 54 (77.1%) out of 70 with normal platelet level, and 47 (90.4%) out of 52 with sputum smear status < 1+ were significantly associated (p = 0.001, 0.01 and 0.0002, respectively) with successful outcomes while 12 (80%) out of 15 with increased TLC (> 9.06 X 10^3/mm^3), 8 (80.0%) out of 10 patients with deranged LFT, 4 (80.0%) out of 6 with deranged KFT and 17 (73.9%) out of 23 with BM1 < 17.5 Kg/m^2 were significantly associated (0.001, 0.001, 0.008, < 0.0001 respectively) with unsuccessful outcomes as shown in Table III.

Table II: Comparison of treatment outcomes with history of contact with a case of TB and drug resistant TB according to presumptive DR-TB suspect criteria.

History of contact of TB/ past history of ATT intake		Group A	Group B	p-value
		No. (%)	No. (%)	
Contact of TB case	Yes	5(21.7)	18 (78.3)	**0.0001**
	No	56 (90.3)	6 (9.7)	
Presumptive DR TB suspect criteria	Any TB patient who is a household contact of MDR-TB case	3 (7.1)	17 (92.9)	**0.001**
	Other DR-TB suspect criteria	58 (15.0)	7 (85.0)	
Past history of ATT	Present	42 (66.7)	21 (33.3)	**0.07**
	Absent	19 (86.4)	3 (13.6)	
Number of times ATT taken	Once	15 (65.2)	8 (34.8)	**0.85**
	More than once	27 (67.5)	13 (32.5)	
Full course of treatment taken	Yes	38 (92.7)	3 (7.3)	**0.001**
	No	4 (18.2)	18 (81.8)	

Table III: Comparison of treatment outcomes according to laboratory parameters and BMI of patients.

Laboratory Parameters		Group A	Group B	p-value
	No. (%)	No. (%)		
Haemoglobin (g/dl)	Reduced (< 12)	25 (52.1)	23 (47.9)	**0.001**
	Normal (12 - 16)	36 (97.3)	1 (2.7)	
TLC (10^3/mm^3)	Reduced (< 3.54)	3 (50.0)	3 (50.0)	**0.001**
	Normal (3.54 - 9.06)	55 (85.9)	9 (14.1)	
	Increased (9.06)	3 (20.0)	12 (80.0)	
Platelets (10^3/mm^3)	Reduced (< 165)	7 (46.7)	8 (53.3)	**0.01**
	Normal (165 - 415)	54 (77.1)	16 (22.9)	
LFT	WNL	59 (78.7)	16 (21.3)	**0.001**
	Deranged	2 (20.0)	8 (80.0)	

KFT	WNL	60 (75.0)	20 (25.0)	**0.008**
	Deranged	1 (20.0)	4 (80.0)	
Baseline sputum	< 1+	47 (90.4)	5 (9.6)	**0.0002**
smear status	> 1+	14 (42.4)	19 (57.6)	
BMI(Kg/m^2)	< 17.5	6 (26.1)	17 (73.9)	**<0.0001**
	> 17.5	55 (88.7)	7 (11.3)	

As shown in Table IV, 16 (94.1%) out of 17 patients with far advanced disease, 16 (64.0%) out of 25 with cavity and 15 (88.2%) out of 17 with more extensive disease on baseline chest X-ray were significantly associated (0.0001) with unsuccessful outcomes.

Table IV: Comparison of treatment outcomes according to baseline chest X-ray findings.

Chest X-ray findings		Group A	Group B	p- value
		No. (%)	No. (%)	
Baseline chest X-ray	Minimal	32 (100.0)	0 (0.0)	**0.0001**
findings	Moderately advanced	28 (77.8)	8 (22.2)	
	Far advanced	1 (5.9)	16 (94.1)	
Cavity	Present	9 (36.0)	16 (64.0)	**0.0001**
	Absent	52 (86.7)	8 (13.3)	
Extent of disease	Less extensive	59 (86.8)	9 (13.2)	**0.0001**
	More extensive	2 (11.8)	15 (88.2)	

At the end of 3 months follow-up, compared to baseline parameters, 42 (97.7%) out of 43 patients with increased weight, 58 (93.5%) out of 62 with sputum smear-negative status, 58 (98.3%) out of 59 with minimal lesion on chest X-ray and 46 (97.9%) out of 47 with improved symptoms were significantly associated (p = 0.0004, 0.0001, 0.00001, 0.00001 respectively) with successful outcome. At the end of 6 months follow-up among 68 patients who followed-up, 50 (98.0%) out of 51 with increased weight and 56 (96.6%) out of 58 with improved symptoms were significantly associated (p = 0.00001) with successful outcomes. 61 (96.8%) out of 63 patients with negative sputum smear status and 61 (98.4) out of 62 with minimal lesion on chest X-ray were also associated with successful outcome as seen in Table V.

Table V: Comparison of various parameters between the groups at 3 months and 6 months follow-up, compared to baseline for patients who continued treatment.

Parameters		No. of patients (n= 85)	Group A	Group B	p value
		No. (%)	No. (%)	No. (%)	
At 3 Months Weight	Reduced or Same	28 (39.4)	19 (67.8)	9 (32.1)	**0.0004**
	Increased	43 (60.5)	42 (97.7)	1 (2.3)	
	Sputum smear status	Negative	62 (87.3)	58 (93.5)	4 (6.5)	**0.0001**
		Positive	9 (12.7)	3 (66.7)	6 (33.3)	
	CXR findings	Minimal	59 (83.1)	58 (98.3)	1 (1.7)	**0.00001**
		Moderately advanced and Far advanced	12 (16.9)	3 (25.0)	9 (75.0)	
	Symptoms	Improved	47 (66.2)	46 (97.9)	1 (2.1)	**0.00001**
		Same or Worsen	24 (33.8)	15 (62.5)	9 (37.5)	
At 6 Months	Weight	Reduced or Same	17 (25.0)	11 (64.7)	6 (35.3)	**0.00001**
		Increased	51 (75.0)	50 (98.0)	1 (2.0)	
	Sputum smear status	Negative	63 (92.6)	61 (96.8)	2 (3.2)	N.A.
		Positive	5 (7.4)	0 (0.0)	5 (100.0)	
	CXR findings	Minimal	62 (91.2)	61 (98.4)	1 (1.6)	N.A.
		Moderately advanced and far advanced	6 (8.8)	0 (0.0)	6 (100.0)	
	Symptoms	Improved	58 (85.3)	56 (96.6)	2 (3.4)	**0.00001**
		Same or worsen	10 (13.2)	5 (50.0)	5 (50.0)	

Discussion

Even in the 21st century with rapid and lifesaving revolutionary advances in medical science and technology, TB continues to remain a disease with high burden and significant morbidity and mortality. In 2017, worldwide, an estimated 9.96 million new people developed TB and 1.3 million died from it. In India alone, there were 2.6 million new cases[1].

When there is resistance to any drug, the regimen needs to be modified and increased in duration based on the pattern of resistance[8]. On an individual level, patients with INH mono-resistant disease are at a theoretically greater risk of developing MDR than those with drug-sensitive TB due to the requirement for only a single additional resistance mutation, with the associated risk of a need for more expensive, toxic and lengthy treatment regimens[9]. This study was conducted to determine the outcomes of the regimen for INH mono-resistant TB.

In the present study, 71.8% of patients had successful outcomes, out of which 9.4% of patients completed the RNTCP definition of cure and 62.3% of patients completed their treatment. 28.2% of patients had unsuccessful outcomes, out of which 15.3% patients were lost to follow-up, 7.1% patients died and 5.9% patients had a treatment failure in the form of microbiological positivity or change of regimen. In the study done by Gegia *et al*, successful outcomes were found in 71% of the patients[10].

Patients of age groups 21 - 40 years had successful outcomes. Gegia *et al*, reported that treatment outcomes

were worse for older patients, among those who had INH mono-resistance[10].

In the present study, cough and sputum were the most common symptoms. Breathlessness, hemoptysis, chest pain and loss of appetite were significantly associated with unsuccessful outcomes as these chest symptoms are related to severity of the disease, increased lung involvement and higher bacillary load.

27.1% of patients had contact with a case of TB and had significant association with unsuccessful outcomes. Báez-Saldaña *et al* stated that there was significant association between unsuccessful outcomes and patients having contact with a case of TB[11]. It may be explained by the fact that contact with a case of TB has a chance of increased transmission of resistant bacilli.

There was a significant association of unsuccessful outcomes among patients who did not complete their full course of ATT. Gegia *et al* stated that unsuccessful outcome was significantly associated with patient with a history of previous treatment[10]. There is an increased chance of emergence of drug resistant bacilli in patients who are lost to follow-up and higher chances of treatment failure. In this study, there was significant association of unsuccessful outcomes and patient with any household contact case of MDR-TB.

Patients who were current smokers were significantly associated with unsuccessful outcomes. In a similar study done by Chien *et al* smoking was significantly associated with unsuccessful outcomes[12]. This may be because smoking affects lung functions and hampers the defense mechanism of airways thus, increasing the symptoms and decreased health status, affecting compliance of the patients towards treatment.

History of alcohol intake was also significantly associated with unsuccessful outcomes. Báez-Saldaña *et al* stated that alcohol intake was an independent factor for unsuccessful outcomes[11]. Majority of anti TB drugs are metabolised by the liver and have adverse effect on liver, thus decreasing metabolism of ATT drugs.

Lower socio-economic class was significantly associated with unsuccessful outcomes. This may be due to unemployment/low family income, people may have limited and delayed access to healthcare services and under-nutrition is also associated with poor outcomes.

Patients with BMI of less than 17.5 Kg/m^2 in all age groups were significantly associated with unsuccessful outcomes. This may be explained by the fact that under-nutrition leads to protein deficiency, which causes inefficient transport of anti-TB drugs in the body. Also, protein deficiency causes immune-compromised state which further deteriorates the health condition of the patient.

A significant association of unsuccessful outcomes was found with deranged biochemical parameters of patients. Deranged biochemical parameters lead to decrease tolerance to medicines and decreased metabolism of ATT, thus increasing the chances of side-effects. In a few patients, due to kanamycin injection, adverse effects like pain at injection site and decreased hearing were observed.

The patients with sputum AFB direct smear 2+ or more were significantly associated with unsuccessful outcomes. In a similar study done by Karo *et al*, sputum smear positivity was associated with unsuccessful outcomes[13]. This suggests that chances of treatment failure and death increases with the increase in initial bacillary load.

Patients with cavity and bilaterally extensive disease on baseline chest X-ray were significantly associated with unsuccessful outcomes. In a similar study done by Kim *et al*, cavity and bilateral extensive lesions on chest X-ray were commonly found in patients who exhibited treatment failure[14]. It can be explained by the fact that extensive lesions had more bacillary load, cause more symptoms and are difficult to treat.

71 out of the total 85 patients continued treatment till 3rd month of follow-up. 68 out of 71 patients continued treatment till 6th month of follow-up and 62 out of the remaining 68 patients till 9th month of follow-up. Rest of the patients, at each follow-up, had unsuccessful outcomes. The patients who were lost to follow-up were non-compliant with medications due to long duration of treatment, requirement of intake of multiple drugs and daily visit to the health facility.

A significant association of increase in weight and improvement of symptoms at 3rd and 6th month was established with successful outcome. Increase in weight and improvement of symptoms were surrogate markers of successful outcome and response to medication.

Negative sputum smear status at 3rd month had significant association with successful outcomes. In 6th month of follow-up sputum smear-positivity had unsuccessful outcomes. There was significant association between minimal lesions on chest X-ray at 3rd month follow-up with successful outcomes.

Conclusion

Early diagnosis of INH resistance and proper treatment along with education, emphasis and early attention to medical care, adequate nutrition, proper hygienic and ventilated living conditions, avoiding any addiction, compliance to regular complete treatment with required follow-up with social and economic support leads to successful management of patients with better outcome.

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REVIEW ARTICLE

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Erectile Dysfunction

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Abstract

Inability to sustain a penile erection to ensure successful vaginal intercourse during sexual activity constitutes erectile dysfunction. It greatly impacts the psychosocial health of a patient, along with his interpersonal relationships, their outlook, attitude and quality of life. The mechanisms involved in erection may be psychogenic, originating in the limbic system of the central nervous system, or in the peripheral nervous system and lower areas of the spinal cord, that is cause a reflex erection in response to touch of the penile shaft. Earlier, psychogenic causes were thought to be the commonest cause; however, that is not the case as a large percentage of these patients have been found to have an organic cause. There has been a better understanding of the pathophysiology of erectile dysfunction leading to evolution of better and effective therapies, both medical and surgical.

Introduction

Erectile dysfunction (ED) prevalence is more in older men above 40 years of age. The aetiology is multifactorial and may be associated with endocrine or non-endocrine causes. Non-endocrine causes may be vasogenic, involving abnormalities of arterial inflow or venous outflow, neurogenic or iatrogenic. Reduced testosterone levels have been implicated in endocrine causes. The importance of ED is now paramount, as its role is not limited to sexual satisfaction alone; it has now been implicated as a measure of systemic endothelial dysfunction. It's presence in a patient is a sign of advent of cardiovascular diseases and associated with major cardiovascular events, therefore these patients should be thoroughly investigated for organic causes and followed up closely for cardiovascular monitoring. A number of lifestyle diseases are associated with ED, such as hypertension, diabetes mellitus, dyslipidaemia, neurological disorders, morbid obesity, stress, depression, anxiety, chronic kidney disease, chronic liver disease, substance abuse and smoking. Various cultural and socio-economic factors also contribute to the problem. It is imperative to completely comprehend the physiology of erection and the various mechanisms playing a part in this process in order to diagnose accurately and manage the problem. A detailed history, a thorough clinical examination can guide us in determining the line of diagnostics that need to be undertaken to guide management of the individual patient. With time, there have been several breakthroughs in management, including pharmaco-therapeutics, lifestyle modifications, devices, prostheses and surgical interventions. The discovery of the role of nitric oxide (NO) system in signalling smooth muscle relaxation has fuelled an expansive research, focussing on sexual dysfunction in men.

Epidemiology

It has been seen in various studies that the prevalence of ED is higher in the United States, Eastern and Southeast Asian countries as compared to South American and European nations. It also has a strong association with patients presenting with lower urinary tract symptoms in benign prostatic hyperplasia (BPH). Both ED and lower urinary tract symptoms due to BPH are more frequently seen in aging men, possibly due to other common associated risk factors. The Sexual Human Inventory for Males or the 'SHIM' scores are used to assess Erectile dysfunction, which is actually an abridged version of the International Index of Erectile Function (IIEF) aimed to diagnose erectile dysfunction (Table I). The 'SHIM' questionnaire is a 5 point questionnaire with 5 points ascribed to each question; the final score is calculated by adding the scores of all the questions. A score of 21 or less is considered as ED, and can be further categorised into categories of mild, moderate and severe. The data from the European Male Ageing Study show that ED increases with age. The prevalence of severe ED, which is defined as an international index of erectile function score of between 1 to 7, increases at a higher rate than that of moderate ED (with score of 8 to 11) in men above 60 years of age. Another study showed that 22.1% of men less than 40 years of age had low (< 21) SHIM scores. ED is strongly related to age, general health status and emotional function.

Physiology of penile erection

Penile erection is a neurovascular event that is regulated by hormonal and psychological factors. Nitric oxide (NO) is the primary neurotransmitter responsible for penile erection

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Table I: SHIM Questionnaire Assessment.

OVER THE PAST 6 MONTHS:

1. How do you rate your confidence that you could get and keep an erection?		Very Low	Low	Moderate	High	Very High
		1	2	3	4	5
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?	No Sexual Activity	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?	Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?	Did Not Attempt Intercourse	Extremely Difficult	Very Difficult	Difficult	Slightly Difficult	Not Difficult
	0	1	2	3	4	5
5. When you attempted sexual intercourse, how often was it satisfactory for you?	Did Not Attempt Intercourse	Almost Never or Never	A Few Times (much less than half the time)	Sometimes (about half the time)	Most Times (much more than, half the time)	Almost Always or Always
	0	1	2	3	4	5

Add the numbers corresponding to questions 1-5. **TOTAL:** _____

The Sexual Health Inventory for Men further classifies ED severity with the following breakpoints:

1-7 Severe ED **8-11 Moderate ED** **12-16 Mild to Moderate ED** **17-21 Mild ED**

and is mainly released from the endothelial cells and parasympathetic nerve terminals. Sexual stimulation generates nerve impulses, leading to the release of neurotransmitters from the cavernous nerve terminals and of relaxing factors from the endothelial cells, resulting in the relaxation of cavernosal arterial smooth muscles. This leads to manifold increase in the penile blood flow along with rapid expansion of the sinusoidal system as shown in Fig. 1. It causes compression of the subtunical small veins between tunica albuginea and the trabeculae, thus occluding the local venous return. This sequence of events traps the blood within the corpora cavernosa resulting in raising the penis from a dependent position to an erect position, with an estimated intracavernous pressure of almost 100 mmHg in the phase of full erection. Sexual activity triggers the bulbocavernous reflex forcing the ischiocavernous muscles to compress the base of the blood-filled corpora cavernosa leading to the penis becoming even harder, with an intracavernous pressure escalating to much higher than hundred millimeters of mercury in the phase of rigid erection. The inflow and outflow of blood temporarily stops during this phase.

Penile detumescence occurs with the sympathetic activation of the adrenergic receptors on the surface of cavernous arteries during ejaculation, cessation of the neurotransmitter release and hydrolysis of secondary messengers (cGMP) by phosphodiesterase type-5 in the trabecular smooth muscles. Thus, resulting in the reduction of arterial inflow and causing a collapse of the lacunar spaces

and decompression of the drainage venules of the cavernous bodies, thereby resulting in the relief of erection.

Penile flaccidity is maintained by the semi-contracted state of the intracorporeal smooth muscles that results from the intrinsic myogenic activity, adrenergic neurotransmission and endothelium derived contracting factors like endothelins and PGF-2 alpha. Calcium influx into cells is regulated by norepinephrine signalling and levels of inositol[1,4,5] trisphosphate, which is produced from phosphatidylinositol[4,5] bisphosphate by phospholipase-C in the cells. The increased intracellular calcium ions binds to calmodulin, facilitating the formation of the calmodulin – myosin light chain kinase (MLCK) complex leading to the phosphorylation of MLC, causing smooth muscle contraction and flaccid penis. Norepinephrine signalling also inhibits adenylyl cyclase and modulates the RHO-associated protein kinase (ROCK) pathway, which increases the sensitivity of MLC to ionic calcium, which is negatively regulated by testosterone. Endothelins and prostaglandins from the endothelium also trigger an increase in the intracellular calcium ions promoting smooth muscle contraction. There is minimal blood inflow through the cavernous artery when the smooth muscle is contracted and blood outflows freely through the subtunical venous plexus. Nitric oxide independent, pro-erectile mechanisms of androgens also regulate expression of smooth muscle myosin isoforms and sphingosine[1] phosphate (S1P). In endothelial cells, activation of S1P receptors trigger the phosphoinositide 3 kinase (PI3K) – AKT pathway, which enables the crosstalk between ROCK and the endothelial nitric oxide synthase (eNOS) pathways. These findings reinforce a beneficial role of androgens on many overlapping NO independent pathways (S1P, PI3K-AKT and ROCK) favouring erectile response[1].

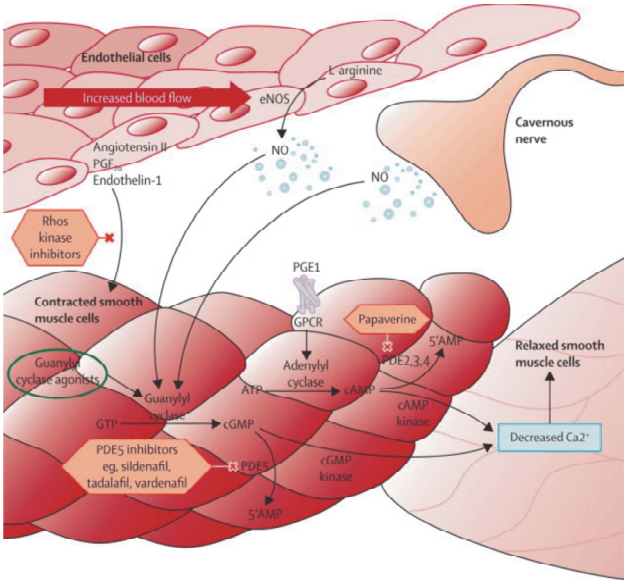

Fig. 1: *Microscopic mechanisms underlying penile smooth muscle relaxction.*

NO is the primary mediator of penile smooth muscle relaxction. After sexual stimuli, NO concentration is significantly increased because of its release from the cholinergic and non-noradrenergic, non-cholinergic fibres and the endothelium. NO works via the GPT/cGMP pathway to decrease intracellular calcium leading to trabecular smooth muscle relaxction. PDE5 enzyme regulates cGMP-dependent penile erection by stimulating hydrolysis of cGMP itself. Another mechanism that can decrease intracellular calcium concentrations is mediated by cAMP. Drugs that enhance erection include PDE5 inhibitors and prostaglandin E1. $PGF_{2\alpha}$ = prostagandin $F_{2\alpha}$. PGE1 = prostaglandin E1. GTP = phospodiesterase. cGMP = cyclic guanosine monophosphate. NO = nitric oxide. eNOS = nitric oxide synthase. PDE5 = phospodiesterase. ATP = adenosine triphosphate. AMP = adenosine monophosphate. GPCR = G-protein-coupled receptor. Reproduced with permission from Headerer and Muller biomedical Art, LLC (2009).

Pathophysiologic mechanisms of erectile dysfunction

ED can be classified into psychogenic, organic (neurogenic, vascular, hormonal, cavernosal or drug-induced) and mixed (both psychogenic and organic). Mixed variant is, usually, the most common cause.

Psychogenic erectile dysfunction

It is also known as adrenaline-mediated or noradrenaline-mediated or sympathetic-mediated ED, as noradrenaline is the primary erectolytic (anti-erectile) neurotransmitter.

Performance anxiety, lack of sexual arousability, strained relationship and overt psychiatric disorders such as depression and schizophrenia are some of the usual causes of psychogenic erectile dysfunction. Performance anxiety associated with sexual dysfunction itself leads to avoidance of sex, low self-esteem and depression.

Factors related to the development of psychogenic erectile dysfunction:-

Predisposing factors

- Traumatic past/childhood experiences.
- Strict upbringing.
- Physical and mental health problems.
- Inadequate sex education.

Precipitating factors

- Acute relationship problems.
- Family or social pressures.
- Major life events; such as pregnancy, childbirth, recent bereavement or loss of a job.

Maintaining factors

- Physical or mental health problems.

- Relationship problems.
- Absence of knowledge of availability of various treatment options.

Religious and cultural differences also influence factors that affect the development of psychogenic erectile dysfunction.

Neurogenic erectile dysfunction

It is caused by a defect in the nerve signalling or conduction to the corpora cavernosa. Such deficits can occur in neurological conditions like – lumbar disc disease, traumatic brain injury, spinal cord injury, multiple sclerosis, Parkinson's disease, radical pelvic surgery (radical prostatectomy, radical cystectomy or abdominoperineal resection) and diabetes mellitus, etc.

Functional and structural alterations owing to the decreased innervation is usually caused by sacral cord lesions (S2 - S4, *nervi erigentes*, being responsible for reflexogenic erections). Reduction of nitric oxide load, that is available to the effectual smooth muscles, results in the functional changes.

Vasculogenic erectile dysfunction

The risk factors associated with penile arterial insufficiency include atherosclerosis, hypertension, diabetes mellitus, dyslipidaemia, cigarette smoking and pelvic irradiation. It's the secondary arterial wall changes in the form of reduced elasticity, and not hypertension per se, that results in ED. Broadly speaking, endothelial dysfunction is the root cause of vasculogenic ED. When ED occurs in men younger than age 60 years, it is strongly associated with an increase in the risk of future cardiac events when compared with men without ED. Blunt pelvic or perineal trauma, (e.g., sustained from bicycling accidents) may result in focal stenosis of the common penile artery causing ED.

Veno-occlusive dysfunction may be caused by the formation of large venous channels draining the corpora cavernosa, degenerative changes to the tunica albuginea (due to Peyronie's disease, old age or diabetes mellitus) or traumatic injury (penile fracture), resulting in ED. Shunts acquired as a result of operative correction of priapism may also cause failure of erection.

Endocrinological erectile dysfunction

Androgen deficiency results in diminished nocturnal erections and libido, although erection in response to visual sexual stimulation is preserved in men with hypogonadism, thus indicating that androgen is not fundamentally necessary for penile erection.

The physiological effects of testosterone are well defined in the regions of the brain that control sexual arousal like – amygdala, medial pre-optic area and hypothalamic nuclei, at the spinal cord level (affecting neuronal firing from the pelvic ganglia) and within the penis (regulating endothelial and smooth muscle cell function). Testosterone is known to regulate the release of nitric oxide from non-cholinergic & non-adrenergic fibres, and the functioning of NO synthase in the endothelial cells. In the smooth muscle, testosterone modulates the activity of phosphodiesterase type 5, the kinase that regulates Ca2+ and K+ levels, and adrenergic receptor sensitivity.

Hyperprolactinaemia from any cause results in both reproductive and sexual dysfunction as prolactin inhibits central dopaminergic activity causing diminished secretion of gonadotropin-releasing hormone, thereby resulting in hypogonadotropic hypogonadism.

Thus, prolactin should be considered for screening, together with testosterone and luteinizing hormone in ED.

Drug-induced erectile dysfunction

Cigarette smoking is known to cause vasoconstriction and penile venous leakage, due to the contractility of the cavernous smooth muscle. Ethanol in small quantities may improve penile erection and also increases libido because of its vasodilatory effect and allaying anxiety, but larger amounts can lead to central sedation, diminished libido and transient ED. Chronic alcohol consumption in significant amount may also result in hypogonadism and polyneuropathy, affecting penile nerve function.

Central neurotransmitters like noradrenergic, serotonergic and dopaminergic pathways are important in the normal sexual functioning and are altered by centrally acting antihypertensive drugs, antipsychotics and antidepressants.

Beta-adrenergic blockers cause ED by potentiating alpha-1 adrenergic activity in the penis. Thiazide diuretics and Digoxin have been implicated in ED, with unknown mechanism. Spironolactone also cause ED as well as gynaecomastia with decreased libido.

H-2 receptor antagonist cimetidine, has been reported to reduce libido and cause ED by acting as an antiandrogen and causing hyperprolactinaemia. Estrogens and some other drugs with anti-androgenic action, such as ketoconazole and cyproterone acetate, are known to cause ED.

5α-reductase inhibitors used in treatment of benign prostatic hyperplasia, anti-androgens and luteinizing hormone-releasing agonists/antagonists used to treat prostate cancer also cause ED[2].

Erectile dysfunction due to aging and systemic/ metabolic diseases

Sexual function declines progressively in healthy aging

men. With increasing age, there is a decline in penile sensitivity to tactile stimulation, decrease in concentration of serum testosterone and an increase in the tone of cavernous muscle. Also, the latent period between sexual stimulation and erection increases, erections are less turgid, ejaculation is less forceful, the ejaculatory volume decreases, and the refractory period between erections lengthens with aging.

More than 50 per cent of men with long standing diabetes mellitus have ED. In addition to affecting the smaller blood vessels, diabetes mellitus adversely affects the cavernous nerve terminals and endothelial function, thereby resulting in the deficiency of neurotransmitters.

Chronic kidney disease is frequently associated with diminished erectile function, impaired libido and infertility. The mechanism is multifactorial, involving low serum testosterone levels, vascular insufficiency, polypharmacy, somatic and autonomic neuropathy, and psychological stress. Individuals with coronary artery disease or cardiac failure usually have ED due to depression, anxiety, polypharmacy and associated penile arterial insufficiency[3].

Diagnosis and screening[4]

The identification of causative factors involved in ED is the mainstay of an accurate diagnosis and successful treatment. ED could be the presenting symptom of a variety of diseases, such as diabetes mellitus, coronary artery disease, dyslipidaemia, hypertension, pituitary tumour and spinal cord pathology.

The main goals of assessment are to establish whether the disorder is actually ED, to identify the cause of the disorder, and to ascertain the risk factors and potentially life-threatening co-morbid conditions associated with ED.

The initial workup includes an assessment of all the aforesaid factors, establishing an accurate medical and sexual history; a detailed general and focused genitourinary examination; and the requisite hormonal and biochemical tests.

A detailed psychosocial history is essential to know any deep-seated psychological problems or relationship conflicts that can be effectively managed only by mental health specialists.

The general physical examination must include the evaluation of the hair distribution and other secondary sexual characters; palpation of peripheral pulses; presence of arterial bruit; blood pressure measurement; examination of local penile deformities like – Peyronie's disease, phimosis, frenulum breve and testing of genital and perineal sensations including bulbocavernous reflex.

Recommended laboratory tests should include urinalysis, complete haemogram, and assessment of serum glucose, thyroid profile, kidney and liver functions, lipid profile and testosterone levels. If the serum testosterone levels are low then serum free testosterone, prolactin, and luteinizing hormone levels should be determined.

Some specific investigations for ED include penile duplex doppler ultrasonography to assess for vascular function and evaluate for Peyronie's disease; nocturnal penile tumescence and rigidity testing using the Rigi Scan device to differentiate between psychogenic and organic causes. Arteriography and dynamic infusion cavernosometry (measuring cavernosal blood pressure) and cavernosography (to assess for venous leak) are done in young individuals only who may be potential candidates for vascular reconstructive surgery after traumatic arterial insufficiency or venous leakage.

Management

In the absence of any specific reversible aetiology, the treatment for ED is mostly empirical and is provided in a step-wise manner. Initial therapy is based on lifestyle modification and psychosexual counselling, followed by first-line therapies, primarily PDE5 inhibitors and vacuum erection devices (VEDs). Intra-urethral suppository (IUS) of prostaglandin E1 (alprostadil) and intracavernosal injection (ICI) of vasoactive substances constitute the second-line therapy. Surgical intervention is only reserved as the last option after conservative options have been exhausted.

Lifestyle modifications

They have a significant role in younger individuals with identifiable reversible risk factors which may contribute to the patient's ED, such as precipitating medications, poor dietary habits, lack of physical exercise, endocrinopathies, stress and anxiety. The major drawback remains the lack of interventional studies assessing the effect of lifestyle changes on ED.

Cessation of cigarette smoking plays a major role in improving ED as there is a direct dose-response relationship between greater number of packs of cigarettes smoked or more years of smoking, with increased erectile difficulties. Mild alcohol consumption might improve erectile function by allaying anxiety; however, chronic alcohol use can have deleterious effects on the liver functions, resulting in low testosterone levels and increased levels of estrogen, both of which contribute to erectile dysfunction. Patients with performance anxiety, interpersonal relationship issues and current life stressors may benefit from confidence restoration with erectogenic medications and/or counselling with a psychologist or a mental health expert specializing in sexual dysfunction.

Adults should do atleast 30 minutes of moderate-intensity aerobic exercises or sporting activities on most days of the week. Weight loss in obese or overweight men, and switching over to a Mediterranean diet, plus exercise, has been shown to improve sexual health.

The European Association of Urology recommends that "lifestyle changes and modification of risk factors must precede or accompany any ED therapy", and classifies the level of evidence for lifestyle modifications as 1b with a grade A recommendation.

Nonsurgical interventions

PDE5-inhibitors[5]

Oral PDE5-inhibitors are the mainstay of the treatment of ED. These drugs facilitate penile erection by inhibiting the phosphodiesterase-5 (PDE5) enzyme, which is responsible for the degradation of cyclic guanosine monophosphate (cGMP) in the cavernous smooth muscles. This inhibition results in the prolonged activity of cGMP resulting in decreased intracellular calcium concentrations and thus maintaining the smooth muscle relaxation, leading to rigid penile erections. Individuals need to be reminded that PDE5-inhibitors still require both physical and mental sexual stimulation, to create arousal and initiate rise in the available nitric oxide levels in order to generate cGMP. They must be administered with adequate time interval before sexual intercourse, to allow for peak drug levels at the appropriate time. Patients should be instructed on optimal conditions for medications to work effectively.

Daily use of PDE5-inhibitors in erectile dysfunction can significantly improve endothelial dysfunction with the potential for a cure. Potential advantages of their daily use include salvage of on-demand PDE5-inhibitor non-responders, apparent disease modification, and development of a more natural sexual function. PDE5-inhibitors lead to improvement of sexual performance and not increase in libido. PDE5-inhibitors lead to shortening of the refractory period and better ejaculatory control in young and potent individuals. Hypogonadal patients who do not respond to treatment with PDE5-inhibitors alone, might show clinical response to a combination of testosterone and PDE5-inhibitors. Physicians should consider trying all available PDE5-inhibitors (Table II) until it is known which one has the best effects on the patient's erections with the least overall side-effects. These drugs should be tried at least four times before deeming them successful or not.

PDE5-inhibitors are contraindicated in nitrate users as they increase the risk of severe hypotension and should be used with caution in patients with serious cardiovascular diseases, uncontrolled hypertension, unstable angina, and in those taking alpha-blockers for blood pressure control. Side-effects related to these drugs are generally mild and well tolerated; like headache, heartburn, facial flushing, nasal congestion and myalgias (especially with tadalafil).

Occurrence of priapism is also a concern but only rarely seen. There have also been concerns regarding PDE5-inhibitors use and auditory changes like hearing loss and tinnitus. Some vision-related conditions are also cause for increased concerns, including retinitis pigmentosa, macular degeneration and non-arteritic anterior ischaemic optic neuropathy. They are contraindicated in patients with vision

Table II: Characteristic properties of PDE5-inhibitors.

	Sildenafil	Vardenafil	Tadalafil	Udenafil	Mirodenafil
Dosage	25, 50, and 100 mg. Usually start with 50 mg. Maximum dose 100 mg daily	2·5, 5, 10, and 20 mg. Usually start with 10 mg. Maximum dose 20 mg daily	2·5, 5, 10, and 20 mg. Usually start with 10 mg. Maximum dose 20 mg daily	100 mg. Maximum dose 200 mg daily	50 or 100 mg. Maximum dose 100 mg daily
Onset	30–60 min	30 min	45 min	30–60 min	30–60 min
Duration	4–8 h	4–8 h	Up to 36 h	12 h	6–12 h
Efficacy	>65%	>65%	>65%	>65%	>65%
Side-effects	Headache, flushing, and dyspepsia	As for sildenafil	Flushing, back pain, and general myalgia	Facial flushing, nasal congestion, ocular hyperemia, and headache	Facial flushing, headache, nausea, and eye redness
Contraindications	Nitrate-containing compounds, recent serious cardiovascular events, non-arteritic ischaemic optic neuropathy, and α blockers	As for sildenafil, but also type 1 or 3 antiarrythmics and congenital prolonged QT syndrome	As for sildenafil	As for sildenafil	As for sildenafil
Food and alcohol interaction	Interacts with food, administer while fasting. No alcohol interaction	Interacts with food, administer while fasting. No alcohol interaction	No food or alcohol interaction	No food or alcohol interaction	No alcohol interaction. Data on food interaction not available

loss due to non-arteritic anterior ischaemic optic neuropathy.

PDE5-Inhibitors are a good first-line therapy, but upto 35% of the patients with ED fail to respond adequately. The common causes of treatment failure include diabetes mellitus and severe neurological and vascular diseases. Although there is no consensus on how to define the failure to PDE5-inhibitors therapy; the inability to attain or maintain adequate penile erection during sexual intercourse on at least four consecutive occasions, despite optimum drug dosing, is an acceptable definition. Management of PDE5-inhibitor treatment failure is dependent on the underlying cause and includes patient counselling, switching over to another PDE5-inhibitor, intracavernosal injection therapy, intraurethral drug administration, combination therapy, or referral to the expert for further evaluation. Patients not responding to any of the medical treatment options may be candidates for penile implant surgery.

Recent findings that ED is a strong predictor of CAD and that the development of symptomatic ED might precede the occurrence of a cardiovascular event by 2 - 3 years have led to stricter measures during the assessment of patients who present with poor erections. A strong recommendation is that all men with ED who are free from any cardiac symptoms should be considered to be cardiac (or vascular) patients, until proven otherwise. After a full medical assessment, the patient's cardiovascular risk should be assessed with stratification to high, medium, or low risk levels as per the Princeton III consensus recommendations (Table III)[6].

Vacuum erection devices

Vacuum erection devices (VED) operate by applying continuous negative pressure to the shaft of the penis drawing blood inside lacunar spaces inside the corpora cavernosa causing tumescence. In order to prevent the backflow of blood, a constriction band is placed at the base of the penis in these devices. About 70% of diabetic men who do not respond to PDE5-inhibitors, are able to have sexual intercourse when using a VED to achieve tumescence. On the other hand, discontinuation rates of nearly 35% are reported owing to bruising on the penis, pivoting at the base of the penis, coldness or numbness of the penis, pain related to the constriction band and/or decreased ability to achieve orgasm. Successful usage of VED requires obtaining a tight seal of the cylinder against the body of the penis using a lubricant and trimming the pubic hair.

Intraurethral Suppository

Table III: Princeton III consensus recommendations[6].

Profile	Description	Sexual activity and PDE5 inhibitor use
Low	• Fewer than three risk factors for coronary artery disease* (excluding sex) • Controlled hypertension • Class I or II stable angina‡ • Successful coronary revascularization • History of uncomplicated myocardial infarction • Mild valvular disease, congestive heart failure without left ventricular dysfunction and/or New York Heart Association class I heart failure	• Cleared to resume sexual activity • Cleared to take PDE5 inhibitors
Intermediate	• At least three risk factors for coronary artery disease* (excluding sex) • Class I or II stable angina‡ • Recent myocardial infarction (within 2–6 weeks) • Left ventricular dysfunction and/or New York Heart Association class II congestive heart failure • Noncardiac sequela from atherosclerotic disease (stroke and/or peripheral vascular disease)	• Cardiac evaluation necessary prior to resuming sexual activity • No contraindication to PDE5 inhibitor use
High	• Unstable or refractory angina • Uncontrolled hypertension • New York Heart Association class III–IV congestive heart failure • Recent myocardial infarction (within 2 weeks) • High-risk arrhythmias • Severe cardiomyopathy • Moderate to severe vascular disease	Sexual activity delayed until cardiac condition stabilized

**Major cardiovascular risk factors include age, male gender, hypertension, type 1 and type 2 diabetes mellitus, smoking, dyslipidemia, sedentary lifestyle and family history of premature cardiovascular disease.*

‡Defined by the Canadian Cardiovascular Society.

The use of intraurethral suppository (IUS) involves the placement of a prostaglandin E1-loaded pellet within the urethra before sexual intercourse. The patient should then massage that area of the penis to help disperse the medication. The absorption of the drug through the urethra into the corpora cavernosa increases the intracellular levels of cyclic AMP (cAMP), leading to decreased intracellular Ca2+ levels, increased smooth muscle relaxation and tumescence. It is a second-line therapy to PDE5-inhibitors, showing efficacy in approximately 55% patients with primarily organic ED. The medication may cause localized pain and burning. Some adverse effects include penile pain, urethral pain, dizziness and priapism. Repeated use with wrong technique may lead to urethral stricture.

Intracavernosal injection

It involves injecting vasoactive substances directly into the corpora cavernosa via a 28G needle. The vasoactive agents include prostaglandin E1, papaverine and phentolamine (and also, atropine), which work alone or in conjunction to elicit penile erection. Phentolamine is an alpha1 adrenergic receptor inhibitor that prevents vasoconstriction to maintain tumescence. Papaverine is a nonspecific phosphodiesterase-inhibitor causing increased levels of cAMP and cGMP. Prostaglandin E1 is approved as a single-agent intracavernosal injection (ICI) for erectile dysfunction, increasing cAMP levels.

Priapism is the major concern with ICI. If it occurs, then the patient needs urgent medical attention, requiring local blood aspiration or surgical shunt formation or ICI of phenylephrine to induce cavernosal vasoconstriction. Dropout rates are high because of fear of penile injections, local pain and occasional bruising[7].

Surgical Interventions

Penile prostheses/implants

Surgical interventions are suitable options in patients who are refractory to medical therapy, have contraindications or adverse effects to first-line drug therapy; in patients having troublesome priapism or local infections; have penile fibrosis due to Peyronie's disease; and in patients with vascular or anatomical penile defects or in cases of genital or pelvic trauma. The current surgical options include insertion of a penile prosthesis and vascular reconstructive surgery. The corporal tissue is irreversibly altered once the penile prosthesis surgery is done and smooth muscle relaxation is impossible thereafter.

Penile implants consist of malleable or inflatable devices as shown in Fig. 2. The malleable penile prosthesis involves two semi-rigid rods that are placed in the corpora cavernosa. The implant does change in size when it is bent upwards before intercourse (Fig.2a). Two-piece inflatable penile prostheses (IPPs) consist of two cylinders with a scrotal pump, enabling transfer of fluid to the cylinder chambers whenever an erection is desired (Fig. 2b). Three-piece inflatable penile prostheses are considered the gold standard. They involve the placement of two inflatable cylinders (in the corpora cavernosa), a pump in the scrotum and a fluid reservoir in the lower abdomen alongside the bladder (Fig. 2c). The pressure applied to the pump causes a transfer of fluid from the reservoir to the cylinders, leading to penile rigidity. The pump has a release valve or button to transfer the fluid back from the cylinders to the reservoir at the end of intercourse. Maximum girth expansion and penile rigidity occurs with these devices, as and when an erection is desired, alongside maximum flaccidity on deflating.

Penile revascularisation surgery

Penile revascularisation surgery was developed to anastomose the inferior epigastric artery to either the dorsal artery or deep dorsal vein (arterialisation), with or without venous ligation to improve penile vascular inflow while reducing venous outflow, on similar principles of coronary artery bypass grafting in coronary artery disease. It is recommended for younger men (< 55 years) who are non-diabetic, non-smokers and have a documented isolated

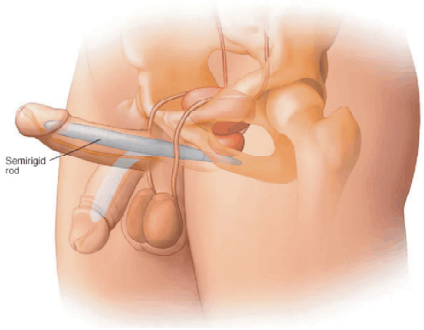

Fig. 2a

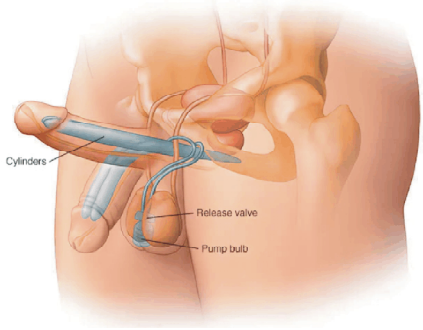

Fig. 2b

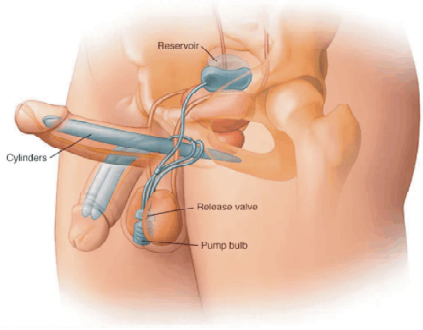

Fig. 2c

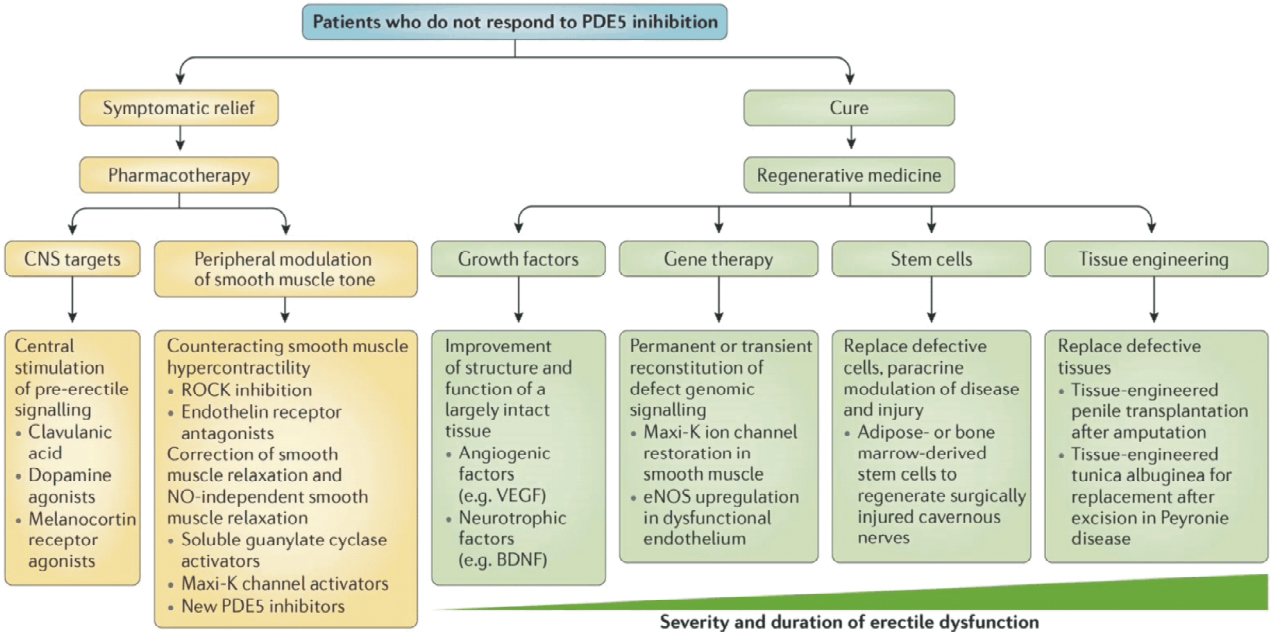

Fig. 3: *Summary of potential future treatment options.*

stenotic segment of the internal pudendal artery without concomitant venous leak. Potential complications of penile revascularisation procedures include glans hyperaemia, shunt thrombosis and inguinal hernias[8].

Potential future treatment options for erectile dysfunction

Only temporary symptomatic relief is provided by the current therapeutic options as they do not halt or slow down the primary disease process. Bioavailability of nitric oxide (NO) is essential for phosphodiesterase type 5 (PDE5) inhibitors, which are the most preferred therapy, to exhibit any effect. Hence, prospective pharmacological interventions will need efficacy in individuals not responding to PDE5 inhibition, particularly in men with neurogenic ED. The site of action may be either the central or the peripheral nervous system controlling the balance between the vasorelaxation & vasoconstriction. The ROCK (RHO-associated protein kinase) pathway plays an important part in maintaining the flaccid state of the penis. ROCK phosphorylates and inactivates myosin light chain phosphatase. This allows the myosin light chain to stay phosphorylated and bind to the smooth muscle actin. ROCK inhibition, Maxi-K channel activators and soluble guanylate cyclise activators provide alternative mechanisms that are independent to nitric oxide mediated smooth muscle relaxation. Central stimulation signalling with clavulanic acid, dopamine agonists and melanocortin receptor agonists are under investigation for utility in therapy for ED.

Stem cell therapy or regenerative medicine might provide definitive symptomatic relief by reversing or halting the disease progression in ED. Regenerative medicine can probably alter the disease course and in many instances possibly regenerate damaged cells, tissues or whole organ systems. Various tools such as gene transfer, stem cells, angiogenic and neurotrophic growth factors and tissue engineering can be used to achieve this goal. Fig. 3 provides a summary of all future options.

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REVIEW ARTICLE

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Approach to A Patient with Tremor

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Abstract

Tremor is a common complaint and a frequently observed entity in neurology clinics. Given the various generation sites and the anatomical substrates which can give rise to tremor, the diagnosis of tremor syndrome and its localisation requires a good history taking and a prudent examination approach. This review focusses on the 'clinical pearls' for diagnosis of various tremor syndromes and their possible aetiological correlates.

Key words: Approach to tremor.

Introduction

Tremor, the most common neurological disorder[1] is defined as a rhythmic involuntary movement produced by either alternating or synchronous contractions of reciprocally innervated antagonistic muscles of one or several regions of the body[2]. The key feature of tremor is its rhythmicity, which is not easy to identify because, despite a fixed frequency, the variable amplitude may give an erroneous impression of variable frequency. Evaluation of tremor requires a comprehensive history and neurological examination. In this review, clinical methods for evaluating various tremor syndromes are discussed.

Classification of tremor

Tremor can be classified based on frequency, amplitude, and body part affected. However, clinically, the most important classification is phenomenological classification into rest and action tremor[3] (Fig. 1). Rest tremor is said to be present when the body part is not voluntarily activated, which may require complete support of body part against gravity. Action tremor is said to occur when it occurs in a body part that is voluntarily activated – whether in maintaining posture (Postural Tremor) or in performing an activity (Kinetic Tremor). Kinetic tremor is further subdivided depending on the range of movement – simple kinetic tremor when tremor is same throughout the movement and intention tremor when tremor markedly increases in terminal portions of the movement.

Approach to a patient with tremor

According to a 2018 classification proposed by the International Parkinson and Movement Disorder Society[3], there are 3 important questions that need to be answered in a patient being evaluated for tremor: is it really tremor, what the tremor syndrome is (Axis 1) and what is the aetiology of tremor syndrome. First and foremost it is important to determine the age of onset of tremor [infancy (birth to 2 years); childhood (3 - 12 years); adolescence (13 - 20 years); early adulthood (21 - 45 years); middle adulthood (46 - 60 years); and late adulthood (> 60 years)], the time course of onset and evolution of symptoms over time with respect to body parts involved and activation conditions, any associated medical conditions or drugs that could exacerbate or precipitate tremor, family history of any movement disorder and presence of any accompanying neurological deficits including but not limited to slowness, stiffness and pulling sensations or pain that may indicate a combined tremor syndrome. The clinician should enquire about activation conditions of tremor, and open-ended questions like "What type of tremor do you have?" may not always be helpful. It may be more prudent to ask specific questions like, whether the tremor occurs at rest as while lying down with arms relaxed, while walking or while sitting with arms supported (indicating tremor in a resting position); or whether tremor occurs while maintaining posture (e.g., while holding things such as glasses, laser pointer, mobile, etc.) or whether it occurs while performing some action (indicating kinetic tremor) such as writing, pouring liquids in cups. One should also determine, whether tremor occurs immediately on holding a thing or occurs after some time (indicating re – emergent tremor). It is also essential to note whether tremor occurs in a specific position or while performing a specific action. One should also ask whether the patient is aware or unaware of the tremor because some patients with essential tremor may be unaware of neck tremor. Finally, clinician should determine how much the activities of daily living are affected, because of tremor. Tremor should be differentiated

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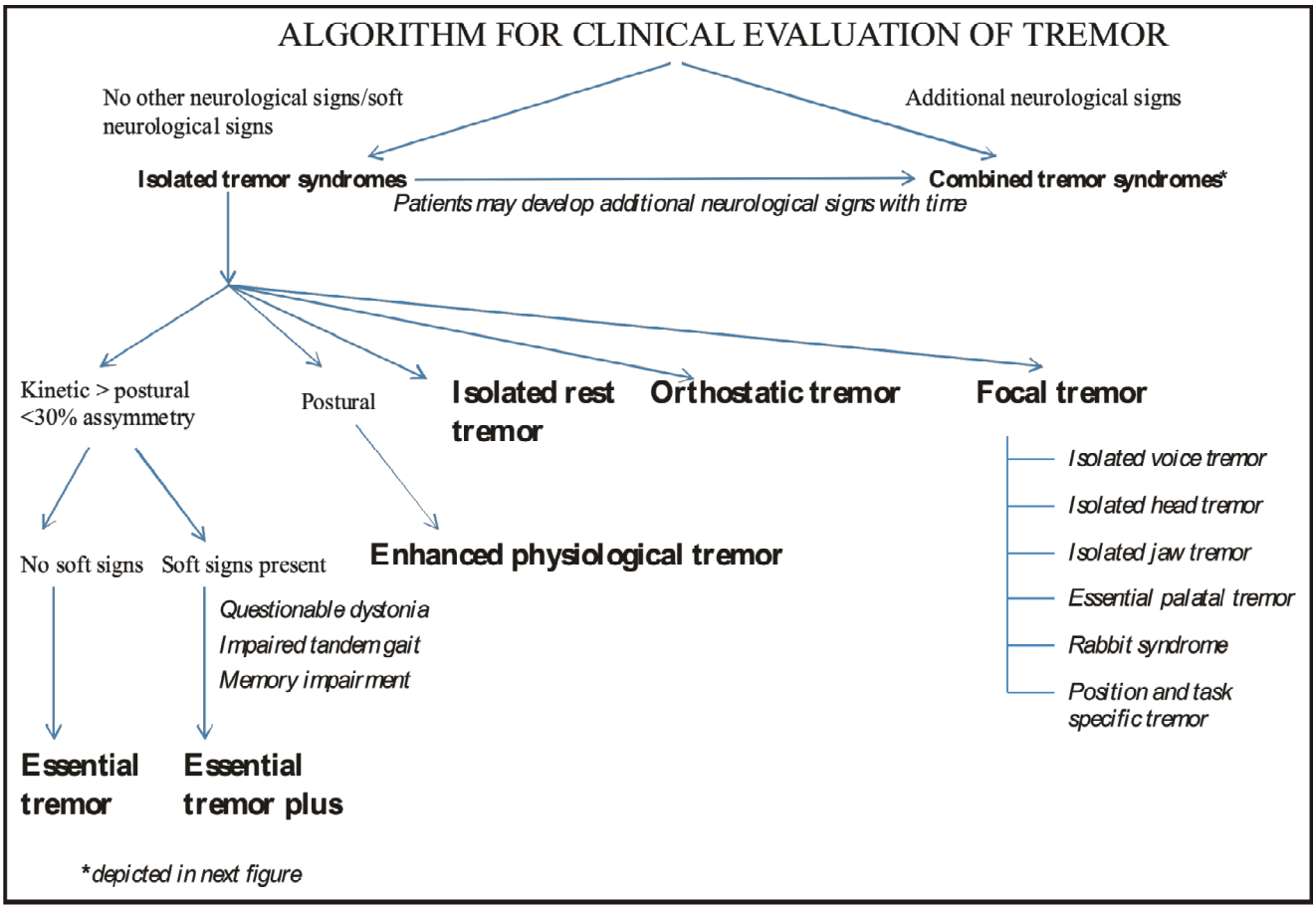

Fig. 1: *Approach to tremor.*

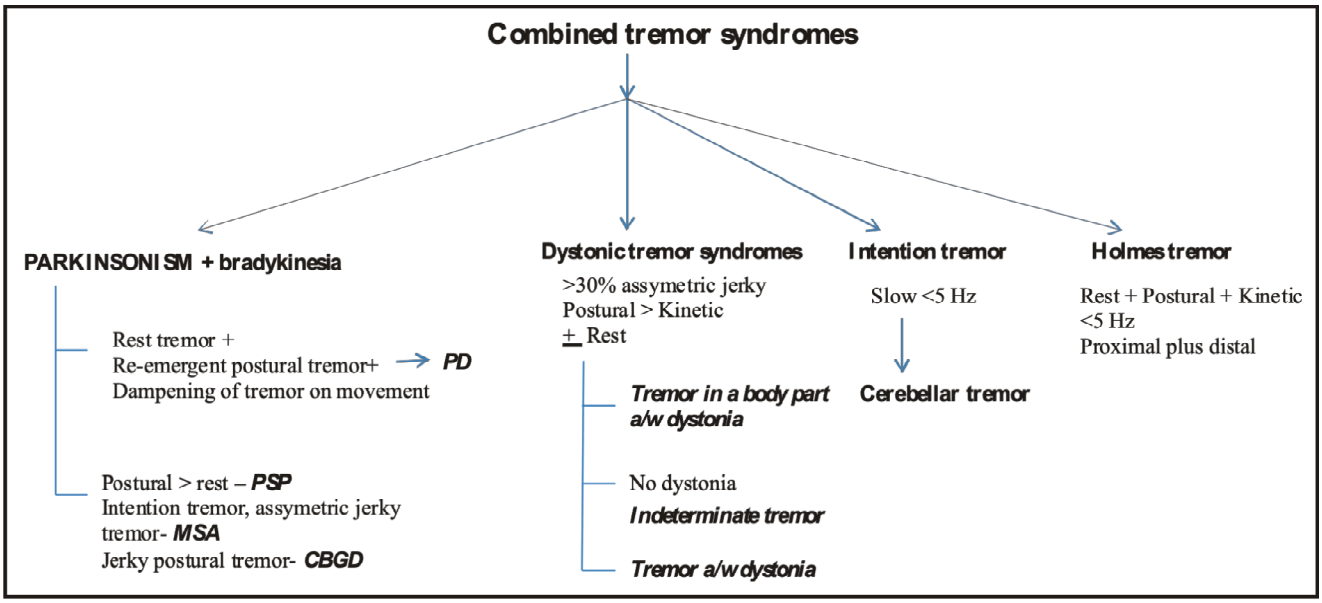

Fig. 2: *Approach to combined tremor syndromes.*

from other movement disorders such as chorea, myoclonus and dystonia[4] (Table I).

Table I: Differentiating features of different movement disorders[43].

Characteristics	Tremor	Chorea	Dystonia	Myoclonus
Jerky character	–	+	–	+ (Jerky irregular "tremor" is usually a manifestation of myoclonus)
Rhythmicity	Rhythmicity is the hallmark	–	–	– Rhythmicity is a feature of segmental myoclonus
Patterned	+	–	+	– Segmental myoclonus-patterned
Sustained character	–	–	+	–
Flowy nature	–	+	–	–
Paroxysmal/continual/continuous*	Continuous	Continual	Dystonic movements-continual Dystonic postures-continuous	Arrythmic myoclonus-continual Rhythmic myoclonus-continuous
Suppressibility**	+	++++	++	–

**Continual-over and over again, continuous-occurs without stopping.*

***Magnitude of suppressibility- No. of '+' denotes the magnitude of suppressibility, highest suppressibility being for stereotypies (++++++) followed by tics and akathisia (+++++).*

Examination of tremor: Examine the patient with his or her arms relaxed, ideally on the arms of a chair or on patient's lap, half pronated completely supported against gravity[5]. Since rest tremor may be intermittent, it may not be apparent immediately in all patients and even severe tremor may temporarily disappear. Certain provocative manoeuvres may be used to make a rest tremor apparent: walking, counting backwards from 100 loudly, motor tasks with contralateral hand or foot, and stroop test[6]. It has been seen that maximum effect of these provocative tests may be seen at about 2 - 3 minutes, so wait for a few minutes before concluding absence of rest tremor. Tremor examination under provocation can potentially distinguish between an overflow of postural tremor into the resting condition and real resting tremor. One should also note across which joints movements are occurring and in what directions. Next, to examine postural tremor, ask the patient to sit with arms stretched out in front and fingers open. Ask the patient to close his or her eyes and count backward again. One should observe latency of onset of tremor after attaining the posture (to look for re-emergent tremor) and any subtle posturing or spooning of the fingers (tendency during arm extension to flex the wrist and hyperextend the metacarpophalangeal and phalangeal joints) that may be indicative of dystonic tremor. Next the patient is asked to hold the arms in different positions (to look for positional variability and position specificity) – in a wing position with the hands facing inward, but not touching each other, arms abducted at the shoulder and bent at the elbows, arms in the same position but with the forearms pronated or supinated), arms outstretched in a karate-chop position, or any other position in which the patient has noticed tremulousness[7]. For kinetic tremor, patient should be asked to do the finger-nose-finger test, draw spirals, vertical and horizontal lines, write a sentence, pour water between cups, or drink from a cup[7]. One should look for any dampening of tremor with movement, and any exacerbation of tremor as the limb approaches the target (intention tremor) and the relative severity of postural and kinetic component. Attempts should be made to distinguish dysmetria (overshoot or undershoot) from intention tremor. Finally, one should look for any cranial tremors: head (i.e., neck) (while seated and while lying), jaw (with mouth closed and then while open), face, chin, tongue, and voice (during sustained phonation)[8]. To test for isometric tremor, ask the patient to push against a wall, flex the wrist against a table, or make a fist. To determine task specific tremor, patient can be asked to perform the particular task that provokes tremor, such as writing. At the end of a neurological evaluation, the clinician should be able to formulate the type of tremor syndrome – isolated (when tremor is the only neurologic manifestation), or combined (when other systemic or neurologic signs co-exist with the tremor); and rest, postural, kinetic or a combination of the three. The next step would be to determine the aetiology, which will depend on the neurological examination and targeted investigations. Brief clinical features of isolated and combined tremor syndromes are discussed.

Isolated Tremor Syndromes: Isolated tremor syndromes include essential tremor, focal tremors, task and position specific tremors, and orthostatic tremors.

Essential tremor: It is the most common cause of an isolated tremor syndrome. ET is a heterogenous disorder and there is considerable variability in the character of the tremor, activation conditions and association with other neurologic deficits. ET has a bimodal peak of onset, most commonly occurring in late life (> 60 years), but early onset before the age of 40 years with slow progression over several years is also seen[9]. The cardinal feature of essential tremor is action tremor (postural > kinetic tremor) which may be observed during a variety of activities on neurologic

examination (extending arms, spiral drawing, pouring water between two cups, finger-nose-finger maneuver). The tremor usually starts bilaterally but may start unilaterally in about 20% of cases. When it starts unilaterally, it progresses to involve the other limb in 2 - 3 years but some amount of asymmetry (about 30%) may persist and in 5% of patients the tremor is markedly asymmetric or unilateral[10]. Classically the tremor is absent on rest, but immediately appears as soon as arms are held outstretched. On movement, tremor may decrease, but again reappears as the target is reached (terminal tremor). This is different from intention tremor, in which tremor oscillations increase steadily before arriving at the target rather than at the termination of goal-directed activity. About 50% of patients with ET have intention tremor which is not limited to arms and can be seen in neck[11] as well as lower limbs[12,13], but clinically visible cerebellar symptoms are generally unusual. The postural tremor may be out of phase in the limbs, which accounts for the observation that functionality may improve when two hands are used, rather than one hand (e.g., while holding a cup)[7]. The tremor has greatest amplitude at the wrist joint, rather than more proximal or distal joints, and generally involves wrist flexion-extension rather than rotation/supination[12]. The tremor of ET is regularly recurrent and directionally symmetrical which can be easily observed on spiral drawings and this helps in differentiating from dystonic tremor[12,14]. Generally, there is no rest tremor, but in 10 - 15% of advanced cases, there may be rest tremor[15] which is most probably because the patient is not able to completely relax the limb[16]. Differentiating from rest tremor of PD may be difficult in these advanced cases but differentiating points in favour of essential tremor are: absence of pill rolling tremor, absence of re-emergent tremor, absence of signs of bradykinesia and rigidity and absence of dampening of tremor on movement. Although head (34%), lower limbs (20%), voice (12%), face and trunk (5%) may be involved, arm tremor in ET is always be more severe than tremor elsewhere[17]. Patients with ET may have a dominant family history of tremor. There may be some improvement with alcohol, but this feature is neither sensitive nor specific[5]. Diagnosis of ET requires absence of other neurological signs, such as dystonia, ataxia, or parkinsonism (Table II). Tremor with the characteristics of ET and additional neurological signs of uncertain significance such as impaired tandem gait, questionable dystonic posturing, memory impairment, or other mild neurologic signs, including rest tremor of unknown significance that do not suffice to make an additional syndrome classification or diagnosis, is now referred to as ET plus[3].

Enhanced Physiological Tremor: All normal people have a very low-amplitude, high-frequency physiologic tremor of approximately 10 to 12 Hertz (Hz) with a much lesser amplitude that sometimes get enhanced because of numerous factors such as fatigue and anxiety – Enhanced Physiological Tremor. It can be demonstrated by holding a piece of paper on the outstretched hand when shaking of the paper may be obvious even though tremor is not grossly visible or by using a laser pointer on a distant screen. Some medications and medical problems can also cause EPT[18]. The main differential is essential tremor (Table III) and treatment is mainly reassurance because it is usually not symptomatic except in fine motor tasks requiring extreme precision (e.g., microsurgery, jewellery making).

Table II: Diagnostic criteria of essential tremor[3].

1. Isolated tremor syndrome of bilateral upper limb action tremor.
2. At least 3 years' duration.
3. With or without tremor in other locations (e.g., head, voice, or lower limbs).
4. Absence of other neurological signs, such as dystonia, ataxia, or parkinsonism.

Table III: Clinical cues for differentiation of essential tremor and enhanced physiological tremor[7].

Features	Essential tremor	Enhanced physiological tremor
Frequency of postural and kinetic component	Lower (5 - 10 hz)	Higher (8 - 12 hz)
Amplitude of tremor	Higher	Lower
Intentional component of tremor	May be prominent (although needs to be differentiated from terminal tremor)	Absent
Body regions involved	May have involvement of voice, limb and head	Head tremor not a part of spectrum

Isolated focal tremors: Patients with isolated focal tremor, without accompanying dystonia, pose a diagnostic challenge of whether the tremor is part of an incomplete phenomenology of dystonia (so-called *"formes frustes"*) or similar in pathophysiology to ET.

Head tremor is a common focal tremor, that can be seen in the context of ET, cervical dystonia and cerebellar disorders. Isolated head tremor is not likely to be ET, because it has been observed that head tremor in ET is often seen in the presence of arm tremor[19] and is more common in women[20]. Moreover, tremor may precede the onset of dystonic postural abnormalities and may remain isolated for extended periods and even for the whole disease course making it a form fruste of cervical dystonia rather than ET. Head tremor in cervical dystonia more often persists when a patient lies down, whereas in ET head tremor usually dampens on lying down[21].

Isolated Voice Tremor: Voice tremor can be seen in PD, ET, ataxic dysarthria, and spasmodic dysphonia. Patients with

visible and/or audible tremor of the vocal apparatus and no signs of dystonia in the vocal apparatus and no tremor, dystonia, or other neurological signs elsewhere are considered to have isolated voice tremor (also labelled as essential voice tremor). Whether this is part of the clinical spectrum of ET[22] or a form fruste of dystonia is still debated[23]. Voice tremor of spasmodic dysphonia is often associated with voice breaks or strangulated speech in contrast to essential tremor.

Jaw tremor: Jaw tremor is a recognised feature of PD (often seen at rest), ET (often seen when the mouth is held open or during speech); hereditary geniospasm; neuroleptic treatment and in normal situations, such as shivering. In all these conditions, jaw tremor is associated with tremor or other abnormal involuntary movements affecting additional body parts, and the tremor frequency usually does not exceed 12 Hz[24]. A high-frequency idiopathic isolated jaw tremor of 14 -16 Hz has also been described[25]. It has been speculated that it could be a focal variant of primary orthostatic tremor affecting the masseter muscles[26].

Palatal Tremor: Essential palatal tremor presents with the symptom of an ear click, mostly attributed to rhythmic contraction of the tensor veli palatini characterised by rhythmic movement of the roof of soft palate at 0.5 to 5 hz. It is not associated with any other neurological abnormality and disappears in sleep which differentiates it from symptomatic palatal tremor[27].

Rabbit Syndrome: This was first described by Villeneuve[28] and is used to describe orofacial movement like that of a rabbit eating and is often associated with a popping sound. It classically occurs after long-term use (months to years) of dopamine receptor blocking agents and imipramine, citalopram, paroxetine, methylphenidate, and phenol intoxication. There are fine rhythmic movements (5 Hz) at rest involving only the vertical axis of the oral, perinasal and masticatory muscles[29]. It is essential to differentiate rabbit syndrome from tardive dyskinesia because unlike tradive dyskinesia, rabbit syndrome usually shows improvement with anticholinergic agents. Differentiating points favoring rabbit syndrome include: absence of tongue involvement, restriction of lip movements in the vertical plane (in contrast to chewing and lip smacking in tradive dyskinesia), and suppressibility.

Position and Task Specific Tremors: Isolated task and position specific tremors are usually focal and occur during a specific task or posture. Isolated task and position specific tremors can be confused with similar syndromes that occur in combination with other neurological signs, such as dystonia (e.g., writer's cramp with dystonic tremor) and parkinsonism (e.g., young-onset PD with dystonia). The most common entity that presents as task specific tremor is writing tremor (previously also called primary writing tremor). It is characterised by prominent pronation/ supination wrist movements that occurs predominantly or exclusively during writing without accompanying dystonia. There may be associated mild postural and terminal kinetic tremor. the frequency of primary writing tremor is like that seen in patients with essential tremor (i.e., 4 hz to 8 hz) and it is relieved by ethanol consumption in 30% to 50% of cases. Writing tremor has been variably classified as an independent entity, an ET variant, a focal dystonia, or an overlap between ET and dystonia[30]. Positional tremors arise only when a tremor is brought on during specific positioning of the involved body part and need to be differentiated from postural tremor, wherein a tremor is elicited in any posture, though it may be more prominent in one posture.

Orthostatic Tremor (OT) syndrome is a rare tremor disorder of the legs and trunk that occurs on standing and dissipates with walking or sitting down[31]. On standing, OT increases in a crescendo fashion over seconds to minutes to the point that the patient cannot continue to stand and must either sit or walk. Patients tend to stand with a wide base, but can walk with a narrow base, tend to avoid standing in queues because of OT. Primary OT has a very high frequency and it may not be visible by naked eye but can be heard with a stethoscope with a sound resembling a distant helicopter during auscultation (helicopter sign)[32]. Diagnosis needs confirmation with EMG recordings that reveal a 13 - 18 Hz tremor[33]. If there are additional signs of dementia, parkinsonism or ataxia it should be labelled as primary orthostatic tremor plus[34]. On the other hand some patients may have a slower orthostatic tremor; often in association with other neurological signs, and have been labeled as slow orthostatic tremor, tremor in orthostatism, and pseudo-orthostatic tremor[35]. Pseudo orthostatic tremor has a frequency of 4 - 6 Hz, may be assymetrical and is seen in conditions such as Parkinson's disease, Lewy body dementia and SCA3.

Isolated Rest Tremor: There is a group of patients with asymmetric rest and postural tremor, mostly resembling a somewhat irregular parkinson tremor, but often do not have other signs of parkinsonism and may show normal dopaminergic striatal innervation measured with Fluorodopa-PET. Various terms have been used for this group of patients - scans without evidence of a dopaminergic deficit' (SWEDDs), Benign Tremulous Parkinson's Disease, monosymptomatic tremor at rest and isolated rest tremor. Its exact aetiology is not yet clear. It has been seen that almost 15% of patients who present with an asymmetric rest tremor resembling PD have a normal dopamine transporter scan[36] and of these only 8 - 13% converted to have an abnormal scan up to 5 years later[37]. Others developed clinical features of advanced

Table IV: Clinical cues for differentiation of essential tremor, dystonic tremor and parkinsonian tremor[44].

Clinical features	Essential tremor	Dystonic tremor	Parkinsonian tremor
Anatomy	Hands > head > voice > others Wrist tremor > metacarpal joint tremor At wrist, flexion extension > rotational	Head >hands>others	Hands > others Metacarpal joint tremor > wrist tremor At wrist, rotational > flexion extension
Symmetry	Largely symmetrical, gross asymmetry (5%)	Asymmetrical	Asymmetrical
Activation	Posture > kinetic > rest	Posture > kinetic > rest	Rest > posture
Tremor suppression at movement onset	No	Rare	Most cases
Mental concentration	Tremor increases	Variable	Tremor decreases
Writing	Tremor increases	Variable	Tremor decreases
Walking	Tremor decreases	Variable	Tremor increases
Sensory trick	None	Most cases	None
Presence of null point*	None	Most cases	None
Alcohol intake	Supresses	Rarely	Rarely
Treatment	Beta blockers, primidone, dbs, botulinum toxin	Botulinum toxin, dbs	Levodopa, dbs

**Relief of tremor occurs by allowing the abnormal dystonic posture to develop without resistance.*

disease by the final third of their disease course and were then indistinguishable from classical Parkinson's disease. As a result, this is a heterogenous group of patients that may have different clinical outcomes including but not limited to: dystonic tremor, early PD, essential tremor plus, PD with striatal dopaminergic deficiency without nigral degeneration, Holmes tremor or atypical parkinsonism. There are certain important caveats, that the clinician must keep in mind while evaluating a patient with isolated rest tremor. First, bradykinesia is the *sine qua non* for parkinsonism and it requires progressive decline in amplitude and velocity of movements (motor decrement). Slowness of initiation of movement or reduced amplitude of movements without motor decrement may be seen in dystonia or pyramidal slowness and this can be one of the reason for patients with dystonic tremor being diagnosed as PD with normal DAT scans. Secondly, although Unified Parkinson's disease rating scale requires to test rapid alternating movements for 10 movements, this may not be enough to rule out bradykinesia in patients presenting with rest tremor. Ideally the patient should be asked to do 64 movements for 15 - 30 seconds before commenting on the absence of bradykinesia[38]. Finally, even if the clinician believes that tremor is isolated, dopamine transporter imaging should be done to exclude a parkinsonian condition, given that some early tremor-dominant PD patients (monosymptomatic tremor at rest) may exhibit no appreciable bradykinesia or rigidity early in the disease. It is best to label these patients as isolated rest tremor and terms such as SWEDDs and Benign Tremulous Parkinson's Disease should be avoided.

Combined Tremor Syndromes: Combined tremor syndromes include syndromes in which tremor is accompanied by other neurological signs such as parkinsonism, dystonia and cerebellar features. The aetiology of combined tremors is exhaustive. The common combined tremor syndromes are discussed.

Tremor combined with parkinsonism: Tremor combined with parkinsonism (bradykinesia and rigidity) is typically a 4- to 7-Hz rest tremor of the hand ("pill-rolling" tremor), lower limb, jaw, tongue, or foot. This is called classic parkinsonian tremor. It is noteworthy that other types of tremor may coexist in patients with parkinsonism, such as postural or kinetic tremor with the same (type 1) or different frequency (type 2) as the rest tremor[1]. Besides bradykinesia, other features that point to PD as the cause of tremor are: cessation or marked dampening of tremor on voluntary movement and its re-emergence on cessation of activity and maintenance of posture. Rest tremor and bradykinesia/rigidity in PD may progress independently and with advancing disease, increasing rigidity of the limbs may obscure the tremor. The tremor-dominant PD may be associated with earlier age at onset, less cognitive decline, and slower progression than the type of PD that is dominated by postural instability and gait difficulty (PIGD)[39]. Rest tremor is uncommon in other parkinsonian conditions such as MSA, corticobasal degeneration, and PSP and a postural, kinetic, dystonic or intention tremor may be more common.

Dystonic Tremor syndromes

These syndromes have a combination of tremor and dystonia as the leading neurological signs. When tremor occurs in a body part that is dystonic – it is referred to as

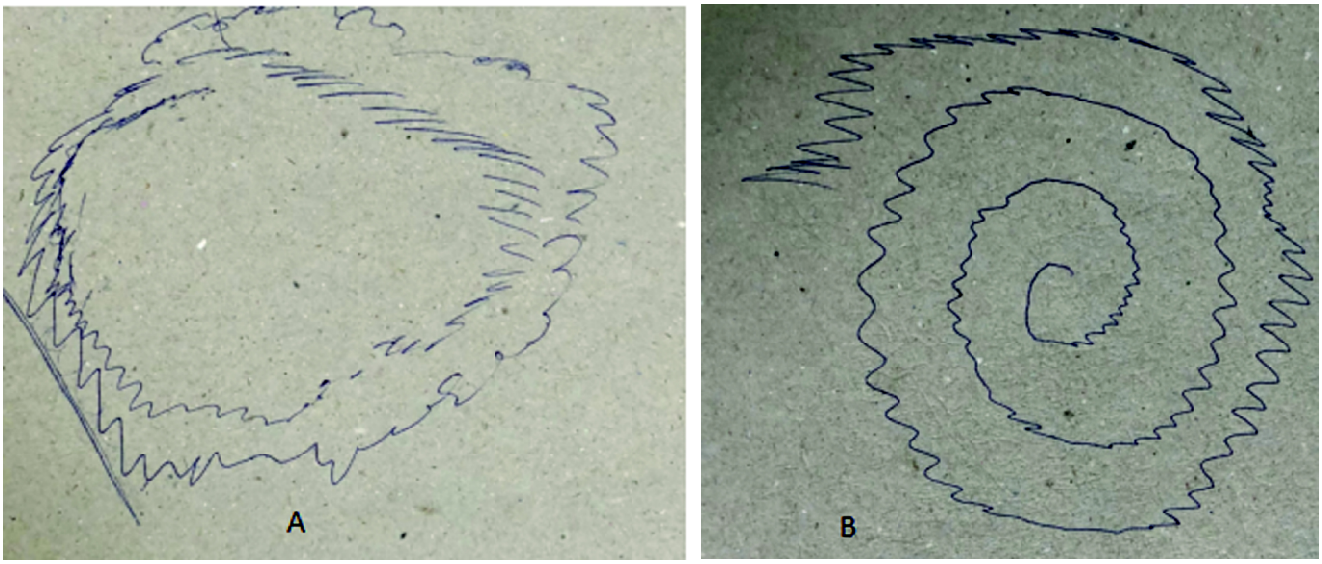

Fig. 2: *Spiral drawings in Dystonic tremor and essential tremor (A) Dystonic Tremor: The axis of tremor is variable and in essential tremor. (B) The axis remains the same throughout of the spiral.*

dystonic tremor, e.g., head tremor seen in cervical dystonia or segmental tremulous dystonia affecting the head and upper limbs. Tremor in dystonia manifests during posture or voluntary movements (action tremor), even though some dystonic patients may have tremor at rest. It is frequently unilateral,in patients with bilateral tremor it is often asymmetric and may be jerky rather than rhythmic[7]. Dystonic tremor may be relieved by sensory tricks (*geste antagoniste*); allowing the abnormal dystonic posture to develop without resistance ("null point") and is worsened by an attempt to maintain certain postures, which may account for the position sensitivity of dystonic tremor. If dystonia and tremor are found in different body parts, this is called tremor associated with dystonia[3], for example tremor in upper limbs in a patient with cervical dystonia. There is an additional group of patients, who have an asymmetric jerky tremor that has features of dystonic tremor mentioned above, but do not have any signs of dystonia anywhere in body. This group of patients may develop dystonia later and probably represent a form fruste of dystonia. Till such time, they develop signs of overt dystonia, it is best to label them as Indeterminate Tremor, thereby avoiding misclassification as ET or premature classification as dystonic tremor. Dystonic tremor may be primary dystonic tremors for example cervical dystonic tremor and hand tremor in primary writer's cramp, genetic [for example anoctamin 3 (ANO3)] or secondary to Parkinsonism, Wilson disease, Neurodegeneration with brain iron accumulation or other neurodegenerative conditions.

A pictorial differentiation from ET is shown in Fig. 3. The clinical pointers to help differentiate ET, PD and Dystonic tremors are summarised in Table IV.

Intention tremor syndromes

Intention tremor syndromes consist of intention tremor at < 5 Hz, with or without other localising signs usually signifying a lesion in the cerebellothalamic pathway. Intention tremor is characterised by usually side-to-side movements perpendicular to the line of travel, predominantly proximal more than distal and amplitude of oscillations increases toward the end of movement[4]. Tremor needs to be differentiated from irregular movements that occur in the line of the travel which are due to dysmetria. Cerebellar intention tremor usually is of low frequency, around 2 - 4 Hz[40].

Holmes Tremor

Holmes tremor is generally a unilateral tremor that has three components: rest, postural and kinetic intention tremor with the relative severity generally being such that kinetic tremor is greater than postural tremor, which is greater than rest tremor. There is both a proximal and distal component and the frequency is usually < 5 Hz[41]. Patients may have other neurologic signs including mild dystonia, oculomotor abnormalities, hemiparesis or ataxia. Common causes include cerebrovascular accident and multiple sclerosis, with a possible delay of 2 weeks to 2 years[42] in tremor onset and the occurrence of lesions. The anatomical localization is in the brainstem in the vicinity of red nucleus causing disruption of both nigrostriatal dopaminergic and cerebellothalamic systems causing the combination of a parkinsonian rest tremor and a cerebellar intention tremor.

Functional Tremor

Functional tremor is often present at rest, on posture and during action, something that is unusual in organic tremor other than seen in Holmes Tremor. Onset is usually abrupt with maximal disability at onset followed by a static or fluctuating course. The key features in differentiating functional tremor from organic tremor are: entrainment (ability of the examiner to alter the rhythm of the patient's tremor by having it match the rhythm of a tremor the examiner produces); exacerbation of tremor on weight loading; pause in tremor with a ballistic movement; distractibility and suggestibility[4].

An algorithm for clinical evaluation of tremors is depicted in Figs. 1 and 2.

Conclusion

Although tremor is the most common movement disorder, its diagnosis is often challenging. The approach to tremor involves a history and careful neurologic examination, focused on the nuances of clinical phenomenology and careful examination of associated findings such as bradykinesia, dystonia and ataxia. There is significant overlap between the common tremor syndromes and the exact nosology of various syndromes such as isolated rest tremor and tremor associated with dystonia is still not clear. If the phenomenology of tremor syndrome is not clear, it is best to label it as Indeterminate Tremor and keep the patient in observation.

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Mrs. Uma Bansal – Prof. B.C. Bansal Best Paper Award (Journal-2022)

1st Prize for Best Original Article – " Comparison of Non-Invasive Scoring Systems with Ultrasound and Liver Elastography in Predicting Non-Alcoholic Fatty Diseases in Health Population" – Dr Kartik Balankhe, Dr Rishabh Ramu Nayak, Dr Rajesh Kumar Modi, Dr Pulin Kumar Gupta, Department of Medicine, ABVIMS and Dr RML Hospital, Baba Kharak Singh Marg, New Delhi - 110 001.

2nd Prize for Best Review Article – "Rickets in Renal Tubular Acidosis: A Clinical Appraisal" Dr Chhavi Agrawal, Dr Partha Pratim Chakraborty, Department of Endocrinology and Metabolism, Medical College and Hospital Kolkata, 88, College Street, Kolkata - 700 073 (WB).

3rd Prize for Best Case Report – "Covid-19- Retated Multisystem Inflammatory Syndrome in Adults; An Uncommon Case" – Dr Ashok Kumar Aggarwal, Dr BM Singh Lamba, Dr Vasudha Kumari, Dr Atul Kaushik, Department of Medicine, SMS & Sharda Hospital, Sharda University, Greater Noida - 201 308 (UP).

CASE REPORT

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ITP Associated Bilateral Adrenal Haemorrhage: Near Kill and Saved

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Abstract

Bilateral adrenal haemorrhage (BAH) is a rare but potentially fatal entity that carries a high mortality rate. Most cases are associated with sepsis, antiphospholipid syndrome, use of anticoagulants, trauma or surgery. In this case report, we present a case of BAH, in a previously healthy man, with a recent history of corticosteroid use for his immune thrombocytopenic purpura (ITP). Our case emphasizes the ambiguous clinical presentation of BAH, that poses a great challenge in the establishment of a early and correct diagnosis. We further explain the pathophysiology, diagnostic clues and therapeutic approach to this rare entity. ITP is an immune-mediated, acquired disease reported in adults as well as children. It is characterised by transient or persistent decreases in platelet count. We present a rare case repot of bilateral adrenal haemorrhage caused by ITP, saved from an adrenal crisis by steroid therapy ongoing for his ITP. Despite the high mortality associated with adrenal haemorrhage, our patient survived and is doing well on follow-up.

Key words: ITP, bleeding crisis, adrenal haemorrhage, adrenal crisis.

Introduction

Bilateral adrenal haemorrhage (BAH) is a life-threatening condition which usually leads to an adrenal crisis and death, if not diagnosed and treated in time[1]. The pathogenesis of this rare entity is thought to be related to the increased vascularisation of adrenal glands in a physiological response to stressful events[2,3]. This vascular congestion causes haemorrhage in the adrenals, usually unilaterally but rarely bilaterally. Post-operative status, thromboembolic disease, and coagulopathy are reported causes of such a response, among many other causes[3]. Identifying the signs and symptoms of an oncoming adrenal crisis is of utmost importance, as it is overshadowed by signs of the underlying cause[2]. Serum cortisol, 24-hour urinary cortisol, dexamethasone suppression test and adrenocorticotropic hormone (ACTH) test, are helpful in confirming diagnosis of adrenal crisis, further supported by computed tomography (CT), which confirms adrenal haemorrhage. CT is pivotal for the early diagnosis of adrenal haemorrhage and commencing corticosteroid replacement therapy to prevent mortality[4].

ITP is as a haematologic disorder which is characterised by isolated thrombocytopenia without any apparent cause. The risk of spontaneous haemorrhage due to low platelet count is important in determining the prognosis of ITP. Patients have an estimated risk of fatal haemorrhage of approximately 5% throughout their lifetime; however, this risk of major haemorrhagic complications exponentially increases with age[5].

The clinical characteristics of ITP are mucocutaneous lesions such as petechiae or ecchymosis, epistaxis, easy bruising, and gingival bleeding[6].

Our patient reported a rare presentation of ITP, causing spontaneous bilateral adrenal haemorrhage, leading to Addison's crisis, which was pre-emptively treated by the ongoing treatment with corticosteroids, for ITP itself.

Case history

A 48-year-old male patient, with no significant medical history, presented to our hospital in September 2021 with complaints of recurrent loose stools (10 - 12 episodes), nausea, 2 - 3 episodes of vomiting, generalised pain in the abdomen, generalised weakness and left-sided chest discomfort since 2 - 3 days. On further history taking there was no fever, sweating, palpitation, black stools or fresh blood in stools. He had no medication or recent vaccination history, did not consume alcohol and did not have any addictions. He had no history of any recent or past illness, such as tuberculosis, COVID. On examination, he was conscious, oriented general examination was normal, and vitals were stable. Rest of systemic examination was normal. With a probable diagnosis of acute gastroenteritis, relevant investigations were sent and treatment started with empirical antibiotics, i.e., inj Ceftriaxone (1 gm IV BD), inj Metronidazole (500 mg in 100 ml ns IV TDS), IV fluids and supportive treatment. Ultrasonography of whole abdomen and chest X-ray were performed, which were normal. Stool examination, LFT,

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KFT, coagulation profile and D-DIMER were normal. However, patient's full blood count showed severe isolated thrombocytopenia (Platelet: 5,000/mm3) with a normal haemoglobin (14.1gm/dl) and normal TLC (8,000/mm2) with normal differential leukocyte count. Further work-up for the cause of thrombocytopenia was done and hematologist reference was taken. Since Dengue is endemic to Delhi during monsoon month of September, Dengue Serology and NS1 antigen were tested as a probable cause of thrombocytopenia which came out to be negative. Further Typhi dot Ig M, WIDAL test, peripheral smear for malaria, malarial serology, urine and blood cultures were negative. Urine routine was normal with no proteinuria, hematuria. Acute phase reactants like ESR, CRP and Ferritin were also within normal limits ruling-out macrophage activation syndrome. Serum Vit B12, Folic acid, Homocysteine, and Iron study were normal. Peripheral smear was otherwise normal except marked thrombocytopenia. Indirect and direct coombs test were negative. HIV, hepatitis C, ANA titre, and lupus anticoagulant were negative. Conservative treatment was continued and platelets were arranged but not transfused as yet, due to absence of any bleeding manifestations. Patient's platelet counts were repeated, which further reduced to 2,000/mm^3 on next day, and he was then transfused 3 unit of RDP (random donor platelets) and 4 units of SDP (single donor platelet) over 2 days. He responded to the platelet transfusion and his platelet increased to 58,000/mm^3 on 3rd day. After consultation with hematologist and explaining risk of procedure to patient and relatives, a bone marrow aspiration (BMA) was done to know the cause of thrombocytopenia. The procedure was uneventful and BMA was reported as a normal reactive bone marrow with normal cell lines. His platelet count reduced further to 30,000/mm^3 on 4th day. Taking all results into consideration and hematologist consultation, a diagnosis of ITP was made. The patient was started on IV Solumedrol pulse therapy (500 mg IV OD*3 days) and T. Revolade (Eltrombopag 50 mg OD). Patient responded well to the treatment and his platelet count started showing a gradual increase and he was discharged on 5th day with a platelet count of 72,000/mm^3 on Tab. Wysolone 60 mg OD, Tab. Revolade 50 mg HS and supportive treatment. Patient was called for review after 5 days, and he presented with severe band like pain in abdomen equally on both sides radiating to the back since 1 day associated with nausea but no vomiting. There was no history of constipation. On examination, the vitals were stable, abdomen was tender and distended and bowel sounds were reduced. All other examination was normal. An urgent X-ray abdomen erect and supine was done to rule-out intestinal obstruction, and a surgery reference was sought.

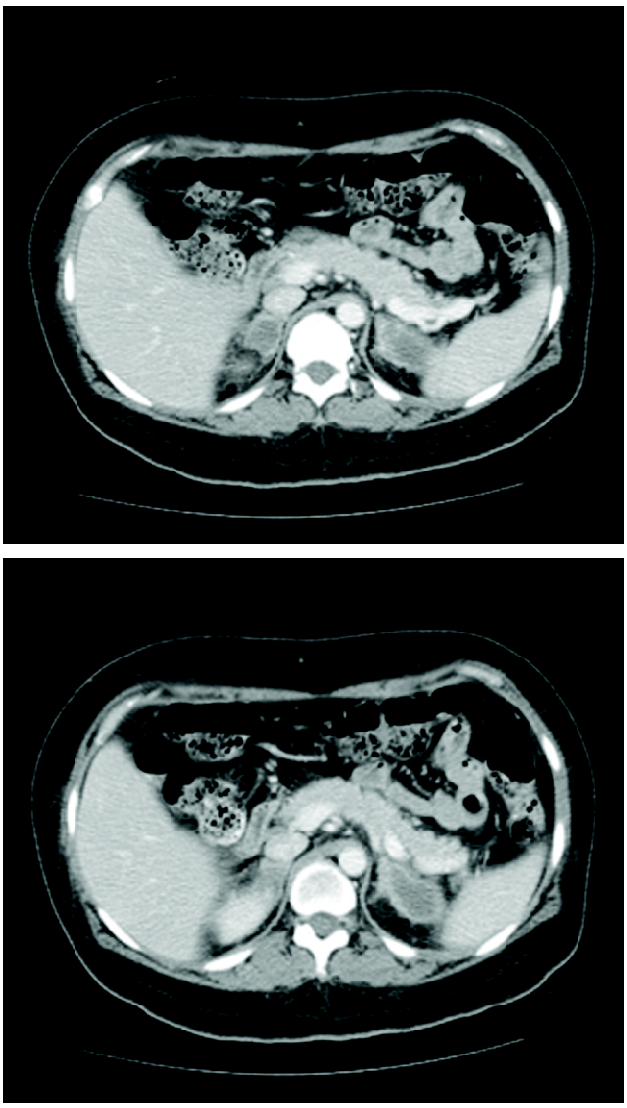

Fig. 1: *Bilateral adrenal haemorrhage on CECT scan of abdomen.*

Liver and Kidney function tests and urine reports were normal and fever profile was negative. Patient's platelet counts on admission were 28000/mm3 while taking Tab. Wysolone 60 mg OD and Tab. Revolade 50mg HS. Patient's USG of the abdomen showed bulky bilateral adrenals with adrenal hemorrhage and extensive surrounding inflammation. Also, there was minimal non-tappable bilateral pleural effusion and mild pericardial effusion. Further, on discussion with the hematologist, patient was suspected to have ITP induced BAH. A contrast enhanced CT scan of the abdomen was performed, which confirmed the diagnosis of BAH. Suspecting a complication of Addison's crisis the following blood tests were ordered, Serum ACTH, Cortisol (8 am) and 24-hr urinary cortisol. Of this Serum ACTH was high (75 pg/ml); all other tests were normal. Also, the patient's vitals electrolytes and blood sugar

levels were normal throughout the admission. On discussion, the steroid therapy given to the patient for ITP, prevented a full-blown adrenal crisis and haemodynamic instability. He was discharged on T. Fludrocortisone (100 mcg thrice a day dose), Tab. Wysolone 60 mg OD, Tab revolade 50 mg twice a day along with iron, vitamin B complex and folic acid supplementation. On subsequent follow-up, the BAH showed gradual resolution. Patient remained haemodynamically stable and showed gradual improvement. There was no clinical or radiological evidence of any arterio-venous thromboembolism. Written informed consent was taken from the patient to report this case with images.

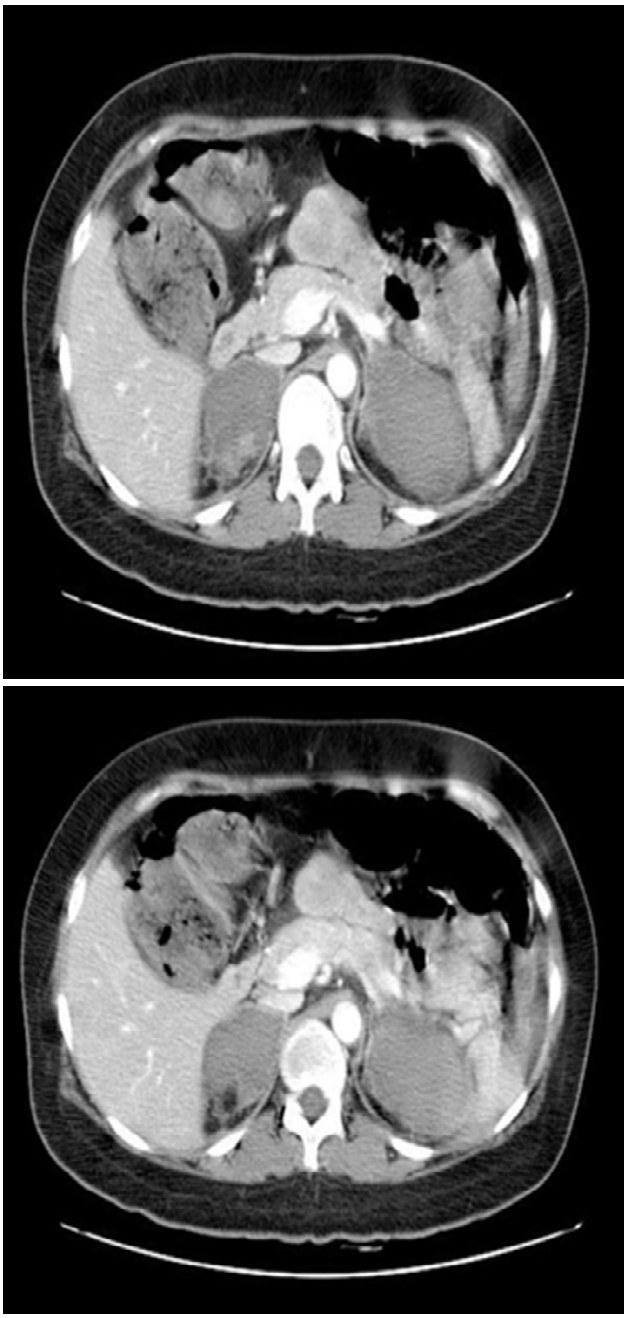

Fig. 2: *Follow-up study revealing decreased size of bilateral adrenal haemorrhage.*

Table I: Investigations on 1st admission

1st Admission	Day 1	2	3 (2 RDP, 1 SDP transfused)	5 (2 RDP, 1 SDP transfused)	7 (2 SDP transfused)
Haemoglobin (13.5 - 15 g/dl)	14.1	14	13.9		13.9
WBC (4 - 11 x 10^3/mm^3)	8,000	12,000	11,000		10,500
Platelet count (per mm^3)	2,000	2,000	15,000	58,000	72,000
INR (0.90 - 1.20)	1.12		1.2		1.0
S creatinine (0.7 - 14 mg/dl)	1.12	1.30	0.9		0.9
S urea (12 - 20 mg/dl)	20		18		15
D-DIMER (< 250 ng/ml)	120				110
S. TSH (0.47 - 4.68 mU/L)	1.34				
NS1 antigen	Negative				
Dengue serology	Negative				
S. Ferritin (6.2 - 137 ng/ml)	120				
S. LDH (120 - 246 U/L)	250				225
CRP (< 0.3 mg/dl)	0.2				0.2
ESR (0 - 22 mm/hr)	30				
S. Procalcitonin (0 - 0.50 ng/ml)	0.1				

Table II: Investigations on 2nd admission.

2nd Admission	Day 1	2	3	5	9
Haemoglobin (13.5 - 15 g/dl)	9.0	9.8	9.1		10.
WBC (4 - 11 x 10^3/mm^3)	8,000	12,000	11,000		10,500
Platelet count (per mm^3)	28,000	50,000	54,000	58,000	98,000
INR (0.90 - 1.20)	1.3		1.1		1.1
D-DIMER (<250 ng/ml)	400				245
S. TSH (0.47 - 4.68 mU/L)	1.34				
S. Ferritin (6.2 - 137 ng/ml)	144				
S. LDH (120 - 246 U/L)	300				
CRP (<0.3 mg/dl)	0.2				
ESR (0 - 22 mm/hr)	50				

Discussion

BAH is a rare condition, with an incidence of around 0.14 - 1.8%, mainly based on postmortem studies[1]. This rare clinical entity is associated with burden of potentially life-threatening consequences, due to acute adrenal insufficiency[2]. A major reason for poor outcome of this condition is that despite treatment with stress-dose glucocorticoids, many cases of adrenal haemorrhage die because of delayed recognition and treatment. A high

mortality rate of up to 15% has been reported; but it varies widely depending on severity of the underlying illness and is exponentially higher if the adrenal insufficiency is not diagnosed and treated promptly[1]. Pathophysiology of BAH is uncertain in most cases. Cortisol has multiple endocrine and metabolic functions, especially during stressful events. Adrenal haemorrhage due to stress is thought to be an exacerbation of the physiological effect of increase in arterial blood flow of adrenals alongwith slowing of venous drainage due to single adrenal vein, causing vascular congestion inside the glands leading to subsequent haemorrhage[2,3]. These physiological changes may be because of multiple predisposing factors, like stress from surgery, sepsis, severe illness, haemorrhagic diatheses (e.g., anticoagulants, thrombocytopenia), burns, thromboembolic disease like antiphospholipid antibody syndrome, etc.[2,7]. Adrenal haemorrhage is not usually suspected and hence missed due to nonspecific clinical and laboratory findings. It presents with non-specific signs of abdominal pain, fever, vomiting, weakness, hypotension or shock and altered sensorium, which are often same as those of the underlying illness making suspicion of adrenal haemorrhage very difficult[3]. Fever is one of the most common physical signs occurring in upto about 70% of cases[2] whereas hypotension is missed until it presents as shock[2,3]. Due to those difficulties, primary adrenal insufficiency secondary to adrenal haemorrhage, in the past, was diagnosed on post-mortem[3,7]. Likewise, in our case, abdominal pain, fever, and hypotension were misinterpreted as sepsis and intestinal obstruction. Also, laboratory findings are not invariably present, as the acute adrenal crisis was masked by the corticosteroid therapy the patient was already taking. Hyponatraemia, hyperkalaemia, and hypoglycaemia are commonly found in adrenal insufficiency but were absent in our case[3]. Although low serum sodium with high serum potassium is suggestive of underlying adrenal insufficiency, its absence cannot exclude this diagnosis[3]. Hormonal diagnosis is confirmed with serum cortisol and plasma ACTH. Acute adrenal insufficiency is diagnosed by combination of increased plasma ACTH and low or low normal <13 mcg/dl) serum cortisol. These are highly suggestive of glucocorticoid deficiency due to primary adrenal insufficiency caused Addison's crisis. The short synocthen stimulation test can also be used to confirm the diagnosis. Basal cortisol and ACTH levels are sufficient to start immediate glucocorticoid replacement therapy[2,3,7]. Recent literature describes the crucial role of imaging, especially CT scan, to confirm the diagnosis of adrenal haemorrhage. As both benign and malignant adrenal conditions may present with massive bleeding, or evolve in partially fluid lesions, it is difficult to differentiate it on basis of scans. But a careful follow-up shows a typical decrease in volume of idiopathic haemorrhage in contrast to neoplasms, which do not decrease in size with time[2]. Furthermore, adrenal haemorrhage should also be suspected when there is ill-defined soft-tissue stranding around adrenal gland, due to infiltration of blood through retroperitoneal fat . In the acute phase, the patient should

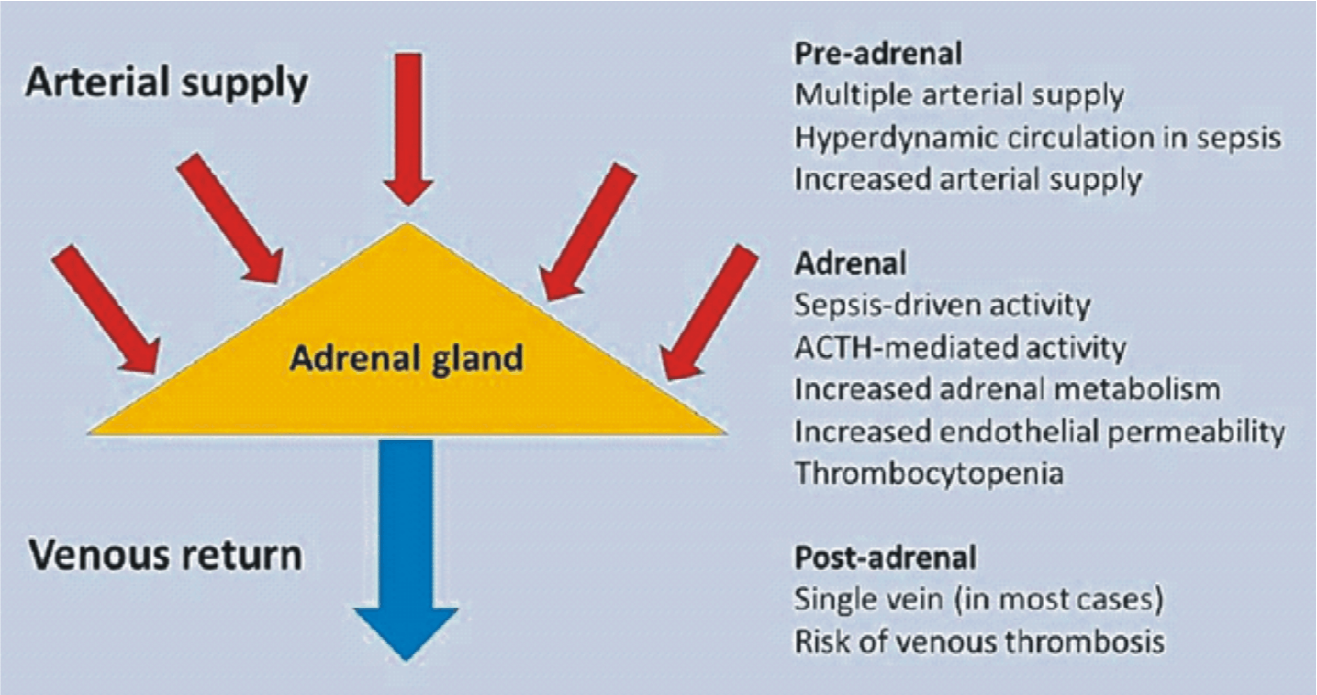

Fig. 3: *Schematic diagram showing the possible mechanisms involved in spontaneous adrenal haemorrhage (ACTH, adrenocorticotropic hormone).*

be immediately treated with hydrocortisone (initially 100 mg intravenous bolus followed by 200 - 300 mg over 24 - 48 hours as continuous infusion) and isotonic saline (1,000 ml within the first hour). After the acute management, long-term glucocorticoid replacement, preferably with mineralocorticoid replacement therapy is necessary, based on the results of adrenal function test[3,4].

ITP is caused by platelet destruction due to immune-mediated mechanisms and inadequate platelet production. ITP is classified based either on duration (acute or chronic) or age (childhood or adult).

Diagnosis of ITP is made by exclusion of other causes of isolated thrombocytopenia. Also, secondary causes of thrombocytopenia like leukaemia, HIV, hepatitis C, congenital causes, drugs and others must be excluded[1]. American Society of Hematology, states that a diagnosis of ITP can be made principally by history, physical examination, haemogram, peripheral smear examination and ruling-out other possible causes of thrombocytopenia[8].

Signs and symptoms of ITP are very variable and can range from the common presentation of an asymptomatic patient with mild mucosal bleeding (e.g., oral or gastrointestinal tract bleeding) or mild bruising to frank bleeding from any site or organ. Symptomatic bleeding is usually uncommon in ITP until severe thrombocytopenia occurs (platelet count <30,000/μl). However there is a poor correlation between severity of thrombocytopenia and bleeding manifestations. Severe cutaneous bleeding, menorrhagia, prolonged epistaxis, gingival bleeding, overt hematuria can develop even at platelet counts more than 10,000/μl[1].

Our case seems to be the first presentation of thrombocytopenia, and despite the low platelet count it was surprising that he has not had any episode of bleeding during the 1st admission. In the adult patient, ITP is generally insidious in onset without preceding illness and has a chronic course, unlike the pediatric population where it tends to follow the illness by a few days to a few weeks[9]. The temporal course of the illness in the case is more like an acute ITP, but the absence of bleeding is surprising given the severity of thrombocytopenia and rapid fall in platelet count in-hospital[10].

Immediate therapy is not indicated for patients with platelet counts between 20,000 and 50,000/μl, with on bleeding or predisposing comorbid conditions such as hypertension, anticoagulation, or recent surgery[1]. In patients with severe ITP, the aim is to increase platelet count immediately above 30,000/μl to prevent any lethal bleeding symptoms because thrombocytopenia in a patient with a platelet count less than 30,000/μl is associated with an exponentially increased mortality risk compared with thrombocytopenia in a patient with a platelet count more than 30,000/μl[11]. Therefore, especially in patients with severe ITP, rapidly increasing the platelet count is crucial. First-line therapy consists of corticosteroids, IVIg or other therapies. High-dose IV immunoglobulin therapy is considered first-line in bleeding emergencies of as it quickly improves symptoms. The small but increased risk of thrombosis in ITP patients has been attributed to patient related factors, treatment related factors, disease pathophysiology and presence of anti-phospholipid antibodies[12,13], but such complications were not seen with our case and he tolerated treatment well. The change in the bleeding phenotype to thrombotic may be due to platelet microparticles and young platelets in circulation along with endothelial activation with activation of natural anti-coagulation pathways and complement activation. In most patients with thrombosis in the setting of ITP treatment post-splenectomy status, patient factors and anti-phospholipid antibodies have been found to be significant. Practically all classes of drugs have been implicated in thrombosis including corticosteroids, IVIG, Thrombopoietin receptor agonists and anabolic steroids.

In conclusion, in spite of an ambiguous initial presentation of adrenal insufficiency, particularly when it overlaps with other manifestations of the concurrent severe illness, an early diagnosis is crucial to avoid catastrophic consequences of adrenal crisis. Therefore, this diagnosis requires a high index of clinical suspicion and rapid confirmation with CT of the abdomen. It is essential to identify early signs of adrenal congestion, such as gland thickening with surrounding fat stranding, a careful monitoring of the patient and eventually prompt replacement glucocorticoid therapy.

Conclusion

Our patient, a 48-year-old man, was diagnosed as ITP, secondary to acute infective gastroenteritis for which treatment was started with platelet transfusion and corticosteroids. Thereafter, patient developed spontaneous BAH secondary to ITP; the complications of adrenal crisis prevented by ongoing steroid therapy. Patient was managed with hydrocortisone followed by regular follow-up which revealed evolution of the BAH over time. This case emphasizes the importance of heightened awareness and clinical suspicion of this life-threatening condition.

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CASE REPORT

JIACM 2023; 24 (1): 64-66

Pirfenidone Induced Severe Photosensitivity Reaction in a Patient with Interstitial Lung Disease (Progressive Fibrotic ILD with UIP Pattern)

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Abstract

Interstitial lung diseases (ILDs) refers to a large and heterogenous group of parenchymal lung disorders with varied aetiologies, including connective tissue disorders, environmental occupational exposures and unknown aetiology like idiopathic pulmonary fibrosis (IPF). IPF is the most common type of idiopathic ILDs[1]. Hereby, we report a rare case of a 63-year-old female patient with erythematous pruritic skin lesions over sun exposed areas due to Pirfenidone therapy used for IPF.

Key words: Photosensitivity, pirfenidone, IPF, ILD.

Introduction

Drug-induced photosensitivity reactions are mainly phototoxic reactions that can be reversed by withdrawing or by substituting the drug. Drug classes responsible for photosensitivity reactions are non-steroidal anti-inflammatory drugs (NSAIDs), immunomodulatory, antimalarial drugs like hydroxychloroquine (HCQ)and some antibiotics. Photosensitivity with pirfenidone is a rare phenomenon and seldom reported. This case report presents a case of photosensitivity reaction by use of pirfenidone in a patient with idiopathic lung fibrosis. This report is presented to guide health professionals regarding these rare adverse drug reactions before using pirfenidone.

Case report

We report the case of a 63-year-old female with 15 days history of erythematous and pruritic lesions over sun exposed areas of face, forehead, neck, and dorsum of hands (Fig. 1). Hair, nails and mucosae were normal. She presented with history of breathlessness for 2 years and was on inhalers. HRCT chest was done which revealed usual interstitial pneumonia (UIP) pattern of ILD. Work-up for ILD aetiology, other than UIP was negative. There was no history of any connective tissue disorder. Her autoimmune work-up including RF (rheumatoid factor), anti-CCP (cyclic citrullinated peptide), ANA (antinuclear antibody), and ENA (extractable nuclear antigen) were negative. There was no drug history causing fibrosis and no plausible history suggestive of hypersensitivity pneumonitis. Therefore, she was diagnosed with IPF and was initiated on antifibrotic therapy with pirfenidone, 200 mg thrice daily and was gradually increased up to 2,400 mg/day. Add-on bronchodilator with ICS formoterol plus budesonide MDI (metered dose inhaler) and mucolytics were also given. She was continuing same therapy since last 2 years and was stable on treatment. Then she presented in OPD with new onset of skin lesions as described and a diagnosis of phototoxic reaction with pirfenidone was made based on history and clinical examination, after ruling-out other possible causes, confounding medications, prevailing viral infections, skin infestations and any skin allergy . Pirfenidone was stopped and patient was treated with oral prednisolone 0.75 mg/kg/day in tapering dose along with antihistamine, topical corticosteroids, sunscreens and strict photo-protection leading to resolution of lesions. Skin biopsy was not done.

Discussion

Pirfenidone is one of the two novel oral antifibrotic therapies approved to treat IPF. It has anti- inflammatory action along with antifibrotic properties, and was found to improve outcomes, decreased diseases progression, and improvement in forced vital capacity among IPF patients[1-3].

Pirfenidone has a favourable safety profile. The common side-effects include gastrointestinal, hepatotoxicity and rarely, a phototoxic reaction[3].

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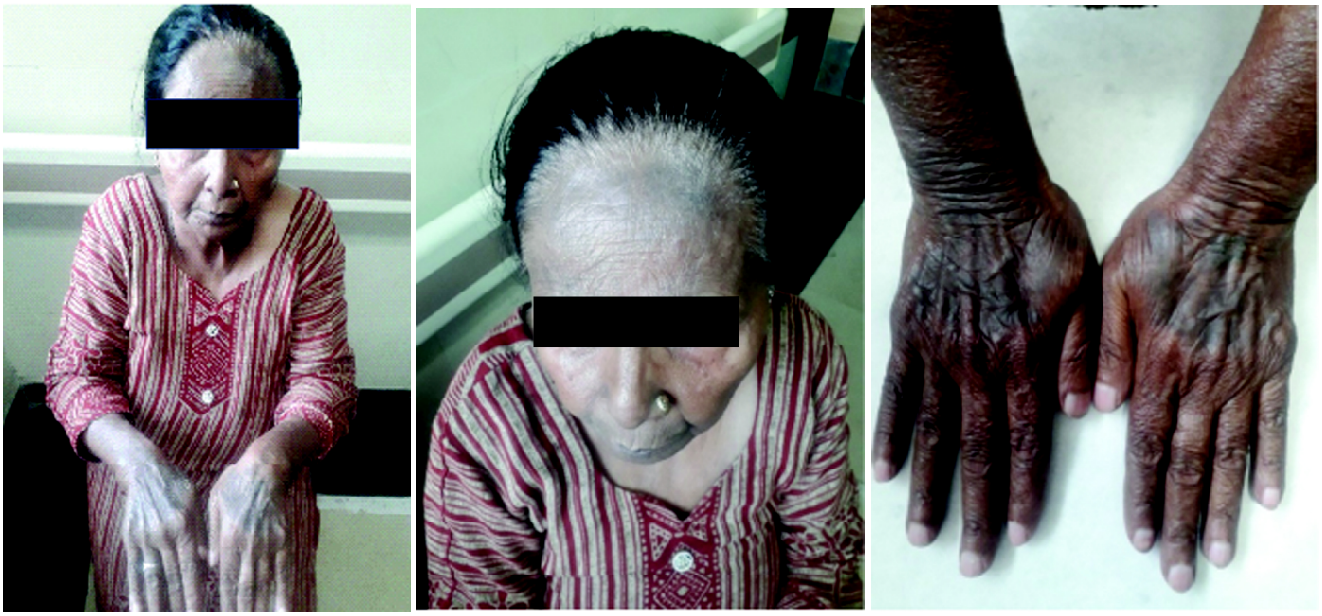

Fig. 1: *Hyperpigmented lesions over face and hand due to photosensitivity.*

Pirfenidone-induced phototoxic effect, is seldom reported, and the underlying mechanism of phototoxicity-phenomenon remainsunclear[4-9]. In previous reports the incidence of occurrence of photosensitivity has varied between 12 to 24%, with a higher occurrence among patients receiving higher doses of pirfenidone[5].

Few studies have conceptualised that it could be due to downregulation of certain growth factors such as transforming growth factor beta, leading to suppression of proliferation of myofibroblasts and collagen deposition. Seto *et al*, in an *in vitro* study had shown that the phototoxicity is likely due to drugs' ability to absorb ultraviolet rays via formation of reactive oxygen species (ROS) via cleavage of DNA and peroxidation of photodynamic lipids due to exposure to sunlight[10]. Droitcourt *et al* studied skin manifestations in patients on pirfenidone therapy and reported the mean duration between starting therapy and a skin manifestation was 5.5 months. Lesions were burning erythematous rashes followed by hyperpigmentation which was sharply limited to sun-exposed areas (bald head, face, neck, upper chest, and/or dorsa of forearms and hands), where sunscreen has not been applied one day after UV exposure. These findings were consistent with a moderate phototoxic reaction[11]. The standard approaches to prevent skin related adverse effects of pirfenidone include avoidance of direct sun exposure, and use of sunscreens with higher sun protection factor. As pirfenidone also causes gastrointestinal and neurological side-effects, these also need to be carefully monitored[12]. Dose reduction can decrease the dermatological and gastrointestinal side-effects.

Conclusion

Pirfenidone is a novel anti-fibrotic medication used in the management of IPF which helps to slow disease progression. It is of utmost importance for treating physicians to be cautious about all possible side-effects of the drug and to educate patients about these side-effects to counsel them about avoiding direct sun exposure, application of sunscreens and use of sun protective clothing. There is a relative increased occurrence of photosensitivity when higher doses are administered, thus in such cases, lower maximum doses should be considered. Moreover, it should be borne in mind to look for phtotosensitivity in every follow-up visit, even if the patient had been on pirfenidone for a long duration, like in the present case for 2 years.

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CASE REPORT

JIACM 2023; 24 (1): 67-69

Primary Hypoparathyroidism: An Uncommon Presentation with Reversible Cardiomyopathy

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Abstract

Primary hypoparathyroidism is an endocrine disorder with numerous causes leading to a low level of Parathormone (PTH) and consequent hypocalcaemia, leading to metabolic disturbances in the body. The authors here describe a case of 53-years-old female who presented with complaints suggestive of hypoparathyroidism. On further evaluation, she was found to have left ventricular dysfunction with valvular abnormality. Her blood investigations showed low calcium, low iPTH and high phosphorus levels s/o Primary hypoparathyroidism. Reversible cardiomyopathy could very well be the first presentation of an endocrinological disorder. The present case highlights that correction of hypocalcaemia is one of the potentially reversible causes of left ventricular dysfunction hence, diagnosing and treating this condition early is very vital.

Key words: Reversible cardiomyopathy, hypoparathyroidism, hypocalcaemia.

Introduction

Parathyroid Hormone (PTH) is involved in the regulation of calcium and phosphorus levels in the body with its neuro-hormonal effects on kidney, bone and gastrointestinal tracts. The most common cause of hypoparathyroidism is post-surgical iatrogenic removal of parathyroid gland (in around 80% of the cases), while less than 20% caseshave autoimmune aetiology[1]. Due to any cause, if the PTH levels decrease, hypocalcaemia develops, leading to various clinical manifestations. The laboratory hallmark of hypoparathyroidism is hypocalcaemia and hyper-phosphataemia.

Hypoparathyroidism presenting with severe hypocalcaemia leading to cardiomyopathy with valvular dysfunction is potentially reversible when hypocalcaemia is corrected after early diagnosis. In sporadic cases, it is reported that long standing hypocalcaemia can lead to irreversible structural damage to the myocardium[2-4]. Various cardiac manifestations that can develop as a consequence of hypocalcaemia are arrythmias (long QT syndrome), and diminished myocardial performance (hypocalcaemic cardiomyopathy).

Case report

A 53-year-old middle-aged female, presented in our emergency department with the complaints of acute onset carpopedal spasm, multiple joint pains, bilateral hand tremors with numbness and paraesthesias of hands and feet. Her spouse gave a history of irritability of behaviour in recent times; however, she denied any other neurological symptoms, or history of fatigue, exertional dyspnoea, chest pain, palpitations, fever, neck pain, lumps, skin changes, hair fall, joint pains, oral ulcers or photosensitivity. She gave no past history of any neck surgery, trauma, or any other chronic disease, nor there was any positive family history suggesting any genetic causes or polyendocrinopathy. There were no symptoms during her childhood or adulthood, until the day she presented to our hospital.

On examination, her vitals were normal (BP - 140/90 mm hg, HR - 78/min, RR - 16/min, afebrile). On neurological examination, there were resting fine bilateral hand tremors, but there was no rigidity, Gait was normal. Both Chvostek's and Trousseau's signs were positive. There were no dysmorphic features, muco-cutaneous manifestations (including evidence of candidiasis/vitiligo) or dental malalignment. Cardiovascular examination revealed no cardiomegaly but had auscultatory evidence of mitral regurgitation (i.e., Pan-systolic murmur at mitral area). Abdomen and respiratory exam were unremarkable. Ocular examination revealed no cataracts or any other abnormal ocular findings.

Patient's blood biochemistry showed initial serum calcium level of 3.9 mg/dl (normal range - 8.4-10.2 mg/dl); phosphorus 7.7 mg/dl (normal range - 2.5 to 4.5 mg/dl); serum PTH level of < 4 pg/ml (normal range 9.2 - 44.60 pg/ml); serum albumin - 4.4 g/dl (normal range - 3.5 - 5 g/dl); serum magnesium 2 mg/dl (1.6 - 2.3 mg/dl); 24-hour urine

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calcium level was normal 200 mg/24 hrs (abnormal > 250 mg/24 hrs), and serum vit D level, liver function and kidney function tests were normal.

ECG showed prolonged corrected QT interval (554 ms) and 2D Echo revealed LV dysfunction with EF - 40% and global LV hypokinesis with severe mitral regurgitation (Fig. 1).

Ultrasonography of neck did not reveal any lump or other abnormality and USG abdomen was normal. CT head showed multiple focal symmetrical areas of calcification in and along the gyri in bilateral frontoparietal region, caudate nucleus, basal ganglion, bilateral medial temporal lobes and bilateral cerebral hemisphere, suggesting long standing hypoparathyroidism.

Serological tests (rheumatoid factor, anti-CCP antibodies, hepatitis B, C and HIV) were negative. Hormonal tests (thyroid profile, serum cortisol, serum ACTH) and serum iron profile were normal.

She was diagnosed with primary idiopathic hypoparathyroidism with extensive CNS calcifications and asymptomatic LV dysfunction (40%) with severe MR. She was started on intravenous calcium initially followed by oral calcium later on after resolution of acute tetanic spasms, and with vit D supplements, ACE-inhibitors and thiazide diuretics, to which she responded well. Patient was further followed-up in OPD after two months, echocardiography revealed increase in EF to 50%.

Discussion

The manifestations of resultant hypocalcaemia, hyperphosphataemia from hypoparathyroidism are both acute and chronic. Acute hypocalcaemia can present with tetany due to neuromuscular irritability, which may be mild like perioral numbness, paraesthesiac of hands and feet, muscle cramps, or severe in the form of carpopedal spasm, focal or generalised seizures, and laryngospasm. Some patients may present with non-specific symptoms of fatigue, irritability, anxiety and depression as well. Some features which are limited to chronic hypoparathyroidism are extrapyramidal disorders due to intracranial calcifications which are detected by CT scan when routine skull radiography fails to identify any calcifications[5]. In particular, the patient may present with movement disorders or parkinsonism due to basal ganglion calcifications[6]. Other manifestations are ocular (subcapsular cataracts, keratoconjunctivitis)[7], ectodermal manifestations (dry coarse skin, patchy alopecia, brittle nails, etc.), dental abnormalities (dental hypoplasia, failure of tooth eruptions, carious teeth, etc.), skeletal defects (osteosclerosis, cortical thickening, cranio-facial thickening) and occasionally cardiac dysfunction.

Any young or middle-age patient presenting with heart failure should be evaluated for reversible causes of cardiac dysfunction. Impact of hypoparathyroidism on cardiac function has been less commonly mentioned in the literature which is mainly due to resultant hypocalcaemia. The presentation of primary hypo-parathyroidism is variable but all patients should be screened for cardiomyopathy, whether they are symptomatic or asymptomatic. The main cause of cardiac abnormality is the hypocalcaemia, with its metabolic effects on cardiac muscle contraction and relaxation[8]. Cardiac contraction occurs when there is a influx of extracellular calcium, leading to generation of myocardial action potential. Hypocalcaemia leads to initiation of the action potential to a lower membrane electro-potential thus increasing excitability[9].

The various cardiac manifestations of hypocalcaemia are heart failure (may be asymptomatic in early stages) with or without reduction in ejection fraction; valvular dysfunction; and cardiac arrythmias like long QT syndrome[4]. Patients with hypocalcaemia can sometimes present with hypotension particularly if hypocalcaemia rapidly develops leading to depressed myocardial performance. Hypocalcaemia causes prolongation of QT interval as it lengthens phase 2 of the action potential leading to depressed myocardial functioning and dysrhythmias like *torsades de pointes*. There are few case reports mentioning association of hypocalcaemia due to hypoparathyroidism leading to significant cardiovascular manifestations. Saini N *et al* observed that hypocalcaemia is a cause of dilated cardiomyopathy when the patient presents with heart failure due to left ventricular systolic dysfunction in association with seizures and other neurological manifestations in hypoparathyroidism. Hypocalcaemic cardiomyopathy is reversible, with early intervention (as in the present case) and can drastically reduce morbidity and mortality[10]. Development of irreversible cardiac manifestations in long standing hypocalcaemia has been reported infrequently. Jariwala, in their case report, mentioned that hypocalcaemia along with hypomagnesaemia and low PTH levels can leads to dilated cardiomyopathy with its neuro-hormonal effects on cardiac contractility[11]. Although it is known, in children, that uncorrected hypocalcaemia can leads to cardiac dysfunction but in adults, primary idiopathic hypoparathyroidism as a cause of cardiomyopathy is reported uncommonly.

The present case highlights that, despite classical clinical manifestations of chronic hypoparathyroidism, LV dysfunction was overlooked. As in the present case, progress of LV dysfunction can be slowed with correction of hypocalcaemia. It should be stressed in the management of primary hypoparathyroidism that cardiovascular

manifestations like LV dysfunction or any valvular abnormality should be actively sought, despite the patient being asymptomatic, as it is reversible with timely treatment.

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CASE REPORT

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Neuro Behcet's Disease Presenting as Hemiparesis

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Abstract

Neuro-Behcet's disease (NBD) is one of the grave manifestations of Behcet's disease (BD), which is a multisystem vasculitis disorder of unknown aetiology, characterised by recurrent oral-genital ulcers, arthritis, and uveitis. Neuro-Behcet's disease is rare, but one needs to consider it in the differential diagnosis of other neuro-inflammatory conditions. We report the case of a 26-year-old male who presented with classical history of oral ulcers, right-sided hemiparesis, and gastrointestinal manifestations. The immunogenetic HLA typing was positive for HLA-B51 genotype.

Introduction

Behcet's disease (BD) is a multisystem vasculitis disorder of unknown aetiology that is characterised by recurrent oral-genital ulcers, arthritis, and uveitis. The age of onset is between 20 and 40 years and is more common in males (3:1). HLA - B51 genotype is seen in 40 - 65%. The central nervous system involvement in Neuro-Behcet's disease (NBD) is either parenchymal or non-parenchymal. Primary presentation with NBD is seen in up to 10% of all patients[1]. NBD needs to be differentiated from other neuro-inflammatory conditions; therefore, its clinical manifestations, and management are important.

Case report

A 26-year-old male presented with a history of recurrent oral ulcers for 7 years, progressive decrease in appetite since 1-year, fresh bleeding per rectum for last 7 months, joint pain from past 1-month, intermittent constipation for 15 days and rashes on chest and back from last 7 days. He developed acute onset numbness and weakness in right leg while irrigating the fields during evening hours followed by dull aching headache for 1 day, which progressed to weakness in right half of the body. There was no complaint of slurring of speech, sweating or palpitation at the time of development of weakness. Bladder control were normal. Patient did not have any history of genital ulceration, nausea, vomiting, fever, weight loss. He had taken several medical regimes for oral ulcers but did not get any relief. No significant family history was present. He was admitted and further work-up was done.

Following are the examination findings: PR = 98 bpm, BP = 130/90 mmHg, afebrile. No oral lesions at the time of presentation, maculo-papular rashes were present on the trunk, swelling and marked tenderness in bilateral wrist joints.

Higher mental functions were normal, speech was intact, motor system findings of limbs are mentioned in Table I.

Table I: Motor examination of right upper and lower limbs.

Motor system examination	Right upper limb	Right lower limb
Power	Grade 1	Grade 3
Tone	Increased	Increased
Deep tendon reflexes	3+	3+
Plantar reflex	Not applicable	Mute

Right upper motor neuron type facial palsy was present. Sensory system was intact. Respiratory and abdominal examination were normal. Per rectal examination was done to rule-out haemorrhoids and fissures. Ophthalmological examination ruled-out uveitis and optic neuropathy. Pathergy test was done, which was negative.

Differential diagnosis

- Acute ischaemic stroke
- Multiple Sclerosis
- Infectious Meningoencephalitis
- Neuro-sarcoidosis
- Systemic lupus erythematosus

Case management

Diagnosis: Laboratory investigations are listed in Table II and Table III.

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Table II: Laboratory investigations.

Investigations	Result	Reference range
TLC	11.6 × 10^9/l	4.5 - 11.0 × 10^9/l
Haemoglobin	14 g/dl	13.5 to 17.5 g/dl
Platelets	3,20,000/µl	1,50,000 to 4,50,000/µl
ESR	43 mm/hr	< 15 mm/hr
Total bilirubin	0.6 mg/dl	0.2 to 1.3 mg/dl
SGOT	22 U/L	15 to 46 U/L
SGPT	38 U/L	13 to 69 U/L
Urea	30 mg/dl	15 to 45 mg/dl
Creatinine	0.7 mg/dl	0.5 to 1.25 mg/dl
Uric acid	4.8 mg/dl	2.5 to 6.2 mg/dl
Total protein	7.0 g/dl	6.3 to 8.2 g/dl
Albumin	4.0 g/dl	3.5 to 5.0 g/dl
Total cholesterol	166 mg/dl	< 200 mg/dl
HDL cholesterol	52.2 mg/dl	40 to 60 mg/dl
Triglycerides	110 mg/dl	< 150 mg/dl
LDL	98 mg/dl	< 180 mg/dl
RA factor	< 8.6 IU/ml	< 12 IU/ml
Anti-CCP	< 20 u/ml	< 20 u/ml
CRP	110.79 mg/l	0 - 10 mg/l
Urine routine	Negative for bilirubin, glucose, protein, blood, leucocyteNo RBC, WBC	
ECG	Normal	
2D ECHO	Normal	
HIV 1 and 2	Non-reactive	
HbsAg	Negative	
Anti-HCV antibody	Negative	
VDRL	Negative	

Table III: CSF analysis.

CSF examination	Result	Reference range
Appearance	clear	
Protein	55 mg/dl	12 - 60 mg/dl
Sugar	94 mg/dl	40 - 70 mg/dl
Cell count	350 cells/mm^3	0 - 5 cells/mm^3
Cell type	Lymphocytes 98%	
Cytology	No malignant cells	
Oligoclonal bands	Not seen	

Neuroimaging – MRI brain with contrast study was done (Fig. 1 and 2).

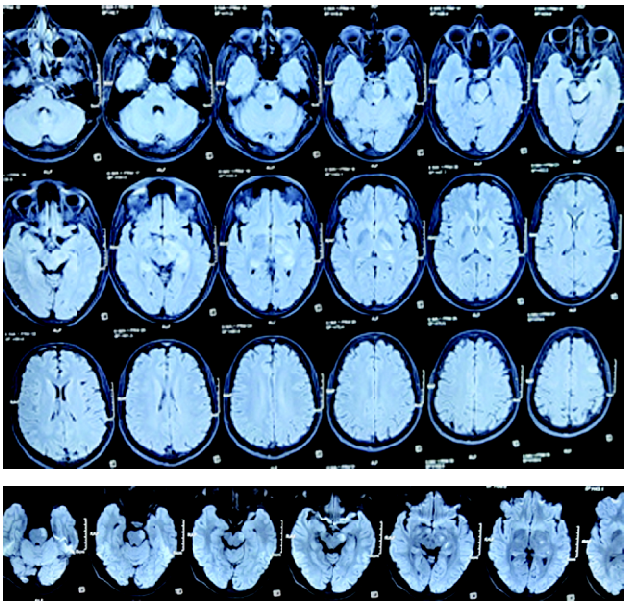

Fig. 1 and 2: *Altered signal intensity within left half of pons, midbrain, left cerebral peduncle, thalamus, posterior limb of internal capsule, left medial temporal lobe and in left basal ganglia with expansion of brainstem and mild mass effect. Hyperintensity is seen to extend in left optic tract. Minimal extension of hyperintensity is seen in right half of pons in paramedian region.*

Ultrasonography of abdomen and CT scan of chest were done to rule-out any other associated disease and revealed no abnormality.

Sigmoidoscopy was done for per rectal bleed evaluation, Fig. 3. Colonic biopsy was suggestive of non-specific colitis.

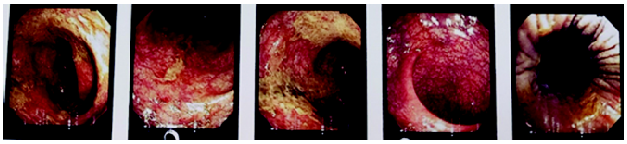

Fig. 3: *Shows erythematous mucosa with erosions and multiple linear white-based ulcers in colon and rectum.*

ENA profile tested negative.

HLA typing revealed HLA-B51 positive status.

Treatment

IV methylprednisolone pulse therapy was initiated in a dose of 1 mg/kg for 5 days. Along with that, limb physiotherapy was done. This led to subsequent improvement in power to grade 3 in the right upper limb and grade 4+ in the right lower limb. Other symptoms were managed symptomatically. There was subsidence of rash and per rectal bleed. Patient was discharged on oral prednisolone 40 mg once a day. Patient is on follow-up and we are gradually tapering the steroids.

Discussion

Behcet's disease is a rare immune-mediated variable vessel systemic vasculitis that is characterised by a triad of aphthous ulcers, genital lesions, and ocular involvement. The pathogenesis of BD is not fully known. Risk factors include genetic and environmental factors. It is associated with autoimmune responses, autoinflammation and vascular injury in the form of neutrophilic angiocentric infiltrates with leukocytoclastic or lymphocytic vasculitis, with or without mural thrombosis and necrosis. Oral ulcers are present during the disease course in almost all patients, are usually the first symptom and may appear years before the diagnosis is made. Other cutaneous lesions include papulopustular lesions, erythema nodosum, cutaneous vasculitis, pseudo-folliculitis, and pyoderma gangrenosum. Nervous system involvement, also called as cerebral angio-Behcet's syndrome, is one of the most serious manifestations of BD. Joint involvement in BD is present in the form of non-erosive mono- or polyarthritis and commonly involved joints are hands, ankles, knees, and feet. Gastrointestinal involvement causes pain, bleeding *per rectum* due to haemorrhage or gut mucosal ulcerations[2]. Patients primarily presenting with neurological symptoms will have history of recurrent oral ulcers and one or more symptoms of systemic involvement.

The two major forms of neurologic involvement in BD are parenchymal involvement (central nervous system involvement) and cerebral venous sinus thrombosis (CVST). They are also described as "intra-axial NBD" and "extra-axial NBD". In CNS-NBD, small vessels are affected causing focal or multifocal manifestations. Extra-axial NBD is due to large vessel involvement, leading to thrombosis of the major cerebral venous sinuses and has limited symptoms with better prognosis. About 75 - 80% of patients with NBD present with parenchymal involvement, commonly affecting the brainstem and/or corticospinal tract especially the telencephalic/diencephalic junction and the brainstem, which are usually large. The major symptoms and signs of CNS-NBD include headache, hemiparesis, dysarthria, cerebellar ataxia and cranial neuropathies (mainly involving motor-ocular and facial nerves) or signs of meningeal irritation and these usually develop in a subacute manner[3].

The revised international criteria for BD include – ocular lesions, oral aphthae and genital aphthae (each assigned 2 points); skin lesions, CNS involvement and vascular manifestations are assigned 1 point each. The pathergy test, when used, was assigned 1 point. A score $\geq$ 4 points suggests BD[4]. CSF findings may show elevated protein level and prominent pleocytosis during the acute phase of CNS-NBD. Neutrophilic predominance is typically seen in acute phase, but later replaced by a lymphocytic form. Many CNS-NBD patients have a relapsing-remitting course initially, with some ultimately developing a secondary progressive course and a few have a progressive CNS dysfunction from the onset. The differentials to be considered are mainly autoimmune and demyelinating illnesses such as multiple sclerosis, granulomatosis with polyangiitis (Wegener's), Polyarteritis Nodosa, Systemic lupus erythematosus and Rheumatoid arthritis[5]. Our case represents the characteristic history and clinical presentation of a young male with MRI brain findings typical of NBD, and it adds on to the existing literature.

Our patient had associated gastrointestinal symptoms which have not been reported very frequently in the published literature of NBD[6]. Though BD is commonly associated with ulcer formation and large bowel bleeding as reported in many case reports[7], it can also present with other gastrointestinal manifestations like colitis[8]. The ileocaecal region is most commonly affected, with ulcerations that may penetrate or perforate. Rarely, the oesophagus and stomach may have ulcerations. Bowel wall thickening is the most common finding on a computed tomography (CT) scan. Pathology shows a vasculitis mainly involving the small veins or, alternatively, nonspecific inflammation[9]. Sometimes NBD can also present with psychiatric symptoms like hallucinations, anxiety, poor communication, rather than neurological symptoms as was seen in our case that presented with sudden onset weakness of one side of body[10]. A case series on pseudo-tumoral NBD was published which differentiated it from classical form of NBD, it revealed that pseudo-tumoral type is more severe and life-threatening and immunosuppressive therapy was the treatment of choice[11]. NBD can also mimic a cerebral tumour, though there was no such presentation in our case[12,13]. NBD is classically recognised on MRI brain. In MRI sequences, DWI is useful for differentiating an acute exacerbation of neuro-behçet's disease from acute infarction[14].

The treatment of parenchymal NBD primarily consists of high-dose intravenous methylprednisolone pulses for 5 - 10 days, followed by the gradual tapering of oral doses over 3 - 6 months. Azathioprine, cyclophosphamide, cyclosporine-A, methotrexate, mycophenolate mofetil, tacrolimus, interferon-α or TNF-α inhibitors can also be used. It has been previously reported that treatment with high dose of steroids has shown good results, as was seen in our case[15]. There have been case reports of use of infliximab in patients of NBD, but results were equivocal, hence not used in our case[16]. Refractory cases of NBD have been reported to improve with infliximab[17]. Long-standing cases of NBD have also been successfully treated with infliximab[18]. Low dose rituximab was also effective for treating relapsing NBD[19].

Conclusion

NBD can cause a high degree of morbidity and mortality. Early recognition and diagnosis help to initiate appropriate treatment, thereby modulating the course of the disease and preventing complications.

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CASE REPORT

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Thrombotic Thrombocytopenic Purpura does not Always Present with a Classical Pentad

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder characterised by thrombosis in microvasculature, microangiopathic haemolysis and thrombocytopenia[1]. This condition is described by a classical pentad; Microangiopathic haemolytic anaemia, Thrombocytopenia, Neurological abnormalities, Fever, and Renal impairment. However, the entire pentad may not be seen in all the patients[1,2]. TTP can affect any organ system, but involvement of peripheral blood, central nervous system and kidneys causes the clinical manifestations. The classic histologic lesion is thrombi in the microvasculature of affected organs. These thrombi consist predominantly of platelets, with little fibrin and red blood cells compared with thrombi that occurs secondary to intravascular coagulation. The ultimate cause of TTP is unknown. Patients with TTP have unusually large multimers of Von Willebrand Factor (vWF) present in their plasma, and lack a plasma protease that is responsible for breakdown of these ultra large vWF multimers. In the congenital form of TTP, mutations in the gene coding this protease have been described. In the more common sporadic form, an antibody inhibitor can be isolated in most patients. This protease has been isolated, cloned and is designated as ADAMTS13 (A Desintegrin like and Metalloprotease with ThromboSpodin type 1 motif 13)[2]. The activity of this protease is normal in most patients with classic HUS, suggesting differing pathogenesis of these closely related entities[3]. Untreated TTP has mortality rate of as high as 90%. With plasma exchange, the mortality rate is reduced to 10 - 20%. Acute morbidities due to TTP include ischaemic events such as stroke, transient ischaemic attack, myocardial infarction and cardiac arrhythmia, bleeding and azotemia[1-4]. TTP during pregnancy may precipitate fetal loss[5]. In general, survivors have no long-term sequelae, with the exception of residual neurologic deficits in a minority of patients. However, relapses are not uncommon.

Case report

A 35-year-old female, presented with complaints of menorrhagia for last 2 cycles, one episode of hematuria, purpura over right thigh and generalised body ache for 40 - 45 days. No other complaints were there. Patient had a past history of seizure disorder (absence seizure) since 12 years of age and was on Carbamazepine. Patient did not have any other significant past history and co-morbidities. Patient was married and had two children, both were normal vaginal hospital delivery. Patient did not have any history of abortion. Patient also had history of multiple RBC and platelets transfusions in last 40 - 45 days before admission, but still had persistent thrombocytopenia and anemia. Patient was vegetarian and did not have any history of any substance abuse.

On physical examination patient was conscious, oriented, comfortable and was vitally stable. Pallor was present on examination. Patient had purpura on right thigh. No other skin pigmentations were present. Abdomen was soft and non-tender without hepatomegaly and splenomegaly. Neurological, Respiratory and Cardiovascular systems were normal on examination. Patient did not have any active bleed from mouth, vagina or rectum at the time of presentation.

On investigation, complete blood count showed the picture bicytopenia despite multiple transfusions, haemoglobin was 7.2 g/dl and platelet count was 15,000/microl. Peripheral blood film suggested anisopoikilocytosis, schistocytes and microspherocytes. Patient's LDH was 2,329 U/L, and reticulocyte count was 5%. Her serum creatinine was 0.6 mg/dl, indirect bilirubin was 1.2 mg/dl. Urine output was adequate, 1,800 - 2,000 ml/day durning her hospital stay and urine routine analysis was also normal.

Patient's direct/indirect Coomb's tests were negative. ANA profile was negative. PF4-H (IgG antiplatelet factor 4) was 0.77 (normal range < 1.00), which ruled-out Heparin induced thrombocytopenia, along with vaccine induced thrombocytopenia as patient also had history of COVID-19 vaccination . Patient's bone marrow aspiration and biopsy was done, which showed marrow was normocellular for age with trilineage hematopoiesis . ADAMTS13 activity was

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done by chemiluminescence immunoassay method, which was 0.40%, less than the normal range of 60.6 - 130.6 and confirmed the diagnosis of TTP.

Differential diagnosis

Idiopathic thrombocytopenic purpura, microangiopathic haemolytic anaemia, vaccine induced thrombocytopenia, carbamazepine induced thrombocytopenia, haemolytic uraemic syndrome (HUS), Evan's syndrome and heparin induced thrombocytopenia were the major differential diagnoses in our case.

Low ADAMTS-13 activity can be observed, primarily in idiopathic TTP, and in a congenital condition with low ADMATS13 (Upshaw-Schumann syndrome) but as our patient developed symptoms in her middle-age, Upshaw-Schumann Syndrome was unlikely. Other secondary clinical conditions are ITP, HUS, DIC, sepsis, pregnancy and post-solid organ or bone marrow transplant.

HUS generally presents with diarrhoea (usually bloody), which was absent in our case. Endotoxins are the culprit causing endothelial damage in HUS. The most common toxin is Shiga toxin from *E. Coli* strain. It is usually associated with a history of eating undercooked/spoiled food. Culture/sensitivity and ADAMTS-13 activity are done to distinguish between the two.

Evan's syndrome is an autoimmune condition that presents with autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia (ITP), with or without immune neutropenia. The type of AIHA present in Evan's syndrome is warm AIHA. In our case Coomb's tests were negative. Further, there is no reduction in ADAMTS-13 activity in Evan's syndrome.

Our patient did not have any history of heparin use, and PF4-H (IgG antiplatelet factor 4) was 0.77 (normal range < 1.00) so heparin induced thrombocytopenia was also unlikely.

As our patient was on carbamazepine since her childhood, for absence seizures, there could be a possibility of carbamazepine induced bone marrow suppression, as the drug carbamazepine can cause bone marrow suppression, but this drug does not cause a decreased activity of ADAMTS-13, which was seen in our case.

Idiopathic thrombocytopenia is a diagnosis of exclusion.

Haematological malignancies were excluded after an unremarkable bone marrow biopsy, and sepsis too was ruled-out with routine blood tests.

Our patient was not taking any drug except carbamazepine for a long time and this was stopped, so the condition was not drug-induced.

Discussion and Review of literature

This 35-year-old female, a known case of seizure disorder on Carbamazepine for 23 years presented, with complaints of generalised weakness, menorrhagia for last 2 cycles and hematuria. CBC showed bicytopenia, not improving even after multiple blood transfusions. Carbamazepine was thought to be the cause of thrombocytopenia and was stopped; later patient was started on levetiracetam after overlapping for three days but patient did not improve. After ruling-out other possible diagnoses like micro angiopathic haemolytic anaemia, and vaccine-induced thrombocytopenia with routine investigations and Bone marrow aspiration/biopsy, she was started on pulse therapy of methylprednisolone for 5 days, for possible diagnosis of idiopathic thrombocytopenic purpura but she did not improve. Plasma exchange along with IVIG were then started, to which she responded well. Diagnosis of TTP was confirmed by low ADAMTS-13 activity, which was ordered before starting IVIG. A low level of ADAMTS-13 (< 5% of normal) can be interpreted as the patient having TTP[6-8]. In some other pathological conditions unrelated to TTP, ADAMTS-13 levels are low or undetectable[9-12]. Patients with both localised and disseminated malignancies have been reported to have reduced levels of ADAMTS-13[11,12]. The effect of inflammation on ADAMTS-13 was studied in pediatric patients with severe sepsis, and ADAMTS-13 activity was reduced[13]. The expression of ADAMTS-13 in acute myeloid leukaemia (AML) patients was decreased and the level of ADAMTS-13 was also related to infections and risk stratification of AML patients[14].

TTP has a high mortality rate, up to 90%, which can be reduced to 10 - 20% with plasma exchange[4]. Along with plasma exchange, IVIG is also used in the treatment of TTP. Therapeutic plasma exchange (TPE) is the most effective therapy; about one-third of TTP patients will relapse, A subset of patients with TTP have antibodies to ADAMTS13 and may become resistant to conventional treatments. It has been observed that adding adjuvant treatment with IVIG helps in achieving remission and may sustain remission in some patients with chronic, relapsing TTP[15]. ADAMTS-13 is an enzyme that specifically cleaves large vWF multimers. If activity of ADAMTS13 is decreased,

either because of an inherited mutation within ADAMTS-13 gene, or because of the development of autoantibody, the accumulation of ultra large vWF multimers may cause microvasculature thrombosis due to platelet aggregation and produce syndrome of TTP. ADAMTS-13 activity assay is performed to confirm TTP diagnosis and may also be used in prediction of TTP relapse, though measurement of ADAMTS-13 activity is not necessary for taking decisions and for diagnosis and initial management. Its severe deficiency is associated with increased risk of relapse.

TTP presents with a classic pentad, mainly involving peripheral blood (Haemolysis and Thrombocytopenia), CNS and kidneys. As our patient's urine output, serum potassium and serum creatinine were normal and she did not have fever, throughout the illness, the possibility of TTP was less likely initially as fever, neurological symptoms and renal impairment were not there. Classical PENTAD may be absent in cases of TTP, and high degree of suspicion is required and a positive ADAMTS-13 test can confirm the diagnosis.

Joly *et al* reported that the first-line therapy for acute TTP is based on daily TPE supplying deficient ADAMTS-13, with or without steroids. Additional immune modulators targeting ADAMTS-13 autoantibodies are steroids and the humanised anti-CD20 monoclonal antibody rituximab. In refractory or unresponsive TTP, more intensive therapies including twice-daily plasma exchange; adding IVIG, pulses of cyclophosphamide, vincristine, or cyclosporine A; or salvage splenectomy are considered[1].

Vesely *et al* pointed out severe ADAMTS-13 deficiency does not detect all patients of TTP-HUS who may respond to TPE[2].

Miller *et al* reported that the incidence of TTP and HUS was higher among women than men. Most cases of HUS occurred before 20 years of age. They confirmed several known risk factors for TTP and HUS like cancer, bone marrow transplantation, and pregnancy[4].

Scully *et al* reported that pregnancies have been successfully managed, guided by ADAMTS-13 levels. Congenital TTP presents more frequently than acquired TTP during pregnancy and must be differentiated by ADAMTS 13 analysis. Careful diagnosis, monitoring, and treatment in congenital and acquired TTP have resulted in excellent pregnancy outcomes[5].

Oleksowicz *et al* found unusually large vWf multimers in patients with metastatic tumours, probably resulting from deficient vWf-cleaving protease activity and may represent a novel mechanism regulating primary platelet-tumour adhesive interactions involved in the metastatic process[6].

Sarode mentions that atypical TTP can be diagnosed by the presence of microangiopathic haemolytic anaemia and thrombocytopenia in a patient who frequently presents with central nervous system involvement and, to a lesser extent, renal dysfunction. Recent understanding of the pathophysiology of TTP due to severe deficiency of ADAMTS-13, has improved diagnosis of TTP. Once the diagnosis is suspected, life-saving TPE is initiated. Occasionally, an unusual clinical presentation makes TTP diagnosis difficult, thus resulting in a delay in management. This review highlights an atypical TTP case. It is intended to bring unusual scenarios to the clinician's awareness, so that timely treatment can be instituted[16].

Conclusion

TTP is a rare disorder and confirmation of diagnosis poses a challenge to the clinician, as the classical pentad of clinical presentation may be absent in some patients and costly ADAMTS-13 test may not be available everywhere. A high degree of suspicion for TTP is required in such patients, after ruling-out other causes. Early diagnosis and management can be life-saving.

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PICTORIAL CME

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Mesenteric Panniculitis: A Very Rare Cause of Abdominal Pain

Rudrajit Paul, Dipanjan Bandyopadhyay***

Abstract

Mesenteric panniculitis is an extremely rare cause of acute abdominal pain. We present a case from Eastern India, which presented with abdominal pain and features of intestinal obstruction. The radiological features have also been described at length.

Key words: Panniculitis; fat halo; prednisolone; IgG4 disease.

Introduction

Abdominal pain is the one of the commonest symptoms faced by physicians in daily clinical practice[1]. While most of them respond to symptomatic management, a substantial portion eludes diagnosis even after the primary care visit[1]. Most cases of abdominal pain can be diagnosed by simple clinical examination; but there are a few instances when initial clinical signs may not be enough for diagnosis and further investigations may be needed. Delay in diagnosis in these cases may lead to a worse prognosis. Thus, clinicians dealing with a case of refractory abdominal pain must take recourse to appropriate diagnostic studies as early as possible. We present an extremely rare case of abdominal pain, which baffled clinicians initially, and the final diagnosis was only clinched after appropriate imaging studies.

Case report

A 60-year-old male patient came to the OPD with sudden onset of abdominal pain and swelling for one day. He had a low-grade continuous fever and a few episodes of vomiting. He also complained of not passing stool for two days. The patient was at first symptomatically managed and rectal enema was advised. He was sent back home. But he came back to the ER the same night with severe holo-abdominal pain. Assuming this to be a case of intestinal obstruction, the patient was put on Ryle's tube drainage and oral feeding was stopped. Palpation of abdomen revealed an ill-defined partly mobile tender mass around the umbilicus. Per-rectal examination revealed rectal ballooning. A straight X-ray of abdomen revealed (Fig. 1) colon loaded with stool, but no evidence of gas-fluid levels. Laboratory tests revealed total leukocyte count of 21,000/cmm with 80% neutrophils. Serum electrolytes were normal, as were the amylase and lipase levels. Finally, a CECT of abdomen was done (both oral and i.v. contrast), which showed (Fig. 2) ground glass attenuation with fat stranding of mesentery, suggestive of Mesenteric Panniculitis. Other laboratory tests were normal. Anti-nuclear factor was negative and serum IgG4 level was 0.55 g/l (N: 0.3 - 2).

The patient was immediately started on i.v. hydrocortisone 100 mg thrice daily for five days, followed by oral prednisolone 40 mg daily. After starting the i.v. steroid, his abdominal pain came down quickly. With this and other symptomatic management including repeated enema, the symptom of bowel obstruction was also relieved. He was discharged home on oral steroids.

Initially, at home, he could not tolerate any solid food and any heavy meal led to relapse of the pain. Thus, at first, he was put on liquid only diet. However, after three weeks, with continuing oral steroids, his diet slowly became normal. Bowel movement was also regularised.

Discussion

Mesenteric panniculitis is an extremely rare cause of

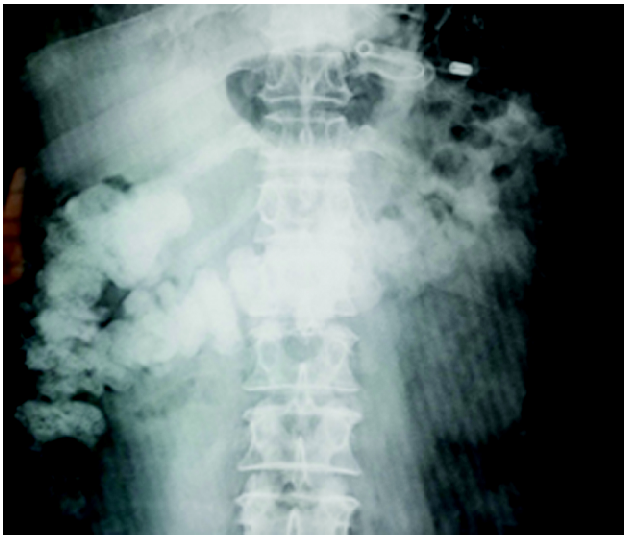

Fig. 1: *Straight X-ray abdomen, showing colon loaded with stool.*

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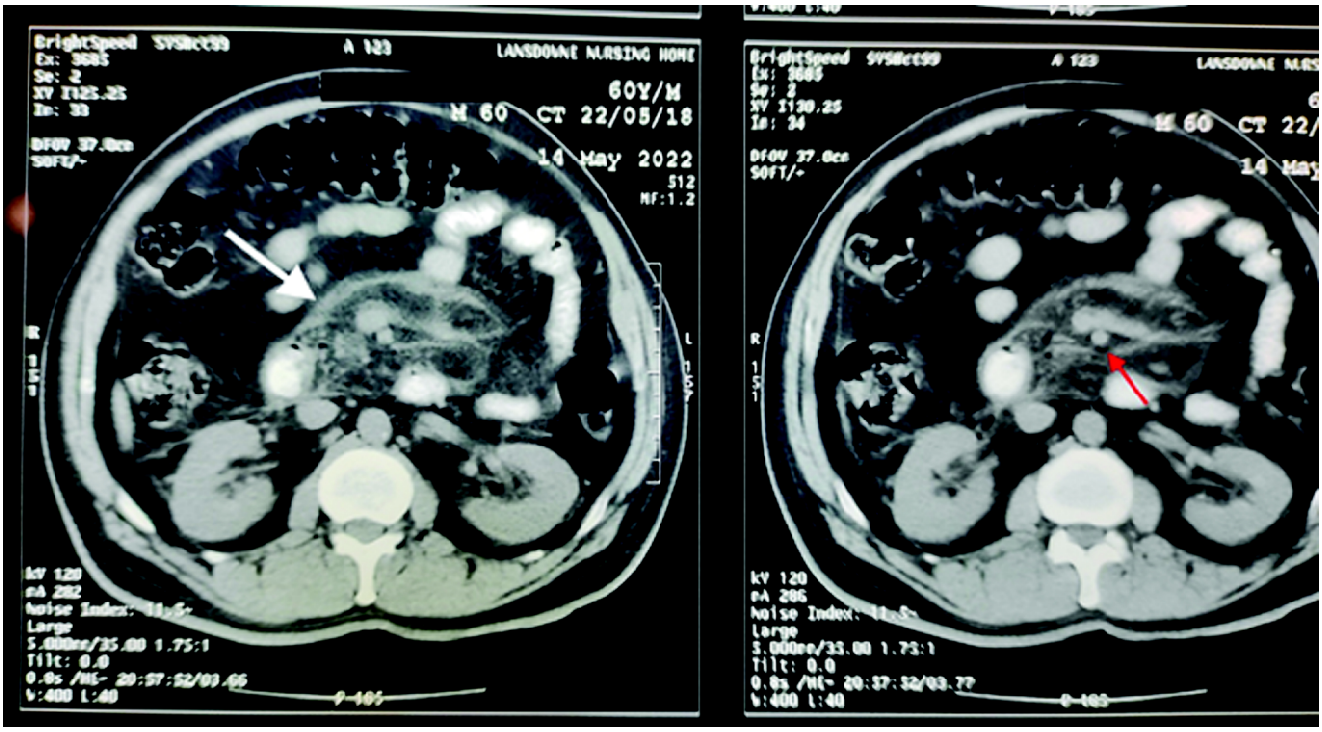

Fig. 2: *CECT Abdomen, showing panniculitis with ground glass attenuation of mesentery (misty mesentery) with fat stranding, giving appearance of a pseudo-mass (White arrow); also seen (Red arrow) fat halo sign around mesenteric vessels.*

abdominal pain, with 100-odd cases reported in the English literature till now. It is caused by acute inflammation of adipose tissue of the mesentery[2]. This inflammation may sometimes lead to fat necrosis and later, fibrosis of the mesentery[2]. Besides mesenteric panniculitis, the other synonyms are mesenteric lipodystrophy, retractile mesenteritis and mesenteric Weber-Christian disease. The disease is more common in males and the incidence increases with age[2].

The condition being extremely rare, its exact aetiology and pathophysiology are unknown. Historical evidence has shown the condition to be mostly idiopathic and only sometimes associated with a variety of factors like bile leakage, pancreatitis, retained sutures inside abdomen, autoimmune disease or avitaminosis[2,3]. Some studies have also linked the condition with tobacco consumption[4]. But the pathogenic mechanism behind mesenteric panniculitis in these cases is still elusive. In our case, the patient had none of the "risk factor"s that have been historically linked with this condition and he was not a tobacco user.

It is almost impossible to diagnose mesenteric panniculitis clinically and initial presenting features are often non-specific[5]. Like our case, diffuse abdominal pain is the commonest symptom and constipation and diarrhoea both may be found[5]. Laboratory results are also not helpful in most cases[5]. CECT abdomen is the most helpful in diagnosis. It shows ill-defined mesenteric mass-like lesion with surrounding misty attenuation. The traversing mesenteric vessels typically are spared and have a "fat halo".

The condition usually responds to oral immunosuppressives as in our case. Steroids are the first line drugs but others like Azathioprine, Colchicine, etc., are also used.

We present this case to sensitize clinicians to this extremely rare cause of abdominal pain. Proper interpretation of the abdominal imaging findings can help in early diagnosis.

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