Original Article

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Internal Medicine Section

Demographic and Clinicoradiological Presentation of Tuberculosis in Patients with Sickle Cell Haemoglobinopathy: A Cross-sectional Study

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ABSTRACT

Introduction: Infectious disease is an important contributor to disability and death in Sickle Cell Haemoglobinopathy (SCH). India has a high burden of Tuberculosis (TB) and SCH is widespread among residents in and around Burla, Odisha. This was the first attempt to find the prevalence of SCH in active cases of TB in Indian adults.

Aim: To estimate the prevalence of SCH in TB and to evaluate the demographic and clinicoradiological presentation of TB in patients with SCH in a subset of Indian population.

Materials and Methods: A cross-sectional study was conducted from October 2010 to September 2012 in Department of Pulmonary Medicine of VSSMC, Burla, Odisha, India. The primary inclusion criterion was patients with TB and SCH. Demographic characteristics, clinical, radiological, microbiological and histopathology data were collected. Statistical analysis was done using Statistical Package of the Social Sciences (SPSS) 18.0. Association between categorical data was calculated using Chi-square test and Fisher's exact test. A p-value of <0.05 was considered to be significant.

Results: Out of 1243 TB patients who were screened, 64 TB patients had SCH. The mean age of the patients were 30.41±13.48 years with female predominance 33 (51.56%). The prevalence of SCH in TB was 51.49/1000, Sickle Cell Anaemia (SCA) was 13.68/1000 and Sickle Cell Trait (SCT) was 37.81/1000. Total 47 (73.43%) patients had SCT and 17 (26.56%) patients had SCA. Majority of patients with SCA 15 (88.23%) and SCT 35 (74.46%) belonged to the age of ≤40 years. Total 38 (59.37%) patients had Pulmonary TB (PTB) and 26 (40.62%) had Extrapulmonary TB (EPTB). EPTB 11 (64.70%) was common in patients with SCA than PTB 6 (35.29%) and vice-versa in SCT 15 (31.91% vs 32 (68.08%) (p=0.018). Among PTB patients, cough was the most common symptom seen in 7 (10.93%) patients of SCA and in 26 (40.62%) patients of SCT. The mean (±SD) haemoglobin in patients with SCA was 7.270 (±2.007) gm% and SCT was 9.021 (±1.578) gm% (p-value=0.002). The most common chest radiographic finding was nodules in patients with SCA 9 (52.94%), reticular opacities and pleural effusion 11 (23.40%) each in SCT.

Conclusion: In the present study, 5.14% of TB patients had SCH. Pulmonary TB (PTB) was more common than EPTB in patients with SCH.

Keywords: Anaemia, Extrapulmonary, Montoux test, Pulmonary tuberculosis, Sickle cell haemoglobinopathy

INTRODUCTION

The two conditions TB and SCH are distinct global health issues, individually accounting for increasing morbidity and mortality. In India, 188 per 100000 population is the estimated incidence of all forms of TB as per global report of TB 2021 and the prevalence of TB above the age of 15 years is 312 cases per one lakh which is twice the global average of 127. India has the second highest burden of SCH cases [1,2]. In the 21st century, to the best of the literature search, authors of the present study found only three original research articles on TB and SCH and the rest were case reports [3-9].

This condition, SCH is more prone to bacterial infections is a well-known fact. The same about TB and SCH is not known. There are two schools of thought regarding the association between SCH and TB. One group of researchers are of opinion that SCH are prone to severe form of TB and another group opines that SCH are not prone to greater risk of TB. Epidemiological factors, pathophysiological mechanisms of SCH and host immunological distortion could predispose a patient of SCH to TB [3]. Local host defense alteration due to organ damage as a result of vaso-occlusion, impaired phagocytosis and opsonization are elucidated in SCA and decrease of factors B and C3 could occur due to complement activation caused by chronic haemolysis [10-14]. These factors in addition to functional asplenia could develop more severe TB in SCH. On the contrary, Droz N et al., and Ba ID et al., concluded there is no increased risk of TB in patients with SCH as immunity against Mycobacterium tuberculosis is provided by Cluster of Differentiation 4 (CD4) T lymphocytes [4,5].

In the few studies done so far on TB in SCH, there is a difference observed in prevalence of TB with SCH. Lionnet F et al., found 2.62% of TB patients had SCH over a span of 8 years whereas Ba I et al., found the prevalence to be 0.97% over 19 years and in 13 years Droz N et al., found a prevalence of 0.42% [3-5]. There was also difference in clinical presentations of TB in the above mentioned studies. Lionnet F et al., found extrapulmonary TB more common than pulmonary TB in contrast to Ba I et al. and Droz N et al., where PTB was more common presentation than EPTB in patients with SCH [3-5].

Lionnet F et al., and Droz N et al., noted that TB and SCH share common geographic distribution [3,4]. Likewise the study population of the current research belongs to the region which has high burden of TB with prevalence of 200/100000 population and also SCH is widespread among the residents with a prevalence of 21%[15,16].

Finally, the authors of the present study could not find any original research articles on TB with SCH in Indian adults. In view of the above mentioned ambiguous observations, much remains unknown about the association of TB with SCH. Therefore the authors of the current research attempted to study both the diseases in concordance. So, this study was aimed to identify prevalence of SCH in TB, with demographic and clinicoradiological features of TB in SCH.

MATERIALS AND METHODS

This was a cross-sectional study conducted in the Department of Pulmonary Medicine in VSSMCH, Burla, Odisha, India, from October 2010 to September 2012. Institutional Ethical Committee approval was obtained prior to the study. (IEC approval No.130/2010). Informed consent from patients were taken. SCH refers to Sickle Cell Haemoglobin (HBSS) and HbSβ^0 thalassemia which are associated with most severe clinical manifestations [17]. Sickle cell disease refers to all the genotypes of disease including sickle cell anaemia and heterozygous disorders such as HbSC, HbSD and HbSβ^+ thalassemia [17].

Inclusion criteria: Patients with tuberculosis (pulmonary and extrapulmonary) with SCH and SCH included patients with SCA and SCT only were included in the study.

Exclusion criteria: People living with Human Immunodeficiency Virus (HIV) and Acquired Immune Deficiency Syndrome (AIDS), patient with diabetes mellitus, chronic kidney disease, other haemoglobinopathies, chronic liver disease, malignancy and long-term steroid/immunomodulators consumption were excluded from the study.

Study Procedure

All TB patients (n=1243) were screened for the presence of SCA or SCT and, 64 patients of all forms of TB having co-existing SCA or SCT were included in the study. TB was diagnosed on the basis of one or more of the following: 1] Smear examination of clinical sample for acid fast bacilli, 2] Mycobacterial culture Lowenstein-Jensen (LJ) medium or Becton Dickinson and Company (BACTEC) 3] Cyto/histopathological examination 4] Clinicoradiological diagnosis. A patient with both pulmonary and extrapulmonary TB was classified as pulmonary TB. In case TB involved organs other than the lungs, it was known as extrapulmonary TB. Patients of TB were screened for SCH. SCH was identified using slide test for sickling and haemoglobin electrophoresis.

A detailed clinical history was taken with emphasis on age, sex, caste, occupation, symptoms which was followed by physical examination. Complete blood count, fasting and random blood sugar, glycosylated haemoglobin, blood urea, serum creatinine, liver function tests and radiograph of chest were performed. The area on the Posteroanterior (PA) chest radiograph which extended below an imaginary horizontal line across the hilum including the parahilar region was termed lower lung field and the area above it was upper lung field [18]. Haemoglobin level of 10-11.9 gm/dL, 7-9.9 gm/dL and <7 gm/dL were classified as mild, moderate and severe anaemia, respectively.

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for the Social Science (SPSS) version 18.0 (IBM, Armonk, United States of America). A p-value of <0.05 was considered to be significant. Association between categorical data was calculated using Chi-square test and Fisher's-exact test.

RESULTS

Total 1243 patients with TB were screened for the presence of SCA or SCT and, 64 patients of all forms of TB having co-existing SCA or SCT were included in the study. Out of 64 patients, 47 (73.43%) were SCT and 17 (26.56%) were SCA. Overall, there were 31 (48.43%) males and 33 (51.56%) females in the study [Table/Fig-1].

Among patients with SCA and SCT, majority of the patients belonged to the age group of 10-30 years 12 (70.58%) and, 29 (61.70%) respectively [Table/Fig-1]. The majority of patients having SCA or SCT belonged to Ganda caste 6 (35.29%) vs 19 (40.42%) [Table/Fig-2]. Cough in pulmonary TB was the most common symptom among the SCA 7 (10.93%) and, SCT 26 (40.62%) patients (p=0.3173). Pallor was the most common sign in both SCA 11 (64.70%) and SCT 18 (38.29%) patients (p-value=0.6087) [Table/Fig-3].

Variables	Total	SCA (17)	SCT (47)	Statistical analysis	p-value
Gender					
Male	31	11 (64.70%)	20 (42.55%)	χ^2- 2.453	0.1172
Female	33	6 (35.29%)	27 (57.44%)		
Age (in years)					
10-30	41	12 (70.58%)	29 (61.70%)		
31-50	17	5 (29.41%)	12 (25.53%)		
51-70	6	0	6 (12.76%)		
Site of TB					
Pulmonary TB	38	6 (35.29%)	32 (68.08%)	χ^2- 5.565	0.018
Extrapulmonary TB	26	11 (64.70%)	15 (31.91%)		
Site of involvement as per chest radiograph (n=38)					
Upper lung field only	26	5 (83.33%)	21 (65.62%)		
Lower lung field only	6	0	6 (18.75%)		
Upper and lower lung fields	5	1 (16.66%)	4 (12.5%)		
Normal	1	0	1 (3.12%)		
Sputum examination for AFB					
Positive	20	5 (29.41%)	15 (31.91%)	χ^2= 0.0364	0.848
Negative	44	12 (70.58%)	32 (68.08%)		
Grade of anaemia in terms of severity (Hb in gm/dL)					
Severe (<7)	12	8 (47.05%)	4 (8.51%)		
Moderate (7-9.9)	37	6 (35.29%)	31 (65.95%)		
Mild(10-11.9)	14	3 (17.64%)	11 (23.40%)		0.002
Normal (≥12)	1	0	1 (2.12%)		
Mean Hb, mean(±SD)		7.270 (±2.007)	9.021 (±1.578)		
Mantoux test					
Positive	6	2 (11.76%)	4 (8.51%)		<0.001
Negative	58	15 (88.23%)	43 (91.48%)		

[Table/Fig-1]: Patient characteristics, forms of TB, radiological site of involvement and sputum positivity for AFB (Acid Fast Bacilli) in SCA and SCT.
SCA: Sickle cell anaemia; SCT: Sickle cell trait
p-value <0.05 was statistically significant

S. No.	Name of caste	SCA (17)	SCT (47)	Total
1.	Ganda	6 (35.29%)	19 (40.42%)	25 (39.06%)
2.	Goud	2 (11.76%)	10 (21.27%)	12 (18.75%)
3.	Kuilta	4 (23.52%)	8 (17.02%)	12 (18.75%)
4.	Teli	0	3 (6.38%)	3 (4.68%)
5.	Khadia	0	2 (4.25%)	2 (3.12%)
6.	Brahmin	1 (5.88%)	0	1 (1.56%)
7.	Chaga	1 (5.88%)	0	1 (1.56%)
8.	Ghasi	1 (5.88%)	1 (2.12%)	2 (3.12%)
9.	Chasa	1 (5.88%)	0	1 (1.56%)
10.	Bairagi	0	1 (2.12%)	1 (1.56%)
11.	Kumbhar	0	1 (2.12%)	1 (1.56%)
12.	Tanti	0	1 (2.12%)	1 (1.56%)
13.	Goswami	1 (5.88%)	0	1 (1.56%)
14.	Kandha	0	1 (2.12%)	1 (1.56%)

[Table/Fig-2]: Caste distribution in SCA and SCT.

Symptom	SCA (17)	SCT (47)	Statistical analysis	p-value
Chest pain	3 (17.64%)	10 (21.27%)	χ^2-0.1016 Yates- 0.0011	0.973
Dyspnoea	3 (17.64%)	16 (21.27%)	1.6077	0.9182
Cough	7 (41.17%)	26 (55.31%)	0.9998	0.3173
Sputum production	3 (17.64%)	17 (36.17%)	χ^2-1.99 Yates- 1.2248	0.2684

Haemoptysis	1 (5.88%)	5 (10.63%)	χ^2-0.3324 Yates-0.0083	0.9274
Pallor	11 (64.70%)	18 (38.29%)	χ^2-3.51	0.6087
Icterus	5 (29.41%)	1 (2.21%)	χ^2-10.93 Yates-7.96	0.0047
Hepato-splenomegaly	6 (35.29%)	2 (4.25%)	χ^2-10.99 Yates-8.3419	0.0038

[Table/Fig-3]: Symptomatology in patients with PTB in sickle cell haemoglobinopathy.

The predominant findings in chest radiograph in SCA were nodules 9 (52.94%), followed by pleural effusion 6 (35.29%), whereas 11 (23.40%) patients with SCT had reticular opacities and pleural effusion followed by consolidation 6 (12.76%) [Table/Fig-4].

Chest radiography findings	SCA (17)	SCT (47)
Nodules	9 (52.94%)	5 (10.63%)
Consolidation	1 (05.88%)	6 (12.76%)
Cavity	2 (11.76%)	3 (6.38%)
Reticular opacities	2 (11.76%)	11 (23.40%)
Pleural effusion	6 (35.29%)	11 (23.40%)
Hydropneumothorax	1 (05.88%)	2 (4.25%)
Normal	0	1 (2.12%)

[Table/Fig-4]: Radiological features* in sickle cell haemoglobinopathy.
*The findings are not mutually exclusive

In patients with SCA, Extrapulmonary TB (EPTB) 11 (64.70%) was found to be more prevalent than PTB 6 (35.29%). However in patients with SCT, PTB 32 (68.08%) was more prevalent than EPTB 15 (31.91%) (p=0.018). Forms of EPTB in SCA and SCT have been shown in [Table/Fig-5].

Site of EPTB	SCA (17)	SCT (47)
Single organ involvement		
Pleural effusion	5 (45.45%)	9 (60%)
Abdominal TB	2 (18.18%)	1 (6.66%)
Skeletal TB	1 (9.09%)	2 (13.33%)
Tubercular lymphadenitis	2 (18.18%)	0
Tubercular pericarditis	0	1 (6.66%)
TB of central nervous system	0	1 (6.66%)
Multiorgan involvement		
Pleural effusion, abdominal TB, skeletal TB	1 (9.09%)	0
Pleural effusion, abdominal TB	0	1 (6.66%)
Total	11	15

[Table/Fig-5]: Extrapulmonary TB in SCH.

DISCUSSION

Tuberculosis remains a global health problem especially in developing and under-developed countries [19]. SCH is an autosomal recessive disorder caused by the mutation in the β-globin gene leading to the formation of Sickled Haemoglobin (HbS) which can present in homozygous state i.e. SCA 'SS', heterozygous state SCT 'AS' and in association with other haemoglobinopathies [20]. SCA is currently one of the most common, lethal, preventable yet neglected genetic disease in the world that mainly affects African, Arabian and Indian population [21]. SCA is a chronic haemolytic anaemia, which leads to vasocclusive crisis, splenic dysfunction and malfunctional immunological system leading to critical bacterial infections [4]. In the current era where immunopathogenesis of TB is yet to be discerned, the contribution of SCH in development of TB remains uncertain.

Lionnet F et al., found 2.62% of TB patients had SCH in adult sickle care centre over a span of eight years whereas Ba ID et al., found the prevalence to be 0.97% over 19 years [3,5]. In 13 years, Droz N et al., found a prevalence of 0.42% of TB in SCA patients [4]. In present study, the prevalence of SCH among TB patients was 51.49/1000, SCA was 13.68/1000 and SCT was 37.81/1000 over a span of two years. This shows a strikingly high rate (5.14%) of SCH among TB patients in the present study. This is because the study was conducted in the western region of Odisha in India which has a large load of both TB and SCH independently. These patients belong to low socio-economic status with malnutrition and over crowding as major contributors to development of TB [15].

In a study done by Lionnet F et al., which included 12 patients of French West Indies or African ethnicity, there were 10 cases of SCA, one patient of $HbS\beta^0$ and $HbS\beta^+$ each [3]. Droz N et al., had six patients whose native was France and five immigrants, of whom five patients had HbSS, three patients had HbSS/G6PD, two patients had HbSC and one patient had HbSβ0 [4]. In the study done by Ba ID et al., patients belonged to Dakar, Senegal and all the 25 patients had SCA [5]. The majority of patients in the present study had SCT 47 (73.43%) compared to SCA 17 (26.56%). SCT was found only in present study.

The mean age range of the patients studied by Lionnet F et al., was 22.6±6.61 years, Ba ID et al., was 12.54 years and Droz N et al., was 11 years [3-5]. The mean age group of patients in the present study was 30.41±13.48 years. Age range in SCA was 10-30 years, whereas in sickle cell trait, it was 16-70 years. So, only the present study had patients with SCT which could explain a wide range of age. Age related attrition of SCA patients may lead to predominance in number of patients with SCT in the course of time [22,23]. Patients with SCT may have normal longevity like an average Indian because they are asymptomatic unless exposed to factors causing sickling like dehydration, hypo/hyperthermia, hypoxia, increased 2,3-DPG levels, increased sympathetic activity and release of inflammatory cells [24].

In the present study, there was female predominance 33 (51.56%) of 64 patients. Similarly, Ba ID et al., had majority of (15,60%) females among 25 cases [5]. The study done by Lionnet F et al., and Droz N et al., had male predominance 6 (85.71% and 7 (63.63%), respectively among a total of 12 and 11 patients respectively [3,4]. Authors of present study were not able to draw any conclusions after comparing their study with other three studies regarding age, gender, type of SCH in TB probably because study populations are small. Large sample size multinational studies are necessary to have enhanced understanding of the association between the both diseases.

The sickle cell gene is highly prevalent among the general castes in Odisha. In Odisha, sickle cell gene has the prevalence of 0.3-20.7% in general caste, 0-8.9% in scheduled castes and 0-5.5% in scheduled tribals due to marital consanguinity which increases multiplication of sickle cell gene leading to increased prevalence of SCH [25].

In the present study, the mean haemoglobin (±SD) in TB patients having SCA was found to be 7.27 (±20) gm% compared to 9.02 (±1.57) gm% in SCT (p-value=0.002). The anaemia in SCT patients could be due to anaemia of chronic disease i.e. tuberculosis and nutritional deficiency [26,27]. Overall the mean (±SD) haemoglobin in SCH was 8.556 (±1.857) gm% in the present study. Droz N et al., had mean Hb of 7.5 gm/dL [4]. Other studies did not mention about haemoglobin values.

Radiological manifestations of pulmonary TB are dependent on several host factors, including underlying immune status. Upper lung field was involved more commonly than the lower lung field in pulmonary tuberculosis both with SCA 5 (83.33%) and with SCT 18 (65.62%). The most common radiological finding in present study was reticular opacities and pleural effusion followed by nodules. The authors of the present study could compare radiological findings with only one case report done by Okar L et al., where chest radiograph showed the presence of large pneumonic patches in both lungs, blunting of left costophrenic angle and atelectatic bands in left basal area. Chest radiographs were not described in any other studies [6].

Lionnet F et al., had screened 457 patients of SCA and identified 12 cases with TB. Out of the 12, seven had tuberculous lymphadenitis, three pulmonary TB and, two vertebral TB. It was concluded that, in SCA patients, tubercular lymphadenopathy is found in higher incidence than in epidemiologically comparable population [3]. Ba ID et al., had pulmonary involvement in 14 (63%) patients, lymph node in 7 (32%), Pott's disease in 4 (18%), cutaneous and pleural involvement in 2 (9%) each and multifocal involvement in 4 (20%) cases [5]. Droz N et al., had pulmonary and mediastinal involvement in 5 (45.45%), pulmonary and pleural involvement 1 (9.09%) cases and 5 (45.45%) cases with EPTB (osteoarticular TB, hepatic TB, cervical and mediastinal TB) [4].

In present study patients with pulmonary TB 38 (59.37%) were more compared to EPTB 26 (40.62%) which significant p-value of 0.018. Two previous studies and the present study have observed that pulmonary TB is more frequent than extrapulmonary TB. But Lionnet F et al., in their study found extrapulmonary TB more common than pulmonary TB. They reasoned out that in patients with SCD, a permanent pulmonary proinflammatory state is created by constant stimulation of the alveolar macrophages and increased level of secretion of local cytokines [28]. This proinflammatory state is usually considered to be detrimental but in patients with SCD patients, it may lead to discrete protection against pulmonary TB [3]. Hence, further studies are required to enlighten the physicians regarding details about various organ involvement of TB in SCH.

Limitation(s)

The sample size is limited to understand the association of TB in SCH and follow-up of the study population was not done.

CONCLUSION(S)

In the present study, 5.14% of the TB patients had SCH which is very high compared to the other studies. PTB was more common than EPTB in patients with SCH. Approximately two-thirds of TB patients had sickle cell trait which was not found in other comparable studies. Future research direction would be to conduct large prospective studies in TB with SCH affected population to understand the nature and course of the disease, to understand complications and cure rates in these patients in comparison to general population.

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