Clinical & Laboratory Profile of Possible Sickle Delta Beta Thalassemia in Telangana State

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ABSTRACT

BACKGROUND

Sickle delta beta thalassemia is a rare genetic disorder, with varied symptoms, signs, requiring careful monitoring for potential complications. It is due to sickle mutation and thalassemia mutation occurring together**,** with sparse data available worldwide. The purpose of this study was to assess the clinical and laboratory profile of possible sickle delta beta thalassemia.

METHODS

The study design is retrospective analysis of clinical information of those selected patients done in our multi-specialty tertiary care referral hospital situated in Telangana state in south India. The case material was collected from December 2017 to December 2019 (2 years duration). All haemoglobin electrophoresis reports were collected with no prior blood transfusions in preceding 4 months. The information collected was analysed and presented.

RESULTS

Total 9 patients were diagnosed as possible sickle delta beta thalassemia, with male to female ratio of 5 : 4 and age ranging from 12 years to 45 years of age. The commonest symptoms were joint pain and jaundice in 5 patients and sign was splenomegaly in 2 patients. Ultrasonogram of abdomen showed that 3 patients had gall stones, 1 patient had gall bladder sludge, 1 patient had auto-splenectomy and 3 patients had splenomegaly. Mild to moderate anaemia was seen with reticulocytosis, sickling test positive in all patients, with haemoglobin in the range of 5.5 g/dl to 12.7 g/dl. 3 patients had iron over load, 2 patients had hepatopathy, 5 patients had unconjugated hyperbilirubinemia, Acute chest syndrome, hepatic necrosis, and nephropathy was seen in 1 patient each. Haemoglobin electrophoresis showed Hb S was from 46.1 % to 76.4, Hb A from 5.3 % to 34.7 %, Hb F from 4.8 % to 22.7 %, Hb A2 from 1.5 % to 3.3 %. 2 patients were treated with hydroxyurea. 2 patients had mutation analysis elsewhere that was reported as compound heterozygous for β-globulin gene for Hb S (GAG-GTG) and IVS 1 - 5 (G-C).

CONCLUSIONS

Sickle delta beta thalassemia presents as mild to moderate anaemia haemolysis, splenomegaly with vaso-occlusive crises. Hydroxyurea may help in the treatment. Genetic analysis helps in diagnosis and future therapies.

KEYWORDS

Haemoglobin S, Haemoglobin A2, Haemoglobin A, Haemoglobin F

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DOI: 10.18410/jebmh/2021/623

How to Cite This Article:
Shetty M, Chandra N, Adiraju KP, et al. Clinical & laboratory profile of possible sickle delta beta thalassemia in Telangana State. J Evid Based Med Healthc 2021;8(39):3435-3440. DOI: 10.18410/jebmh/2021/623

Submission 23-04-2021,
Peer Review 29-04-2021,
Acceptance 20-09-2021,
Published 27-09-2021.

BACKGROUND

δ β thalassemia is a rare disease, due to decreased production of δβ chains.[1] This may be due to mutation of δβ genes or may be due to substitutions in promotor regions.[1] The clinical presentation of δβ thalassemia is mild disease.[2] Haemogram shows decreased haemoglobin, mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH). Haemoglobin electrophoresis shows decreased haemoglobin A and haemoglobin A2, but elevated haemoglobin F.[3] Sickle cell disease more commonly in central east India,[4] with prevalence range of 3 - 17 %, with highest frequency of 9 % from Orissa state and beta-thalassemia prevalence range is 1 - 44 % and seen in all parts of India.[4] The World Health Organisation (WHO) reported 5 % world population as carriers of inherited hemoglobinopathies[5] and UNICEF in 1996 estimating 29.7 million carriers in India of beta thalassemia trait,[6] with carrier for beta thalassemia gene in north India 3 % to 15 % and in south India 1 to 3 %[7] and high frequency of beta thalassemia trait reported from Gujarat state 10 % to 15 %,[4] Tamil Nadu 8.4 % and Punjab 6.5 %.[4]

Balgir[4] RS first described double heterozygosity of abnormal haemoglobins i.e., haemoglobin E, haemoglobin S with B-thalassemia for the first time from Orissa state. Sickle beta thalassemia presenting with clinical features similar to homozygous sickle cell disease with increased Hb A_2 along with reduced fertility, fetal wastage and more maternal morbidity.[8] Haemoglobin E–B thalassemia presents as anaemia, jaundice, hepatomegaly, maxillary bone bossy, multiple transfusions, raised haemoglobin F levels with survival up to 5th or 6th decade of life and majority die in infancy due to secondary infection.[9] High levels of haemoglobin F in haemoglobin E, haemoglobin S with B-thalassemia reduce clinical severity in some but not in all patients.[8] Hence, sickle cell disease and thalassemia causes double heterozygosity which is rare in India, causing genetic and health care challenge.[8]

Different thalassemia mutations are associated with sickle disorder,[3] combination of sickle mutation and thalassemia mutations in patients result in haemoglobin S, low haemoglobin A, with no elevation in haemoglobin A2 and reactive rise of haemoglobin F.[3] These results are seen in sickle delta beta thalassemia, which is sparingly reported in literature worldwide,[10,11] hence we are presenting our experience with possible sickle delta beta thalassemia.

METHODS

This is a retrospective observational study. Patients attending General Medicine and Haematology out patients department (OPD) of a multispeciality tertiary care referral hospital in Telangana state, Nizam's Institute of Medical Sciences, Hyderabad were screened when there was suspicion of congenital hemoglobinopathy. Information of total 9 patients was collected and tabulated. The retrospective analysis of clinical information of those selected patients was done in our multi-specialty tertiary care referral hospital situated in south India. The case material was collected from December 2017 to December 2019. All haemoglobin electrophoresis reports were collected with no prior blood transfusions in preceding 4 months.

Objectives

1. To study the clinical profile of sickle delta beta thalassemia.
2. To study the haematological pattern in patients of sickle delta beta thalassemia.
3. To study the complications in patients of sickle delta beta thalassemia.
4. To study iron studies pattern in sickle delta beta thalassemia.

Inclusion Criteria

Cases suspected to have congenital hemoglobinopathy with haemoglobin electrophoresis suggestive of sickle delta beta thalassemia

Exclusion Criteria

1. Cases with other hemoglobinopathies like pure sickle cell disease, thalassemia, sickle C disease, sickle D disease, auto immune haemolytic anaemia and hereditary persistent fetal haemoglobin.
2. Information from all patients recruited for analysis was reviewed. In the history, demographic details, symptoms with the duration, blood transfusions were noted.
3. Clinical findings specifically noted were presence of pallor, jaundice, enlargement of spleen and liver.

Laboratory Investigations

Haemoglobin (Hb), total leukocytes count (TLC) and differential counts (DC), absolute neutrophil count (ANC), platelet count (PC), reticulocyte count (retic. count), red cell indices, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), red cell distribution width (RDW), serum lactate dehydrogenase (LDH), serum iron profile [ferritin, total iron binding capacity (TIBC), transferrin saturation %], serum vitamin B12 & folate levels, blood grouping, cross matching Sickling test, and peripheral smear were done in all these patients.

Indirect and direct anti-globulin test (Coomb's test), haemoglobin electrophoresis were done in all patients. Renal function tests (RFT), liver function tests (LFT) like aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), total bilirubin (TBR), conjugated bilirubin (CBR), and screening for hepatitis B, C and HIV were undertaken in every patient. Chest radiograph and ultrasonography (USG) of abdomen (carried with MYLAB60 model, e Saote company from Ahmedabad) was done in patients if indicated. The study was retrospective audit with no patient direct identifiers; hence consent was

not taken. Hospital ethics committee was informed about the study.

Statistical Methods and Data Analysis

Data was collated in a Microsoft Excel® spreadsheet and statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) software version 26. The demographic and baseline characteristics which included age, sex, haemoglobin level, total leukocyte count, ANC, absolute lymphocyte count, reticulocyte percentage, platelet count, serum iron profile [ferritin, TIBC, transferrin. saturation %], haemoglobin electrophoresis, lag from the diagnosis have been summarized using descriptive statistics [number of patients (n), mean, standard deviation (SD), median, proportions].

RESULTS

Total 9 patients (Table - 1) were diagnosed to have possible sickle delta beta thalassemia disorder. Male : Female ratio was 4 : 5. Age varied from 12 years to 45 years with a mean age of 25.2 years. Only one patient was asymptomatic, rest 8 patients had symptoms. Symptoms noted were recurrent jaundice in 5 (5 %), arthropathy in 5 (5 %), weakness in 4 (4.5 %), shortness of breath in 4 (4.5 %) and chest pain in 1 (1.1 %). The commonest sign (Table - 2) was pallor and icterus in 5 patients (5 %) followed by, pedal oedema and splenomegaly in 2 (2.3 %) patients and hepatomegaly in 1 (1.1 %) patient. 5 patients had history of blood transfusion. Two had history of pain abdomen and two patients already underwent splenectomy. 3 patients were noted to have gall stones on ultrasonogram of abdomen (Table - 3). One patient underwent laparoscopic cholecystectomy with a stent placement in bile duct. Clinically splenomegaly was noted in 2 patients.

Mild to moderate anaemia was noted in all with haemoglobin ranging from 5.5 g/dl to 12.7 g/dl and mean of 8.76. RBC count was within normal limits. Normocytic anaemia was present in majority 5, macrocytic anaemia in 3 and microcytic anaemia in 1. Though MCH was variable from 22.6 pg to 36.4 pg with mean of 32.13, MCV was 69.7 fl to 113.2 fl with mean of 94.71. MCHC was ranging from 30.2 g/dl to 36 g/dl with mean of 33.78, RDW was raised in all. Reticulocyte count varied from 4.1 to 11 %. Three patients showed sickle cells on peripheral smear, but rest of the 6 patients showed sickling on induction. Serum ferritin was done in 8 patients ranging from 128 ng/dl to 2079 ng/dl with 2 patients showing iron overload state, 5 patients were given blood transfusion, serum vitamin B12 was done in 7 patients ranging from 145 pg/dl to 846 pg/dl and serum folic acid was done in 7 patients ranging from 3.55 ng/ml to 24 ng/ml.

Haemoglobin electrophoresis (Table - 5), (Figure - 1) was done in all patients. Haemoglobin S was present ranging from 46.1 % to 79.2 % with mean of 69.2, haemoglobin A was present ranging from 5.3 % to 30 % with mean of 12.65, haemoglobin F was present ranging from 4.8 % to 22.7 % with mean of 15.95, haemoglobin A2 was present ranging from 1 % to 3.3 % with mean of 2.15.

P. N.	Age in Years	Sex	Hb (13 – 17 g/dl)	MCV (83 – 101 fl)	MCH (27 – 32 pg)	MCHC (31.5 - 34.5 g/d)	SF (20 - 250 ng/ml)	B12 (200 - 680 pg/ml)	FA (3 - 12 ng/ml)
1	22	F	8.9	99.0	33.2	33.0	521	NA	NA
2	29	M	5.5	101.4	35.6	35.1	635	498	3.55
3	41	M	11.0	102.6	36.4	35.5	NA	NA	NA
4	45	F	6.7	88.0	26.5	30.2	1470	2000	24.00
5	12	F	9.9	95.6	34.4	36.0	302	145	24.00
6	19	M	12.7	113.2	38.5	34.0	263	461	21.00
7	20	F	5.9	69.7	22.6	32.5	2079	846	24.00
8	20	M	10.1	86.3	29.7	34.4	893	568	24.00
9	17	F	8.2	96.6	32.3	33.4	128	516	24.00
Mean	25.2		8.76 g	94.71	32.13	33.78			

Table 1. Demographic and Laboratory Parameters in Our Patients

Note – PN - Patient number, NA - Not available, Hb - haemoglobin, SF - serum Ferritin, B12 - Vitamin B12, FA - Folic acid
MCV - Mean corpuscular volume, MCH - Mean corpuscular haemoglobin, MCHC - Mean corpuscular haemoglobin concentration.

Symptoms	Number of Patients	Percentage %
Weakness	4	4.5
Jaundice	5	5.5
Joint pain	5	5.5
Abdominal pain	2	2.3
Shortness of breath	4	4.5
Chest pain	1	1.1
Signs		
Pallor	5	5.5
Icterus	5	5.5
Pedal oedema	2	2.3
Hepatomegaly	1	1.1
Splenomegaly	2	2.3

Table 2. Symptoms and Signs

Findings	Number of Patients	Percentage
Hepatomegaly	1	1.1
Gall stones	3	3.3
Splenomegaly	2	2.2
Splenectomy	2	2.2

Table 3. Ultrasound Abdomen Findings in Our Patients

Patients	AST (< 36 U/L)	ALT (< 41 /L)	ALP (< 131 /L)	TBR (< 1.2 mg/dl)	cBR (< 0.3 mg/dl)	S.Cr (07 -1.3 mg/dl)
1	30	40	125	1.0	0.2	0.8
2	76	34	294	11.4	5.15	1.34
3	25	14	79	0.8	0.1	0.7
4	95	51	439	1.8	1.22	0.36
5	45	21	175	1.6	0.30	0.50
6	47	27	117	6.9	0.70	0.48
7	225	185	434	2.7	1.85	0.40
8	30	12	119	3.8	0.64	0.42
9	38	9	88	4.2	1.20	0.26

Table 4. Liver Function Test and Serum Creatinine

Note; AST – Aspartate transaminase, ALT – Alanine transaminase, ALP - Alkaline phosphatase, TBR - Total bilirubin, CBR - Conjugated bilirubin, S Cr - Serum creatinine.

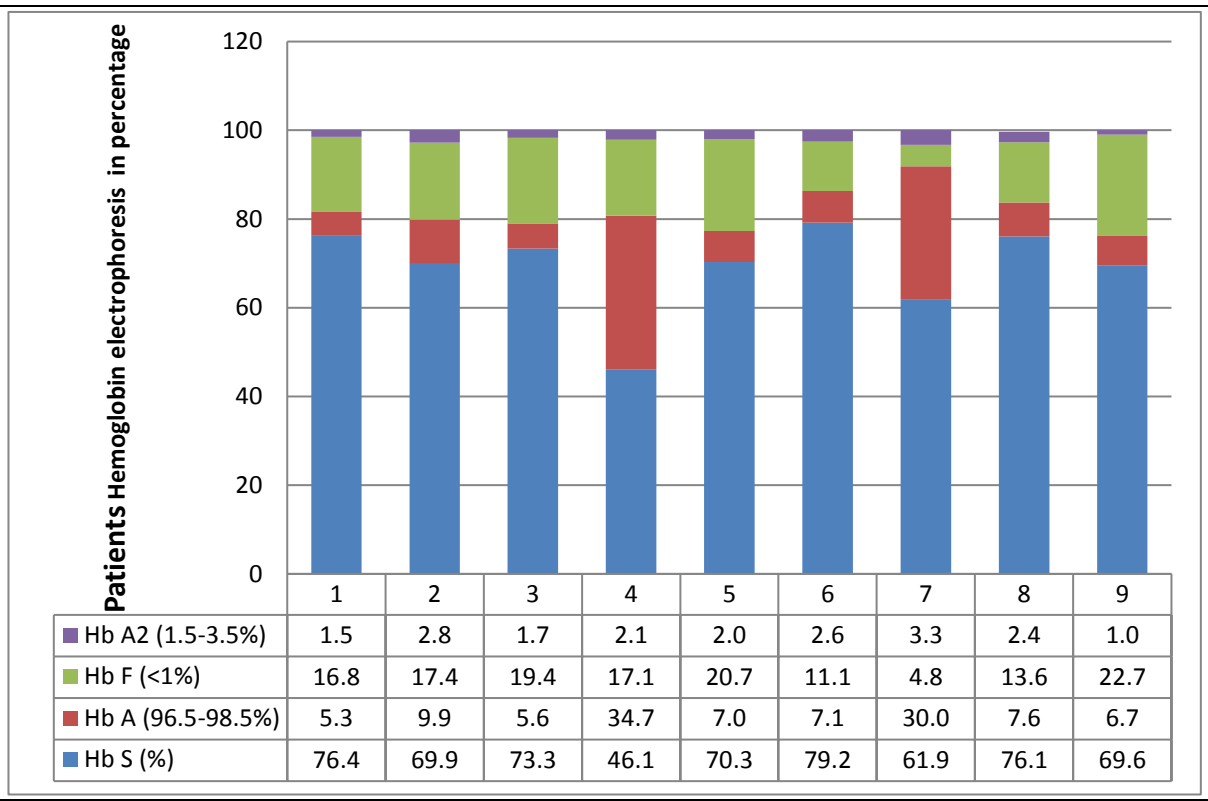

Figure 1. Details of Haemoglobin Electrophoresis in Each Patient

Patient Number	HbS (%)	HbA (96.5 - 98.5 %)	HbF (< 1 %)	HbA2 (1.5 - 3.5 %)
1	76.4	5.3	16.8	1.5
2	69.9	9.9	17.4	2.8
3	73.3	5.6	19.4	1.7
4	46.1	34.7	17.1	2.1
5	70.3	7.0	20.7	2.0
6	79.2	7.1	11.1	2.6
7	61.9	30.0	4.8	3.3
8	76.1	7.6	13.6	2.4
9	69.6	6.7	22.7	1.0
Mean	69.2	12.65	15.95	2.15

Table 5. Haemoglobin Electrophoresis in Study Subjects

The HbS was more than the HbA in all patients, HbF was < 25 % in all 9 patients indicating the possibility of thalassemia element and with reactive rise of HbF. Haemoglobin A2 was less than 3.5 % (the upper limit normal), indicating decreased δ chain production hence possible of sickle delta beta thalassemia was considered. In all these patients co-existing iron deficiency was excluded

Only two patients had mutation analysis elsewhere that was reported as compound heterozygous for β-globulin gene for HbS (GAG-GTG) and IVS 1 – 5 (G-C). One patient had azotaemia, acute chest syndrome, another patient had proteinuria (sickle nephropathy), iron over load was seen in 2 patients (due to recurrent packed red cell transfusions), one patient had hepatic crisis. Two patients had mild hepatopathy and 5 patients (Table - 4) had unconjugated hyperbilirubinemia. 5 patients had requirement of blood transfusion, 2 patients required 60 units of packed red cell, 1 patient required 30 units of packed red cell and in remaining 2 patients details of blood transfusions were not known. Among 5 patients of blood transfusion, 2 patients had undergone splenectomy outside hospital but details were not known, 3 patients had splenomegaly among them 2 were requiring blood transfusion and they had iron over load state. 1 patient had auto splenectomy seen on ultrasound abdomen and was requiring blood transfusion.

DISCUSSION

Sickle delta beta thalassemia is variant of sickle cell disease sparingly seen [10,11], commonly in Senegalese descent[12] and other variants like sickle beta thalassemia and haemoglobin E beta thalassemia are seen in Srilanka,[13] Thailand[14] and central–east India.[9] We studied 9 patients with male to female ratio of 4 : 5, age range from 12 years to 45 years, Shivashankara[15] et al. Deepthi V[16] et al. Grace O[17] et al. had 1 patient each of 6 years, 16 years and 18 months respectively. Cohen[18] et al. had 2 patients with pregnancy but Balgir R S[8] had 12 patients of sickle beta thalassemia (SBT) and 9 cases of haemoglobin E beta thalassemia (HEBT) age ranging from 2 years to 72 years. In our patients, haemoglobin was from 5.5 g/dl to 12.7 g/dl. Shivashankara[15] et al. patient had haemoglobin of 8 g/dl, Deepthi[16] V et al patient had haemoglobin of 4.3 g / dl both were male patients, Grace[17] O et al. patient had haemoglobin of 15.4 g/dl. In Balgir R S[8] study group, patients haemoglobin was in the range of 5.5 g/dl to 13 g/dl, and majority had moderate to severe anaemia but in our study majority had mild to moderate anaemia. Marcus[19] SJ et al. also reported similar findings.

In our study, majority of the patients had jaundice and arthropathy (5 patients), similarly reported by Deepthi V[16] et al. Balgir[8] R S, Cholelithiasis was seen in 2 patients, and 1 patient had gall bladder sludge; splenomegaly was seen in 3 patients and auto-splenectomy in 1 patient. Deepthi[16] V et al. Cohen[18] AW et al. Pearson[20] HA, Balgir[8] R S patients too had splenomegaly. MCV in our patient was 69.7 to 113.2 fl patients with mean of 94.7, Grace[17] O et al. patient had MCV of 67.5 fl, in Balgir[8] RS group of patients had reduced

values of MCV, MCH, MCHC majority patients. Reticulocytosis, and sickling test was positive in all patient, similarly seen by Deepthi[16] V et al. Marcus[19] SJ et al. Coheen[18] A et al. Serum ferritin in 8 of our patients was in the range from 128 ng/ml to 2079 ng/dl with 2 patients showing iron overload state due to repeated blood transfusions, Wood[21] JC et al. reported similarly, 5 patients were requiring blood transfusion in our study, Balgir[8] R S all patients had blood transfusions regarding iron over load status was not known. One patient had azotaemia, acute chest syndrome, another had proteinuria (sickle nephropathy), hepatic necrosis, similarly seen in sickle cell diseases (SCD).[22,23]

Haemoglobin electrophoresis (Table - 5) of our patients showed HbS in our patients was from 46.1 % to 76.4, HbA from 5.3 to 34.7 %, HbF from 4.8 % to 22.7 %, HbA_2 from 1.5% to 3.3 %, Deepthi V et al.[16] patient had HbS of 19.6 %, HbA 62.3 %, HbF 13.8 %, HbA_2 3.3 %, Grace[17] O et al. HbS of 55 %, HbA 0 %, HbF 41.2 % and HbA_2 3.3 %. Balgir[8] R S patients had HbS in the range of 25 % to 76.7 %, HbA ranging from 5.5 % to 66.7 %, HbF from 4.5 % to 38.1 %, HbA_2 from 3.7 % to 6.6 %, Marcus[19] SJ et al. had HbF range from 3.2 % to 21.8 % with mean of 9.2 %, Shivashankara[15] et al. patient had HbS of 60 %, HbA 27 %, HbF 8 %, and HbA_2 5 %. In our study, HbF levels were not suggestive of severity of symptoms or signs or complications of the disease but Balgir[8] R S reported in their study high levels of HbF in some patients reduce the severity of clinical symptoms. In our study, more the HbS levels, more is the severity of symptoms and complications which is similarly reported in SCD.[22,24]

	Balgir[8] RS (SBT)2007	Shivshankar[15] et al. 2008	Grace[17] et al. 2017	Deepthi[16] et al. 2014	Our Study 2021
Number of patients	12	1	1	1	9
Age in years	2 to 72	6	1.5	16	12 to 45
Haemoglobin g/dl	5.5 to 13	8	15.4	4.3	5.5 to 12.7
Splenomegaly	12 patients	NA	NA	1 patient	3 patients
Blood transfusion requirement	12 patients	NA	NA	NA	5 patients
Haemoglobin electrophoresis in percentage					
HbS	25 to 76.7	60	55	19.6	46.1 to 76.4
HbA	5.5 to 66.7	27	0	62.3	5.3 to 34.7
HbF	4.5 to 38.1	8	41.2	13.8	4.8 to 22.7
HbA_2	3.7 to 6.6	5	3.3	3.3	1.5 to 3.3

Table 6. Comparison of Our Data with Other Studies

Note – NA - Not available.

Gene analysis was done in 2 patients reported as compound heterozygous for β-globulin gene for HbS (GAG-GTG) and IVS 1 - 5 (G - C), similarly Grace [9]o et al. reported in their patient HBB genotype, genotypesβ S/($\delta\beta$) 0, genetic significance. Three patients had compound heterozygous for the missense mutation, c. 20 A > T, in HBB, and a 13.4 kb deletion that includes the HBB and HBD genes, NG 000007.3: g. 64336 77738del13403 (13.4 kb Sicilian ($\delta\beta$) 0 – thal deletion). Rest of the 7 patients gene analysis could not be done due to financial issues and non-availability of genetic testing; we diagnosed these patients as possible sickle delta beta thalassemia.

Two patients were on hydroxyurea had mild symptoms, but the percentage of increase was not known because of non-availability of old reports, hydroxyurea is known to increase haemoglobin F of 2 % to 13 % with a mean of 11 % and decrease symptoms as reported by Charache[25] et al.

As a whole, sickle delta beta thalassemia is difficult to distinguish in majority from homozygous sickle cell disease and in some behaves partially as beta thalassemia. The main clinical features of sickle delta beta thalassemia are of homozygous sickle cell disease anaemia, jaundice, gall stones but majority requiring blood transfusions and have splenomegaly.

CONCLUSIONS

Sickle delta beta thalassemia presents as mild to moderate anaemia, reticulocytosis, joint pain, jaundice, splenomegaly, haemolysis with vaso-occlusive crises. Haemoglobin electrophoresis helps in diagnosis and genetic analysis helps in confirming it. This in turn helps in diagnosis, management strategy for future patients and to develop guidelines for screening during prenatal and newborn screenings.

Haemoglobin electrophoresis can be done in suspected cases of hemoglobinopathies. Genetic counselling and if possible genetic analysis too. This will help in prenatal diagnosis of hemoglobinopathies.

Limitations of the Study

It is a retrospective study with small study patients. Lack of follow up data, lack of screening of family members and genetic analysis was seen in majority of our patients.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
Disclosure forms provided by the authors are available with the full text of this article at jebmh.com.
Department of Biochemistry, Wife Keerthi, Daughter Saanvi and patients.

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