Frontiers in Medical Case Reports, ISSN: 2582-8142

Sickle Cell Hemoglobin E Disorder – A Case Study in Balasore District of Odisha, India

Somali Das[1] | Apratim Sai Rajesh[1] | Nibarana Satapathy[1] | Bisnu Prasad Dash[1,2]*

***Correspondence:** Bisnu Prasad Dash

Address: [1]Department of Biosciences and Biotechnology, Fakir Mohan University, Balasore – Odisha, India; [2]Dept. of Zoology, Biological Sciences Division, AIPH University, Bhubaneswar – Odisha, India

e-mail ✉: bisnubsbtfmu@gmail.com

Received: 11 October 2021; **Accepted:** 08 November 2021

ABSTRACT

Hemoglobinopathies are the cause of some major genetic and social health problem in many countries including India and sickle cell disorder is one of the most debilitating genetic disease affecting a large population. Though recognized, in and as various groups of genetic mutations, double heterozygous state of sickle cell and hemoglobin E (HbSE) is uncommon in Odisha state. Due to migration and racial inter-caste marriages between the populations of different neighboring states the possibilities of detecting Hb SE disease in Odisha is rising but this rare case of Hb SE has never been reported in Balasore district so far. In the present instance, a 24 year old male was diagnosed with sickle cell hemoglobin E disorder. The case was confirmed through Hb electrophoresis, slide based sickle test, HPLC and ARMS PCR. The peripheral smear analysis showed the presence of microcytic RBC and Hypochromasia. No splenomegaly and hepatomegaly was observed. The case was mostly asymptomatic and with history of joint and bone pains once or twice per year.

Keywords: *HbSE, Sickle Cell, Hemoglobin SE, Balasore*

Introduction

Hemoglobinopathies are one of the most commonly encountered monogenic disease of human blood, which constitutes some of the most affected genetic and social health problem in regions of Africa, South America and Southeast Asia, particularly in India (Weatherall and Clegg, 2001; Chhotray *et al*., 2004).

In the medical history of hemoglobinopathies, sickle cell disease (SCD) is the oldest known molecular disease (Frenette and Atweh, 2007). Among them HbE disease caused by a mutation where in lysine is substituted for glutamic acid in the 26th position of the beta chain of hemoglobin A (HBB Glu26Lys) and it is one of the most widely reported hemoglobin related disorder after the HbS (HBB Glu6Val) disease (Thornburg, 2009; Acipayam *et al*., 2015). Reports have designated it as the second most common hemoglobinopathy variant globally with observations that this mutation has evolved to provide

resistance against malaria (Williams and Weatherall, 2012).

In India, a considerable size of population spanning across Central India, from Odisha in the east to Maharashtra and Gujarat in the west is affected by the SCD (Colah *et al*., 2014; Wajcman and Moradkhani, 2011). Three major variants of this disease are widely reported in India –Sickle Hemoglobin (HbS), Hemoglobin E in West Bengal and Northeastern India (Hb E) and Hemoglobin D (HbD_{Punjab}) in Northwestern India (Kate and Lingojwar, 2002; Dash and Kar, 2006).

The HbE disorder in India is commonly seen in north-eastern states and West Bengal (Flatz, 1967) and gene frequency has been reported to be about 10.9% in north eastern regions (Balgir,1996). Tribal communities constitute a major part of the Indian population and are particularly vulnerable to hemoglobinopathies. In a tribal population, i.e. Delki Kharia in Odisha, 1.4% prevalence of HbE disorders (10 traits and one disease case) was recorded (Balgir, 2005; Kishore *et al*., 2007).

The disease pattern resembles that of *β-thalassemia* and is a clinically benign condition which includes mild hemolysis (Acipayam *et al*., 2015). For instance, *β-thalassemia* major is marked with a higher level of HbA_2 and HbF (up to 90%). Similarly, HbE trait is reported to have a content of approximately 30% of HbA_2 along with HbE whereas homozygous HbE patients have approximately 90% HbE+A_2 with minor elevation of HbF (Kishore *et al*., 2007).

Types of Complication Described in HbSE Disease

Although often described as a mild condition and a relatively unknown variant of the sickle cell disease, the HbSE disease reports across the world actually point to a plethora of clinical features and observations in the patients. These symptoms range from episodes of acute painful vaso-occlusive crisis (VOCs) to conditions such as acute chest syndrome and splenic thrombosis, which were observed in adult patients (Masiello *et al*., 2007; Khamees and Rozi, 2021). The VOCs in HbSE are attributed to possible accumulation of subclinical microinfarcts which manifests during adulthood upon encounter of stressful conditions such as hypoxia, high altitude travel and metabolic abnormalities (Fucharoen and Weatherall, 2012; Masiello *et al*., 2007).

The age factor involving the severity of the HbSE disease is again a debatable issue. While some studies report the majority of cases belonging to be in age group of 20+ (Masiello *et al*., 2007), some recent studies also indicate to patients suffering from complications such as cerebro-vascular stroke and bone infarction leading to bone marrow embolism at ages as young as just 5 years (Acipayam *et al*., 2015). The HbSE disease also reports cases with multiple clinical manifestations such as bone infarction and acute chest syndrome (Tay *et al*., 2011) and parvovirus B19 infection and acute chest syndrome

(Eichhorn *et al*., 1999). With the study and understanding of these facts, we had look at the occurrence of HbSE disease in Odisha.

HbSE Disease case in Odisha

Among the different double heterozygous combinations of sickle susceptible hemoglobins, the commonly observed variants includes HbSS, HbAS, HbE-β thalassemia, Hb SC disease, Hb SD disease and HbS-β Thalassaemia. HbS and HbE are globally well known hemoglobinopathies (Iyer *et al*., 2015; Sahu *et al*., 2012). The HbE disease (HBB Glu 26 Lys) is caused by a single nucleotide substitution GAG > AAG in codon 26 of the β globin gene. This mutation has been found to reside on several DNA haplotypes linked to the β -globin gene cluster (Masiello *et al*., 2007). The double heterozygous state for sickle cell and Hemoglobin E is uncommon in Odisha state.

A report on Hemoglobin E occurrence in southern Odisha has been published very recently which includes cases of HbAE trait, HbE *β-thalassemia* and HbSE (Sahu *et al*., 2021). HbE cases have been reported previously in the Western Odisha (Jit *et al*., 2019; Purohit *et al*., 2019).

But to the best of our knowledge this is the first case of HbSE disease being reported from the Northern Coastal regions of Odisha, precisely in the Balasore district. This finding can be attributed to the present conditions of rapid movement of population across the state. Owing to migrations and the consequent rise in inter-racial and inter-caste marriages between different population groups within and outside the state, the possibilities of detecting Hb SE disease in Odisha is on the rise.

Case Presentation

A 24-year-old bachelor male belonging to Balasore district of Odisha, in Eastern India, was referred to us for symptoms of anemia. After initial counseling and consultation with patient along with his family, the entire family history was noted. To conduct the necessary scientific tests for ascertaining the case, the patient voluntarily agreed to share his blood sample. A part of the sample thus collected was sent for HPLC analysis at a private facility. The sample was subjected to the standard slide-based sickle test (Emmel Test) followed by hemoglobin (Hb) electrophoresis both in alkaline (pH 8.6) and acidic (pH 6.2) medium. After initial indication from lab test, the HPLC report confirmed the case to be one of Hb SE disease. For further confirmation, ARMS-PCR using specific oligonucleotide primers from the patient sample was performed which also gave appropriate results confirming the case to be of a HbSE disease. (Newton *et al*., 1989)

The different hematological parameters of the patient were: Total Hemoglobin -14.1gm/dL, HbF-5.2%, HbE/A_2-32.3% and HbS-62.9%, TRBC-6.1x10^6/µl, WBC-6.2x10^3/µl, Platelets-188x103/µl. The peripheral smear analysis showed that he was having microcytic RBC and Hypochromasia. Interestingly, there was no history of hospitalization and blood transfusion for this patient, as also no report of splenomegaly and hepatomegaly. On the whole, the case was mostly asymptomatic and history of joint and bone pains were noted only once or twice per year. However, after the case detection and confirmation, the patient was referred to the District Headquarter Hospital, which also has a fully functional blood bank attached to it.

Further he has been continuing to visit the DHH in any case of any occasional cause of pain and uneasiness. To the best of our information till date, the patient is maintaining an almost normal health without any major complications. He has been advised against any heavy physical and mental work along with maintaining a moderate diet and most importantly to take genetic counseling before marriage and to undergo prenatal diagnosis before planning parenthood.

Family Background

The family consisted of the parents and grandparents of the patient along with a younger sister. Subsequent to the patient's test, the parents also agreed to be tested for all the necessary procedures. It was thus found that the 48-year-old mother was sickle cell carrier i.e. HbAS. She was found to have abnormal MCHC and microcytosis red blood cell, when examined by HPLC analysis. Her total Hb was 10.9 g/dL, RBC - 3.72 x 10^6/µl, WBC - 3 x 10^3/µl, Platelets–264x10^3/µl, HCT–27.5%, MCV–73.9fL, MCH–29.3pg, MCHC–39.6g/dL, RDW – 29.9%, MPV – 9.1fL, PDW-15.6%. Similarly the 50 year old father, upon testing and analysis, was found to be a carrier of Hb E gene having HbA_2/E – 24.5%, RBC – 4.07 x 10^6/µl, WBC-2.5x10^6/µl, Platelets-178x10^6/µl, HCT-31.1L, MCV–76.4L, MCH–27pg, MCHC–35.4g/dL, RDW-29.8%, PCT-0.12%, MPV–6.8fL, PDW–16%. Thus, the possibility of having a progeny with HbSE was quiet evident.

Table1: Health parameter of the Patient and his family member at a Glance.

Sl.No.	Name	Age/Sex	Hb (g/dl)	HbA (%)	HbS (%)	HbE/A_2 (%)	HbF (%)	MCV	RBC^6 (10/µl)	WBC^3 (10/µl)	Plt^3 (10/µl)
1	Patient	24M	14.1	4.3	58.6	27.5	5.2	72.9	6.1	6.2	188
2	Father	50 M	11	63.1	-	24.5	1.2	76.4	4.1	5.6	178
3	Mother	48F	10.9	50.6	36.4	3.4	1	73.9	3.7	5.3	264
4	Sister	22F	12.7	96.6	-	2.5	0.9	74	4.6	5.6	308
5	GrandFather	70M	11	70.3	-	28.8	0.9	66.2	3.5	4.6	423
6	GrandMother	68F	10.5	96	-	3.2	0.8	81.6	3.9	4.8	241

Discussion

The HbE disease was first described in 1957 in case of a 70-year-old woman and her 30- year-old son among Eti-Turk kindred in southern Turkey (Acipayam*et al*., 2015; Altay*et al*., 1981; Aksoy and Lehmann, 1957) and since then many cases have been reported. It has been widely reported to be found in areas of Southeast Asia including Sri Lanka, East India and Southwest China (Masiello *et al*., 2007) and in population of different ethnic origin in the United States of America (Rey *et al*., 1989). The first HbSE case in India was reported in Bombay (Vishwanathan *et al*., 1992). They were able to trace 4 families with symtoms of the HbSE combination. Most of these patients were found to maintain substantial and stable levels of hemoglobin, slightly normal RBC, along with hyper -bilirubinemia, reticulocytosis and high HbF. But none had the history of blood transfusions. It was understood that the resultant HbSE disease was mild in all of them, because of the presence of high levels of HbF which helps in preventing sickling of RBCs (Mishra *et al*., 2005). In the present case belonging to the Balasore district of Odisha, the patient has mostly been asymptomatic, in accordance with studies described previously (Ahmed *et al*., 2007; Mishra *et al*., 2005; Masiello *et al*., 2007). Except for minor pain in body, especially in bone and joints, the patient hardly had any major clinical symptoms.

This study also indicates the validity of previous reports that hematological parameters and levels of Hb S, E or F cannot be directly implicated in prediction of clinical severity (Mishra *et al*., 2005). Regarding the occurrence and frequency of detection of such cases it can be said that the district of Balasore is bordering the state of West Bengal which is well known for its population with Hb E (Flatz, 1967; Kate and Lingojwar, 2002) and which also points to the possibility of people migrating across the region.

However, for more concrete establishment of the disease history and occurrence, there must be more widespread mass screening of the regional population. One possible reason as to why such a study has not yet been conducted is that, the eastern part of Odisha does not contain any significant population affected by SCD. Hence the frequency of testing, diagnosis and disease record is relatively quiet less as compared to West and South Odisha.

There are no strictly defined management guidelines available for the HbSE disease and since most complications of the disease arise due to HbS, the management is mostly based in accordance with SCD guidelines (Pajak *et al*., 2020). Antiplatelet or anticoagulant therapy have been unable to show an impact on crisis duration, symptom control, or prevention of recurrence (Charneski and Congdon, 2010). Thus, traditional management strategies using fluids and analgesia are reported to be typically adequate for resolution of symptoms (Eaton and Bunn, 2017; Charneski and Congdon, 2010). Globally, in all cases of

painful crisis, hydroxyurea (HU) is most practiced therapy and same applies to the SCD patients of Odisha as well. The present case has also been treated with HU at instances of acute pain but a particular study to elucidate the remedial action of increase in HbF due to administration HU in HbE patients of this regions remains to be studied. In case of hyper anemic conditions, blood transfusion can be recommended due to immediate action as a life saving measure (Howard, 2016).

Conclusion

In conclusion it can be said that, with changing demography and increasing population, along with a continuing trend of temporary and permanent migration, it is possible to find cases of HbSE disease in any part of Odisha. There is a need to establish thorough practices of testing and evaluation in almost all regions of the state, where population susceptible to sickle cell disease might exist. Though in the present case the patient was asymptomatic, the possibility of having Sickle haemoglobin E disease (HbSE) cases with mild to moderate or severe symptoms cannot be ruled out.

References

Acipayam C, Oktay G, Ilhan G, Mehmet AC. Hemoglobin SE Disease in Hatay, in the Southern Part of Turkey. *Thal Rep* 2015; 5: 4597.

Ahmed MM, Gravell, D, Ganesh A. Sickle Cell – Haemoglobin E (HbSE) Compound Heterozygosity: A Clinical and Haematological Study. *Int J Lab Hematol* 2017; 29: 292–301.

Aksoy M and Lehmann H. The First Observation of Sickle-Cell Hæmoglobin E Disease. *Nature* 179: 1248–1249.

Altay C, Niazi GA, Huisman THJ. Hb E and Hb E-Like Variants in Individuals from Turkey. *Hemoglobin* 1987; 5: 743–748.

Balgir RS. Genetic Epidemiology of the Three Predominant Abnormal Hemoglobins in India. *J Assoc Physicians India* 1996; 44: 25–28.

Balgir RS. The Spectrum of Haemoglobin Variants in Two Scheduled Tribes of Sundargarh District in North-Western Orissa, India. *Ann Hum Biol* 2005; 32: 560–573.

Charneski L and Congdon HB. Effects of Antiplatelet and Anticoagulant Medications on the Vasoocclusive and Thrombotic Complications of Sickle Cell Disease: A Review of the Literature. *Am J Health-Syst Pharm* 2010; 67: 895–900.

Chhotray GP, Dash BP, Ranjit MR, Cohla RB, Mohanty D. Haemoglobin E/Beta-Thalassaemia - an Experience in the Eastern Indian State of Orissa. *Acta Haematol* 2003; 109: 214–216.

Chhotray GP, Dash BP, Ranjit MR. Spectrum of Hemoglobinopathies in Orissa, India. *Hemoglobin* 2004; 28: 117–122.

Colah RB, Mukherjee MB, Ghosh K. Sickle Cell Disease in India. *Curr Opin Hematol* 2014; 21: 215–223.

Dash BP and Kar BC. Sickle Cell-Haemoglobin Dpunjab Disease in Orissa State, India. *HAEMA* 2006; 9: 652–654.

Eaton WA and Bunn HF. Treating Sickle Cell Disease by Targeting HbS Polymerization. *Blood* 2017; 129: 2719–2726.

Eichhorn RF, Buurke, EJ, Blok P, Berends MJH, Jansen CL. Sickle Cell-like Crisis and Bone Marrow Necrosis Associated with Parvovirus B19 Infection and Heterozygosity for Haemoglobins S and E. *J Intern Med* 1999; 245: 103–106.

Flatz G. Hemoglobin E: Distribution and Population Dynamics. *Humangenetik* 1967; 3: 189–234.

Frenette PS and Atweh GF. Science in Medicine Sickle Cell Disease: Old Discoveries, New Concepts, and Future Promise. *J Clin Investig* 2007; 117: 850–854.

Fucharoen S and Weatherall DJ. The Hemoglobin E Thalassemias. *Cold Spring Harb Perspect* 2012; 2: a011734.

Howard J. Sickle Cell Disease: When and How to Transfuse. *Hematology* (United States) 2016; 2016: 625–631.

Iyer S, Sakhare S, Sengupta C, Velumani A. Hemoglobinopathy in India. *Clinica Chimica Acta* 2015; 444: 229–233.

Jit BP, Mohanty PK, Pradhan A, Purohit P, Das K, Patel S, Meher S, Sinha S, Mohanty JR, Behera RK, Das P. Erythrocyte cAMP in Determining Frequency of Acute Pain Episodes in Sickle Cell Disease Patients from Odisha State, India. Hemoglobin 2019; 43: 88-94.

Kate SL and Lingojwar DP. Epidemiology of Sickle Cell Disorder in the State of Maharashtra. *Int J Hum Genet* 2002; 2: 161-167.

Khamees I, Rozi W, Yassin MA. Acute chest syndrome in sickle cell disease/HBE patient, A case report. *Clin Case Rep* 2021; 9: e04575.

Kishore B, Khare P, Gupta RJ, Bisht S, Majumdar K. Hemoglobin E Disease in North Indian Population: A Report of 11 Cases." *Hematology* 2007; 12: 343–347.

Masiello D, Heeney MM, Adewoye AH, Eung SH, Luo HY, Steinberg MH, Chui DHK. Hemoglobin SE Disease - A Concise Review." *Am J Hematol* 2007; 82: 643–649.

Mishra P, Pati HP, Chatterjee T, Dixit A, Choudhary DR, Srinivas MU, Mahapatra M, Choudhry VP. Hb SE Disease: A Clinico-Hematological Profile. *Ann Hematol* 2005; 84: 667–670.

Newton CR, Graham A, Heptinstall LE, Powell SJ, Summers C, Kalsheker N, Smith JC, Markham AF. Analysis of any point mutation in DNA. The amplification refractory mutation system (ARMS). *Nucleic Acids Res* 1989; 17: 2503–2516.

Pajak A, Li JC, Liu A, Nazare S, Smith B. Hemoglobin SE Disease Presenting as a High-Altitude Massive Splenic Infarction Complicated by Hemorrhagic Conversion and Splenectomy. *Cureus* 2020; 12: 9–14.

Purohit P, Mohanty P, Panigrahi J, Patel S. Infection with Plasmodium falciparum malaria in a patient with homozygous hemoglobin E. *Muller J Med Sci Res* 2019; 10: 36.

Rey KS, Unger CA, Rao SP, Miller ST. Sickle cell-hemoglobin E disease: clinical findings and implications. J Pediatr 1991; 119: 949–951.

Sahu P, Purohit P, Mantri S, Tudu R, Nayak J, Agrawalla SK, Behera SK, Patro MK, Karmee N, Tripathy D, Mishra B, Mishra DP. Spectrum of hemoglobin disorders in southern Odisha, India: a hospital based study. *Porto Biomed J* 2021; 6: e126.

Sahu PK, Pati SS, Mishra SK. Genotype-phenotype correlation of *β-thalassemia* spectrum of mutations in an Indian population. *Hematol Rep* 2012; 4: e9.

Tay SH, Teng GG, Poon M, Lee VKM, Lim, AYN. A case of hemoglobin SE presenting with sickle cell crisis: Case report and histological correlation. *Ann Acad Med Singap* 2011; 40: 552–553.

Thornburg CD. Hemoglobin SE Disease in Maine and Severe Thalassemia in New Hampshire. *Pediatr Hematol Oncol J* 2009; 31: 307.

Vishwanathan C, Agarwal MB, Bichile LS, Bhave AB. Double heterozygosity for hemoglobin S and E. *Indian Pediatr* 1992; 29: 895–897.

Wajcman H and Moradkhani K. Abnormal haemoglobins: Detection & characterization. *Indian J Med Res* 2011; 134: 538–546.

Weatherall DJ and Clegg JB. Public Health Reviews Inherited haemoglobin disorders: an increasing global health problem. Bull. *World Health Organ* 2001; 79: 704–712.

Williams TN and Weatherall, DJ. Health Burden of the Hemoglobinopathies. *Cold Spring Harb Perspect Med* 2012; 2: 1–14.