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BRIEF REPORT



Sickling Disorder Caused by Co-Inheritance of Hemoglobin Maputo and Hemoglobin S: Case Report and Review of the Literature

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ABSTRACT

We report a family study wherein the index patient, a 6-year-old Mozambican female, was diagnosed with compound heterozygous HbS and Hb Maputo. She presented with acute pain, swelling and tenderness in the right fronto-temporal region of the skull, which raised suspicion of sickle cell disease (SCD). Prior to this presentation, a two-year history of vague clinical symptoms (viz., periodic fever, joint pain and abdominal pain) was obtained. Both parents were clinically asymptomatic. Hemoglobin separation studies were performed using hemoglobin electrophoresis and high performance liquid chromatography. Next generation sequencing technology was employed for gene sequencing analysis of globin genes. Both parents were also fully investigated. Hemoglobin separation studies on the index patient detected two hemoglobin variants that were identified on gene sequencing analysis as HbS and Hb Maputo. The mother and father were demonstrated to have heterozygous HbS and Hb Maputo, respectively. The α globin genes in all the family members had a normal wild type configuration. Conclusion: Hb Maputo in the heterozygous state is an uncommon β chain variant that is clinically silent whereas co-inheritance of Hb Maputo and HbS causes a sickling disorder with vaso occlusive disease.

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Sickle cell disease; hemoglobin Maputo; compound heterozygosity; rare hemoglobin variant

Introduction

Sickle cell disease (SCD) is an autosomal recessive condition caused by a point mutation in the 6th codon of the β globin gene, which results in substitution of glutamic acid by valine in the 6th position of the β globin chain ($\beta^{6\text{Glu}\rightarrow\text{Val}}$) [1]. This is the most common inherited hemoglobinopathy, particularly among those whose ancestors came from areas where malaria is or was common viz., Sub-Saharan Africa, South America, the Caribbean, Central America, Saudi Arabia, India, and Mediterranean countries including Turkey, Greece, and Italy [2–5]. An estimated 7–8 million people are living with the homozygous form globally. Over half a million babies were born with homozygous SCD in 2021, with more than three quarters in countries of sub-Saharan Africa [6].

The primary reason for persistence of the sickle gene in malarial endemic areas is partial protection against malaria in the heterozygous state [7]. Since South Africa is not a malarial endemic area, the prevalence of SCD is predictably low (<1%) [8]. Following the first free election in 1994, relaxed border controls led to a steady influx of people from other parts of Sub-Saharan Africa, consequent to which, South Africa is exposed to the previously uncommon SCD and other inherited hemoglobin disorders.

The spectrum of SCD encompasses a heterogeneous group of disorders that include: i) Homozygous SCD, ii) Heterozygous SCD and, iii) Compound heterozygous states such as HbS/C disease, HbS/ β -thalassaemia, etc. Homozygous and select compound heterozygous SCD patients manifest with clinical disease of varying severity that is influenced by genetic, biological and

environmental factors [9–11]. The hallmark acute clinical presentation symptom is a sickle cell crisis, which is caused by vaso occlusion of smaller vessels with ensuing ischemia and pain in the affected region [12]. Repeated episodes of infarction causes organ damage and may eventually lead to organ failure. Heterozygous SCD is generally asymptomatic with no long term clinical sequelae.

Hb Maputo ($\beta^{47\text{Asp}>\text{Tyr}}$) is an uncommon β chain variant that was first described in a 2-year old patient in 1983 [13]. The patient was from Maputo, Mozambique, who presented with a sickling disorder. Hb separation studies demonstrated the presence of compound heterozygous HbS and an unknown variant which was later shown to have the mutation $\beta^{47\text{Asp}>\text{Tyr}}$ on the β globin chain. This new variant was named Hb Maputo.

Subjects with heterozygous Hb Maputo are clinically asymptomatic with no long term adverse clinical effects. Case reports of homozygous Hb Maputo have not been reported in the literature.

Clinical presentation

We describe here features typical for SCD in a heterozygous HbS individual who also co-inherited Hb Maputo, a β chain variant.

The patient is a 6-year old girl from Maputo, who had a long standing history of being unwell since 21 months of age, with periodic episodes of myalgia and joint pain accompanied by pyrexia. A drop in hemoglobin was noted during these episodes with recurrent hospital admissions but rarely required a red cell transfusion. However, two units of red cell concentrate were administered 8 weeks prior to the current hospital admission. At this stage, a provisional diagnosis of undefined systemic auto-inflammatory disease was considered. However, gene sequence analysis of autoinflammatory syndromes (109-gene-panel) did not reveal pathogenic variants.

During the current admission, the patient presented with fever, acute pain, swelling and tenderness in the right fronto-temporal region of the skull. Further enquiry revealed a history of recurrent severe abdominal pain mimicking acute pancreatitis and an episode of acute lower back pain. There was no palpable hepatomegaly or splenomegaly on record. The current clinical scenario prompted the attending pediatrician to probe for a possible sickling disorder.

She was noted to have clinical features of a hypermobility syndrome.

The mother was a known sickle cell trait carrier but the father had no record of being tested for a

hemoglobinopathy. Both parents gave a history of being clinically well.

Methods

Ethics approval

Relevant ethics approval has been obtained: University of the Witwatersrand Human Research Ethics Committee, clearance certificate (medical) no. M210147

Radiological examination

Skull X-ray showed biparietal soft tissue swelling. Ultrasound examination demonstrated ill-defined thickening of subcutaneous tissue in the right fronto-temporal region. In addition, a bilateral genu varus deformity was noted on X-ray.

Magnetic resonance imaging (MRI) revealed the following: a) skull, spine and pelvis- a mottled signal (signifying bone marrow hyperplasia) and sclerosis (signifying bone infarcts), b) abdomen- splenic infarction

Laboratory investigations

Full blood count results (Sysmex XN-1000 analyser) of the patient and parents are depicted in Table 1. The hemoglobin of 9.2 g/dL is post transfusion. A thrombocytopenia (platelet count $90 \times 10^9/\text{L}$) was noted, though there was no clinical splenomegaly. Computerized tomography scan and ultrasound examination ruled out sub-clinical splenic enlargement.

Peripheral blood smear microscopy (Figure 1) revealed a variety of red cell shapes including sickle cells, irregularly contracted forms, target cells, nucleated red cells and occasional Howell Jolly bodies.

Table 1. Blood count results of patient and both parents.

Blood counts	Propositus	Father	Mother
WBC count ($\times 10^9/\text{L}$)	6.7	5.47	5.46
N ($\times 10^9/\text{L}$)	3.4	1.8	2.04
L ($\times 10^9/\text{L}$)	2.7	2.88	2.99
M ($\times 10^9/\text{L}$)	0.47	0.64	0.31
E ($\times 10^9/\text{L}$)	0	0.13	0.07
B ($\times 10^9/\text{L}$)	0	0.02	0.05
RBC count ($\times 10^{12}/\text{L}$)	3.39	4.19	6.07
Hb (g/dL)	9.2	13.5	13
MCV (fL)	78.2	93.3	67.7
MCH (pg)	27.1	32.2	21.4
MCHC (g/dL)	34.7	34.5	31.6
Platelets ($\times 10^9/\text{L}$)	90	309	259
NRBC count (per 100 WBCs)	109		

Key: WBC=white blood cell, N=neutrophils, L=lymphocytes, M=monocytes, E=eosinophils, B=basophils, RBC=red blood cell, Hb=hemoglobin, MCV=mean cell volume, MCH=mean cell hemoglobin, MCHC=mean cell hemoglobin concentration, NRBC=nucleated red blood cell.

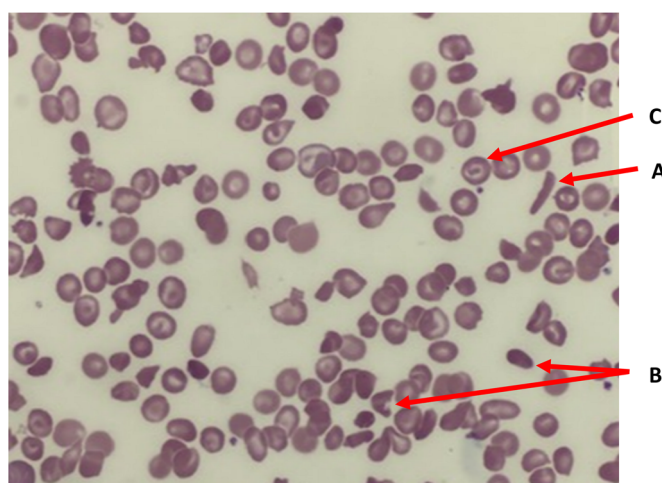
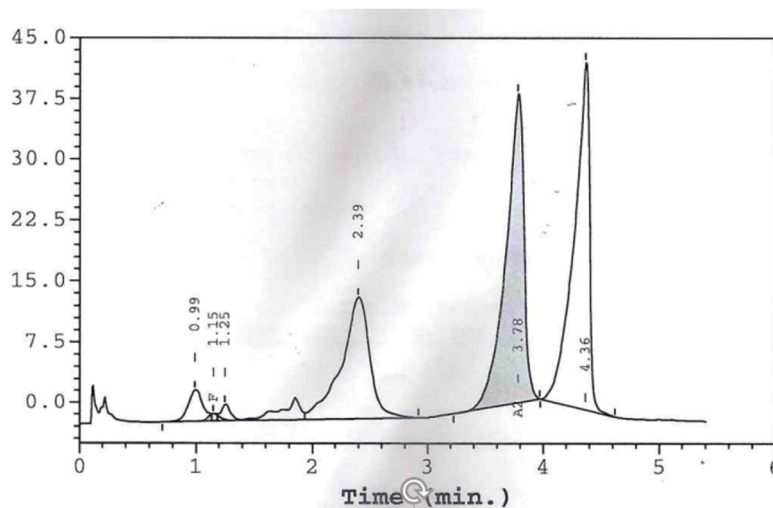


Figure 1. Peripheral blood smear microscopy x50 magnification (Giemsa stain). Arrows point to: A) Sickle cell, B) Irregularly contracted red cell and, C) Target cell.



Peak Name	Calibrated Area %	Area %	Retention Time (min)	Peak Area
Unknown	---	3.1	0.99	35385
F	0.5	---	1.15	6389
P2	---	1.0	1.25	11428
Ao	---	22.9	2.39	257978
A2	38.2*	---	3.78	412699
S-window	---	35.6	4.36	400846

Figure 2. HPLC tracing of patient sample. The HbA is that of transfused blood.

High performance liquid chromatography (HPLC) analysis (Bio-Rad Variant II analyser) detected 2 variant hemoglobin peaks viz., HbS and an unknown Hb variant coinciding with the HbA₂ window (Figure 2). The HbA peak represents residual Hb from a recent blood transfusion. Hb separation on gel electrophoresis (Sepsi Interlab G26 analyser) demonstrated bands in the HbA and HbS positions in alkaline as well as acid pH medium (Figure 3).

Parental screening (Images not included):

HPLC analysis: The father's blood revealed 2 major peaks in the HbA and HbA₂ (variant Hb) windows. Hb Maputo has the same retention time as HbA₂. The mother's blood revealed 2 major peaks in the HbA and HbS windows, in keeping with heterozygous sickle cell disease.

Hb electrophoresis: The father's blood displayed similar Hb mobility as the offspring. The mother's blood showed 'A' and 'S' bands in alkaline as well as acid pH medium, in keeping with heterozygous sickle cell disease.

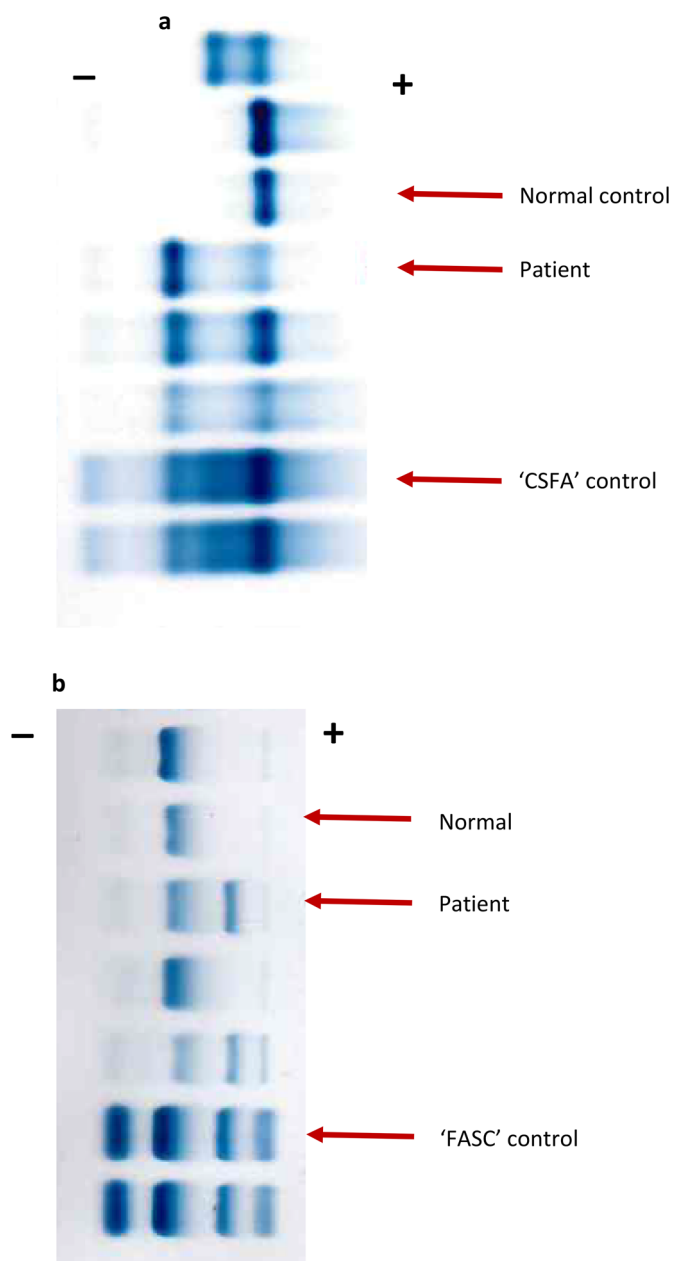


Figure 3. Hb electrophoresis.

3a: Alkaline pH electrophoresis, **3b:** Acid pH electrophoresis. The patient run shows 'HbS' and 'HbA' bands

NGS methods and analysis

Targeted next-generation sequencing (NGS) was performed using an Agilent SureSelect^{XT} HS protocol, with a custom designed panel, with a size of 152.16 kbp (Design ID: 3366281) according to the manufacturer's protocol. The resulting libraries were sequenced on an Illumina NextSeq 2000 using a P1 flow cell, generating 6.25 million reads per sample. Bioinformatics analysis was completed via the Illumina DRAGEN somatic pipeline, which included FastQC, read trimming (Trimmomatic), read alignment (BWA) to the

HG1 human reference genome, germline calling and functional variant annotation (VEP). The HbS and Hb Maputo mutations were confirmed by NGS data analysis (Table 2).

Mutation detection

Mutations detected in this family study are listed in Table 2. Hb Maputo and HbS mutations were detected in the father and mother, respectively, whereas the proband had both the HbS and Hb Maputo mutations.

Table 2. Hb Genetic Profile of patient.

Sample	Genomic Position (Chr11)	cDNA Change	Codon change	Protein Change	rsID
Hb Maputo	5247980	c.142G>T	Gat>Tat	p.Asp47Tyr (D/Y)	rs33932070
HbS (Sickle Cell)	5248232	c.20A>T	gAg>gTg	p.Glu6Val (E/V)	rs334

Discussion

Sickle cell heterozygosity is asymptomatic with no significant long term clinical sequelae. Co-inheritance with selected β chain variants including HbC, HbD and HbO-Arab or β thalassemia causes a sickling disorder [9–11]. Co-inheritance of less common β chain variants include Hb G-Ferrara, Hb Lepore and Hb Maputo.

Hemoglobin (Hb) Maputo is a β -chain variant [β 47 (CD6) Asp>Tyr HBB: c.142G>T] in which tyrosine substitutes aspartic acid at position 47, located on the outer surface of the molecule. Aspartic acid is a polar negatively charged amino acid, whereas tyrosine has an aromatic relatively non-polar side chain that is likely to play a role in copolymerization with HbS [13]. Notwithstanding, the mutant Hb is shown to be molecularly stable, with normal affinity for oxygen [14]. At alkaline pH the electrophoretic mobility is the same as HbS, but coincides with HbA at acid pH electrophoresis [15]. Hence, Hb electrophoresis alone does not suffice in identifying Hb Maputo as it cannot be distinguished from HbD. Hb separation through a second method such as HPLC is necessary for further characterization. In our patient, the HbA band in acid Hb electrophoresis and HbA peak in HPLC reflects recent blood transfusion.

Hb Maputo was first described in a 2-year old child from Mozambique who also had compound heterozygous HbS. His Hb concentration was 8.5 g/dL, the blood smear showed anisocytosis and target cells, the Hb A₂ percentage was slightly increased, and the HbF percentage was within the reference limits. The spleen was palpable 3 cm below the left costal margin. No history of bone pain was reported by the parents. The father and mother had sickle cell trait and heterozygous Hb Maputo respectively. Both parents gave a history of being clinically asymptomatic.

Reports of Hb Maputo in the literature are few and far between, reflecting the rarity of the mutation and the asymptomatic nature of the heterozygous form [16–19]. The majority of subjects are of black ethnicity, although Hb Maputo was also described in a heterozygous Caucasian individual from the United States without any clinical or hematological changes [17]. In a newborn screening program in Brazil, spanning the period 1998 to 2012, about 4 million newborns (~250 000 per year) were screened for hemoglobin disorders. This screening program detected 2700 newborns with

SCD and >1200 less common variants that included 2 Hb G-Ferrara and 2 Hb Maputo neonates. Parents who were carriers of Hb Maputo were asymptomatic including one who also had compound heterozygous HbS [14]. In this latter report, Hb Maputo was aptly categorized under ‘rare Hb variants.’

In our patient, the prior recurrence of clinical symptoms and the current clinical presentation led to a high index of suspicion for a sickling disorder. The HbS and Hb Maputo mutations were confirmed by DNA analysis on the NGS platform. Interestingly, the first described case of Hb Maputo also had co-inherited HbS [13]. Case reports of compound heterozygous HbS/Maputo generally describe patients with a sickling disorder [16–19]. However, one parent who was detected with HbS/Maputo in the newborn screening programme in Brazil was clinically asymptomatic, possibly due to a favorable epigenetic profile [14]. Since the acute clinical manifestation of our case has been vaso occlusive in nature, clinical management is based on the South African management guidelines for sickle cell disease [20].

Given the vast array of genes that can be sequenced on the NGS platform, this method is proving to be a cost effective and efficient diagnostic tool for inherited hemolytic conditions, even in resource limited settings, as demonstrated in our case report and family study.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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