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Case Report

A Patient with Sickle Cell Disease and Beta-Mannosidosis: A Case Report

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Abstract

Sickle Cell Disease (SCD) is one of the global health problems, with estimates of approximately 300,000 new cases per year diagnosed with SCD worldwide. It is defined as a homozygous status of the sickle hemoglobin (HbS) gene which results in substitution of the amino acid valine to glutamic acid at the 6th position of the B-globin chain. B-mannosidosis is a rare glycoprotein lysosomal storage disease inherited as an autosomal recessive pattern caused by a deficient activity of beta manosidase enzyme. We report here Eight years old male patient diagnosed with Sickle Cell Disease and Beta-mannosidosis, to our knowledge this is the first case to report a patient with SCD and B-mannosidosis.

Keywords: Sickle Cell Disease; Beta mannosidosis; Hypersplenism; Acute Chest Syndrome; Splenic Sequestration

Introduction

Sickle Cell Disease (SCD) is one of the global health problems, with estimates of approximately 300,000 new cases per year diagnosed with SCD worldwide. It is defined as a homozygous status of the sickle hemoglobin (HbS) gene which results in substitution of the amino acid valine to glutamic acid at the 6th position of the B-globin chain [1,2]. B-mannosidosis is a rare glycoprotein lysosomal storage disease inherited as an autosomal recessive manner caused by a deficient activity of beta manosidase enzyme [3]. Acute Chest Syndrome (ACS) is the leading cause of death in SCD patient and the 2nd most common complication of Sickle Cell Disease, after vaso-occlusive crisis [4]. Splenic sequestration and hypersplenism is a known complication as well of SCD [5]. We report a case of SCD with B-mannosidosis who is having a recurrent ACS and hypersplenism with acute splenic sequestration.

Case Presentation

An 8 years old boy, a product of a full term, Spontaneous Vaginal Delivery (SVD), the second child to consanguineous parents. The patient presented at age of 4 months with pallor and shortness of breath with a complete blood count hemoglobin level of 7.8mg/dl with a sickle cell screen positive, and diagnosed as a sickle cell disease based on hemoglobin electrophoresis (HbS: 34.7% and HbF: 63.7% with no detectable HbA) which was repeated at age of one year and confirmed the diagnosis of SCD with alpha-Thalassemia trait, X-ray chest showed cardiomegaly and Echo was done and results were as dilated left ventricle and atrium with moderate mitral regurgitation and the left ventricle function of FS 17.2% and labelled as having cardiomyopathy. At age of 3 years the patient had global developmental delay, growth parameters were below 3rd centile for height and weight, he had hepatosplenomegaly, speech retardation with hearing loss and recurrent otitis media requiring later bilateral myringotomy, T tube insertion and a hearing aid. He had coarse facial features (gargoyle-like features) as frontal bossing, flat nasal bridge, large tongue with thick lips and gapped teeth, gibbus malformation with skeletal deformities (Figure 1-4) (Table 2).

Table 1: Enzymatic assay of Mannosidase enzyme activity in our proband.

Source	Enzyme	Activity	Reference Range
Serum	Beta-mannosidase	0.004 umol/ml/min	1.49 – 8.33 umol/ml/min
Serum	Alpha-mannosidase	0.14 umol/ml/min	0.1 – 0.2 umol/ml/min

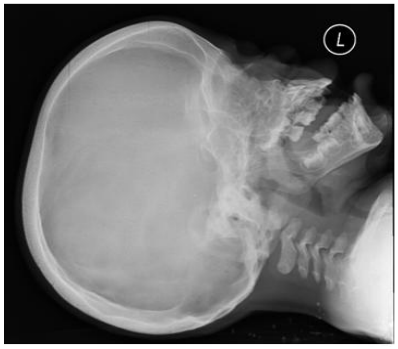

Figure 1: X-ray skull showing calvarial thickening and bullet shaped vertebrae.

At 4 years of age he was diagnosed as Bronchial Asthma, Allergic Rhinitis, myopic astigmatism and Attention Deficit Hyperactive Disease (ADHD) with a lower IQ of 70 at age of 7 years. He underwent splenectomy at age of 5 years. The patient was investigated for a lysosomal storage disorder, urine Glycosamino glycan (GAG) was negative for the patient, normal blood Tandem mass spectrometry, and chromosomal analysis of 46, XY. Whole Exome Sequence (WES) detected a homozygous variant of exon 6 of the MANBA gene mutation C.704T>G (p.lle235Arg) and both parents are with a heterozygous status. Enzymatic assay of manosidase activity in serum (Table 1).

He has a sister who had the same presentation of coarse facial features, hepatosplenomegaly, and gibbus malformation with sickle

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Table 2A: Beta-mannosidosis phenotype and laboratory findings in reported cases.

Case	1	2	3	4	5	6	7	8	9	10	11
Sex	Male	Male	Male	Male	Male	Female	Male	Female	Female	Male	Male
Ethnicity	European	Hindu	Hindu	Turkish	Turkish	Czech	Czech	Jamaican	Turkish	European	African
Consanguinity	Negative			Positive	positive			Negative	positive	Negative	Negative
Diagnosis age (Yr)	1.5	44	19	8	6	20	30	1	6	3	14
Presenting symptom	Dysmorphology	Mental retardation		Feeding difficulty		Developmental delay		Seizures	Absent speech	Speech impairment	Speech impairment
Mental retardation	Positive	Positive	Yes	Yes	Yes	Positive	Positive		Positive	Positive	Negative
Behavioral problems	Hyperactive	aggressive		Troublesome		Aggressive			Hyperactive aggressive	Hyperactive	Disinterest
Hearing impairment	Mild	Present	Present	Present	Present	Present	Present	Negative	Present	Negative	Negative
Neurological	Speech retard			Speech retard		Developmental delay		Developmental delay	Motor delay	Speech impairment	Peripheral neuropathy
dermatologic		Angiokeratoma				Erysipelas					
Facial dysmorphism	Present	negative	Negative	Negative	Negative	Present	Present	Present	Present	Present	Negative
Skeletal deformation	Present	Negative	Negative	Negative	Negative	Present	Present	Negative	Present	Negative	Negative
Respiratory infections				Positive	positive	Positive	Positive		Positive	Positive	Negative
mannosidase	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient
Urine disaccharides	Positive	Positive	Positive	Positive	positive	Positive	Positive	Positive	Positive	Positive	Faint
Reference	Wenger et al. 1986 [7]	Cooper et al. 1986-1988 [21,22]	Cooper et al. 1986-1988 [21,22]	Dorland et al. 1988 [8]	Dorland et al. 1988 [8]	Kleijer et al. 1990 [6]	Kleijer et al. 1990 [6]	Cooper et al. 1991 [9]	Wijburg et al. 1992 [10]	Poenaru et al. 1992 [11]	Levade et al. 1994 [3]

Table 2B: Beta-mannosidosis phenotype and laboratory findings in reported cases (To our knowledge).

											Sibling sister	our case
Case	12	13	14	15	16	17	18	19	20	21	22	23
Sex	Female	Female	Female	Female	Male	Male	Female	Female	Male	Female	female	Male
Ethnicity	white		Arabic	Arabic	Japanese	French	Spanish	Arabic	Algerian	Asian	Arabic	Arabic
Consanguinity	Negative	Positive	Positive	positive	Positive	negative		Positive	Positive	Positive	positive	Positive
Diagnosis age	22 years	7 months	2 years	3.5 years	51 years	18 years	24 years	36 years	12 years	5 months	7 years	5 years
Presenting symptom	clumsiness	Feeding difficulty	Seizures	Seizures	Angioke-ratoma	Develop-mental delay	Angioke-ratoma	Angioke-ratoma	Clumsiness	Seizures	Dysmorphism	Dysmorphism
Mental retardation	Negative		Positive	positive	Positive	Positive	Negative	Positive	Positive	Positive	Positive	Positive
Behavioral problems	Scantly communi-cative					ADHD	Negative	Aggressive			ADHD	ADHD
Hearing impairment	Negative		Negative	negative	Present	Present	Mild	Present	Present	Present	Present	Present
Neurological	Negative	Develop-mental delay	Develop-mental delay, speech delay	encepha-lopathy	Peripheral neuropathy	Develop-mental delay, speech delay	Negative		Cerebellar ataxia	Develop-mental delay	Develop-mental delay	Develop-mental delay
dermatologic	Angioke-ratoma		Negative	Negative	Angioke-ratoma	Negative	Angioke-ratoma	Angioke-ratoma	Negative		Angiokeratoma	Negative
Facial dysmorphism	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Positive	Positive
Skeletal deformation	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Positive	Positive
Respiratory infections	Negative	positive	Negative	Negative		Positive		Negative		Positive	Positive	Positive
mannosidase	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient	Deficient
Urine disaccharide	Positive	Positive				Positive	Positive				Positive	Positive
Reference	Rodriguez et al. 1996 [12]	Gourrier et al. 1997 [13]	Cherian et al. 2003 [14]	Cherian et al. 2003 [14]	Suzuki et al. 2004 [15]	Sedel et al. 2006 [16]	Gort et al. 2006 [17]	Molho et al. 2007 [18]	Levade et al. 2009 [19]	Broomfield et al. 2012 [20]	Almadani et al 2019	Almadani et al. 2019

cell Trait and Beta-mannosidosis confirmed by genetic whole exome sequencing (homozygous status of MANBA gene mutation)C. 704T>G) and enzyme assay (Figure 5).

Discussion

Beta-mannosidosis is a pan-ethnic disorder with an autosomal recessive inheritance [6]. Two siblings from Saudi Arabia, described in our report, was associated with gargoyle like facial dysmorphism, hearing impairment, mental retardation, and recurrent respiratory tract infections. To our knowledge the number of patients reported in the literature is small, (Table 2) so, it is difficult to conclude specific symptoms and signs to characterize B-mannosidosis. Various degrees

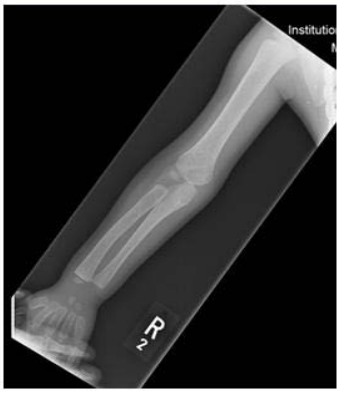

Figure 2: X-ray of right upper limb showing expansion of medullary spaces with short tubular bones of the hand.

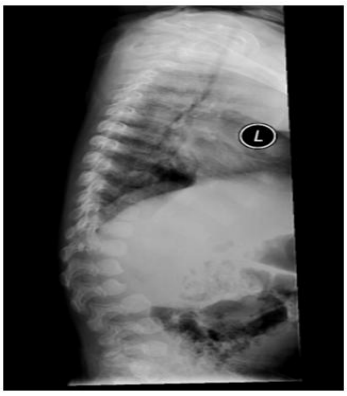

Figure 3: X-ray lateral spine showing L2 vertebral beaking with gibbus malformation.

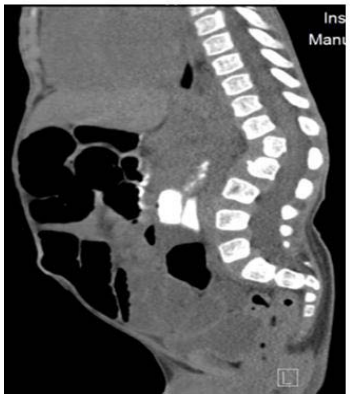

Figure 4: CT Abdomen showing anterior inferior beaking of L2 vertebrae with gibbus malformation.

of developmental delay, hearing loss, and mental retardation are common findings. The older sibling has angiokeratoma as an isolated observation as reported previously [21,22]. The observed skeletal changes in our proband are beaked vertebral bodies, thick calvarium, bullet shaped vertebrae, and gibbus malformation (Figure 2).

This patient who is a known case of hypersplenism with multiple splenic sequestration with one intensive care admission with critical

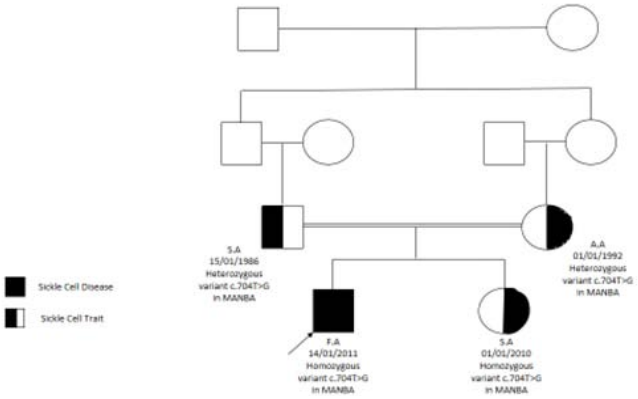

Figure 5: Family pedigree.

hemoglobin level mg/dl. Post elective splenectomy the patient had significant decreased rate of admission and blood transfusions. It was noticed that in our proband who has beta-mannosidosis the most frequent complication of sickle cell disease are hypersplenism with sequestration and acute chest syndrome with fewer painful crisis's although it is the most common feature of sickle cell disease [23]. The patient had frequent admissions as an acute chest syndrome in which after starting azithromycin as an anti-inflammatory agent [24,25] by our pulmonologist, the rate of acute chest syndrome related admission decreased.

The association of Beta mannosidosis and SCD to our knowledge has not been reported before, this combination of both diseases need further reported cases to establish the impact.

Conclusion

This is the first case to report a patient with SCD and B-mannosidosis. We recommend splenectomy for cases of Sickle Cell Disease with B-mannosidosis and hypersplenism, we recommend using azithromycin as an anti-inflammatory prophylactic agent to reduce Acute Chest Syndrome in patient with Sickle Cell Disease and Beta mannosidosis.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. Consent is available upon request.

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