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Case Report

Alpha thalassemia trait in a child with juvenile diabetes: a case report

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ABSTRACT

Alpha thalassemia trait (two missing α-globin genes) manifests as a microcytic anaemia that can be mistaken for iron-deficiency anaemia**.** A 12-year-old female child, who is a known case of type 1 diabetes mellitus presented with persistent microcytic hypochromic anaemia which failed to improve even after iron therapy. She was evaluated for her low haemoglobin values with the peripheral smear showing microcytic hypochromic anaemia which eventually was diagnosed as alpha thalassemia trait. This case reiterates the association between a metabolic disorder and a haemoglobinopathy, which is rarely reported in children.

Keywords: α-Thalassemia trait, Microcytic hypochromic anemia, Type 1 diabetes mellitus, Hemoglobinopathy

INTRODUCTION

Type 1 diabetes mellitus (T1DM) results from deficiency of insulin secretion because of pancreatic β-cell damage and type 2 diabetes mellitus (T2DM) is a consequence of insulin resistance occurring at the level of skeletal muscle, liver, and adipose tissue, with various degrees of β-cell impairment.[1] Here, we discuss about a 12 year old girl who was a previously diagnosed case of T1DM and presented with moderate diabetic keto-acidosis and microcytic hypochromic anemia not improving despite iron therapy and evaluation showed alpha thalassemia gene mutation. α-Thalassemia trait is a single-gene disorder in humans (two missing α-globin genes on chromosome 16) which manifests as microcytic anemia that can be mistaken for iron-deficiency anemia. The Hb analysis is normal, except during the new-born period, when Hb Bart's is typically <8% but >3%.[2]

CASE REPORT

A 12-year-old girl child is a second born of non-consanguineous parentage, developmentally normal and immunised up to age. Her initial presentation of T1DM was at the age of 5 years and was on basal bolus regimen since then. Family history is remarkable for the presence of T2DM on the paternal side.

She presented with complaints of low-grade fever, vomiting and generalised weakness of 2 days. On clinical examination, she had tachycardia, respiratory distress (tachypnea), normal axillary temperature and pallor with oxygen saturation of 99% (finger pulse oximetry). Systemic examination findings were unremarkable. Head to foot examination showed no significant findings. Anthropometric indices were appropriate for age; the weight of 32 kg (between 10th and 25th centile), a height of 141 cm (between 10th and 25th centile), body mass index of 16.1 kg/m^2 (between 10th and 25th centile) and body surface area of 1.12 m^2. Random blood glucose at presentation was 325mg/dl with moderate metabolic acidosis (pH-7.186) and ketonemia. HbA1c value was 10 mmol/l. Urine was tested positive for glucose and acetone. The admitting haemoglobin was 8.3 gm%, total white blood cell (WBC) were 7.6×10^9/l, neutrophils 52%, lymphocytes 37%, monocytes 08%, eosinophils 03% and platelets 3.300×lakh/cumm. Hyponatemia was recorded at the time of admission (130 mEq/l). Peripheral blood smear showed microcytic hypochromic blood picture with few microspherocytes (<5%).

The diabetic ketoacidosis was managed with close monitoring of vitals, neurological status, correction of serum electrolytes and other biochemical parameters were ensured. Peripheral blood smear showed microcytic hypochromic blood picture with microspherocytes. She was discharged with a plan to start iron therapy at review and repeat haemoglobin values after 1 month of iron therapy.

At review, baseline haemoglobin value was 8.5 gm% with low MCV-55.2fl and peripheral smear showing moderate microcytic anemia. She was empirically started on iron (ferrous fumarate), deworming carried out and advised to include adequate iron sources in diet. The response was to be evaluated after one month.

One month after receiving iron therapy, blood investigations were repeated which showed no rise in the haemoglobin values which advocated the need for further evaluation of anemia. Serum iron values were normal (71 mcg/dl). Stool occult blood test was done which was negative. Serum ferritin values were normal (114 ng/ml). Hb electrophoresis was done and beta thalassemia was ruled out. Whole exome sequencing was done to check for any deletions or duplications α-thalassemia and the report yielded pathogenic deletions in HBAP1, HBA2, HBA1, HBQ1 and HBA2 which were suggestive of alpha thalassemia trait.

Since, there is a moderate anaemia without complications or requirement of transfusion (non-transfusion dependent thalassemia), she was started on folic acid supplementation and iron was stopped with regular follow up. As the parents completed family, no screening was advised and her sibling was evaluated and not found to be anemic.

Table 1: Deletion/duplication analysis.[1]

S. no.	Deletions/duplications	Regions deleted/duplicated[$]	Type	Disease (OMIM)	Inheritance	Classification
1	Heterozygous deletion	HBAP1, HBAP2 (upstream, exon 1, 2 and 3) and HBQ1 (upstream and exon 1)	-Alpha 3.7/--SEA	Alpha thalessemia	-	Pathogenic
2	Heterozygous deletion	HBAP2 (exon 3, intron 2 and exon 2)				

[$]Genetic test results are reported based on the recommendations of American College of Medical Genetics

DISCUSSION

Hemoglobin is a tetramer consisting of two pairs of globin chains. Abnormalities in these proteins are referred to as hemoglobinopathies. The prevalence of α-thalassemia syndromes is highest in Southeast Asia, with deletions being the most common genetic mutation observed in α-thalassemia cases.[3,4] In α-thalassemia, there are four α-globin genes, and the deletion of one α-globin gene, known as a silent carrier, cannot be detected through hematological analysis. When two α-globin genes are deleted, it leads to the development of α-thalassemia trait. These deletions can occur in a trans configuration (−α/−α) or a cis configuration (α,α/ -SEA).[5] Individuals with α-thalassemia trait, characterized by the absence of two α-globin genes, present with microcytic anemia, which may be misinterpreted as iron-deficiency anemia. While hemoglobin analysis is typically within normal range, infants with α-thalassemia trait may exhibit Hb Bart's levels below 8% but above 3% during the neonatal period. The clinical presentation of children with a double deletion of α-globin genes often resembles iron deficiency due to low mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) values. To differentiate between iron deficiency and α-thalassemia trait, a detailed dietary history should be obtained. Iron-deficient children often have a diet lacking in iron and consume significant quantities of cow's milk.[6] Alternatively, a short-term trial of iron supplementation combined with monitoring of erythrocyte indices can aid in confirming an iron deficiency diagnosis. In cases where both parents of a child with α-thalassemia trait are carriers in the cis configuration, there is a risk of a future hydrops fetalis pregnancy.[7] Therefore, it is recommended to conduct family screening and provide genetic counselling for at-risk individuals.

Diabetes mellitus (DM) is a condition characterized by disrupted energy metabolism involving carbohydrates, proteins, and fats due to a shortage of insulin secretion or resistance to insulin. Elevated blood sugar levels are responsible for the classic symptoms of excessive urination, thirst and weight loss. If uncontrolled, these metabolic disturbances can lead to a range of microvascular and macrovascular complications including retinopathy, nephropathy, neuropathy and blockages in major arteries resulting in a reduced lifespan and diminished quality of life. T1DM is typically characterized by its correlation with specific histocompatibility locus antigens (HLAs) and various genetic markers that play a role in the immune response to self or foreign antigens. Additionally, individuals with type 1a diabetes often exhibit circulating antibodies targeting cytoplasmic and cell-surface components of islet cells, insulin, glutamic acid decarboxylase (GAD), IA-2, and the zinc transporter molecule (ZnT8). Children may have profound insulin deficiency and require insulin treatment in case of type 1 diabetes (type 1b).[8] While exceptions exist, insulin-dependent diabetes in children typically falls under the type 1a category. T1DM may occur at any age but predominantly in childhood.[9]

In the above-mentioned case, child had a diagnosis of both T1DM and alpha thalassemia trait which individually is of high prevalence, but together is rare. This raised a question of whether the underlying alpha thalassemia could have precipitated the development of diabetes in our child. According to some previous studies, transfusion dependent beta thalassemia which required regular blood transfusions, chelation therapy and novel therapies improved the life expectancy and life quality of patients with hemoglobinopathies and these management techniques could have resulted as one of the factor in the pathogenesis of endocrine dysfunction.[10] Another study done in Iran in 2015 on thalassemia patients had shown that 78.5% of patients had pancreatic hemosiderosis based on their MRI T2 weighted images which could have been an etiology for the diabetes or glucose intolerance that have either developed or may develop in their future.[11] In general, the prevalence of insulin resistance and diabetes was higher in patients with thalassemia minor than the general population and recommendation screen for glucose tolerance in thalassemia minor patients was advised after a study conducted in Iran in 2012.[12] There also have been various studies showing effects of Hb variants on HbA1c measurements and how the HbA1c values are not totally reliable in case iron deficiency anemia, vitamin B12 deficiency, iron therapy, chronic liver disease, hemoglobinopathies, hypertriglyceridemia and conditions of RBC destruction. Therefore, care should be taken by the doctors so that overtreatment or undertreatment of patients is avoided.[13,14]

Although various studies were done which showed diabetes potential in beta thalassemia patients, limited data is available to associate alpha thalassemia to diabetes. However, in a study conducted in Iran about Insulin resistance, impaired glucose tolerance and alpha-thalassemia carrier state, the risk of the impaired glucose tolerance state (pre-diabetes or diabetes) was higher in the α-thalassaemia than the normal population and the patients with α thalassemia are almost three times more at risk.[15] There was another study done on pregnant women with measurement of incidence of gestational diabetes in alpha thalassemia trait pregnant women which showed that the incidence of gestational diabetes mellitus was higher in patients with higher pre-pregnancy body mass index and lower haemoglobin concentrations by which they concluded that women who were at risk of gestational diabetes, the presence of the α-thalassaemia trait was an added risk factor for gestational diabetes mellitus.[16]

CONCLUSION

The current case report and the previous studies point to a significant association between the presence of hemoglobinopathy and a subsequent development of glucose intolerance irrespective of the age group. A special emphasis to check the glucose tolerance in a case with established diagnosis of a hemoglobinopathy may prove useful to the early management and prevention of complications. Patients diagnosed as a case of hemoglobinpathy may practice early glycemic control and lifestyle modifications to reduce the risk of development of diabetes in future ultimately enhancing the quality of life and life expectancy.

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