CASE REPORT

Thiamine responsive megaloblastic anaemia complicated with acute Parvovirus infection: A case report

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Abstract

Thiamine responsive megaloblastic anaemia syndrome also known as Rogers syndrome is a very rare autosomal recessive disorder. The hallmark of the disease is the presence of the classic triad of anaemia, diabetes mellitus, and sensorineural deafness. We report the case of a 14-year-old boy who presented to us with severe megaloblastic anaemia, diabetes mellitus, and sensorineural deafness. The anaemia was further complicated by acute parvovirus infection. He was put on high doses of thiamine (vitamin B1) which led to an improvement.

Keywords: Thiamine, Megaloblastic Anaemia, Deafness, Diabetes Mellitus.

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Introduction

Thiamine responsive megaloblastic anaemia (TRMA) is an extremely rare autosomal recessive disorder with only 40 pedigrees reported so far.[1] SLC19A2 is a gene that encodes a thiamine transporter protein which belongs to a group of solute carriers.[2] This protein has a very significant part in the uptake of thiamine at cellular level.[1,2]

The type of diabetes mellitus in TRMA is insulin-dependent diabetes mellitus (non-autoimmune). The onset could be from early infancy till adulthood. The onset of diabetes could be delayed if the patient is given thiamine supplementations in high doses. It has been reported that thiamine, if given regularly, could result in reduced insulin requirement.[3]

The type of deafness in TRMA is sensorineural and irreversible, and presents in early infancy. It is still unclear if hearing impairment could be improved by administering thiamine supplementations.[1]

Here we describe the case of a boy who presented with the classic triad of megaloblastic anaemia, diabetes mellitus, and sensorineural deafness with superimposed parvovirus infection.

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Case Report

A 14-year-old boy presented to us with complaints of progressive pallor and generalised bruises in the Haematology OPD of Fauji Foundation Hospital, Rawalpindi, in January 2018. He was the third child of first-degree consanguineous marriage in a Pathan family. He was born of an uneventful full-term delivery. Two elder male siblings were alive and healthy; one of his female siblings died at the age of eight months, the cause of her death was not known to the parents.

The developmental milestones of this patient were normal except for a bilateral hearing impairment detected at the age of one year. He was diagnosed as having megaloblastic anaemia at the age of 18 months and was treated with on-and-off injection B12, multivitamins and folic acid supplementations. Throughout his lifetime, he had only twice received blood transfusions from a local hospital as, according to the mother, he felt really sick, but no documented record of his previous admissions was available.

He presented to us with generalised bruises for the past one week. On general physical examination he had normal height of 53 inches and weight of 51 kg. He had pallor and jaundice. Abdomen was soft and non-tender with no visceromegaly. Chest examination was clear. Cardiovascular examination revealed a soft systolic murmur. Ophthalmological examination was normal. Audiological examination revealed bilateral sensorineural hearing loss on pure tone audiometry. The patient was responsive and alert with no neurological deficit.

Laboratory investigations showed a total leucocyte count of 2.45 X 10^9/L (4-11 X 10^9/L), haemoglobin 7g/dL (13-16 g/dL) and a platelet count of 22 X 10^9/L (150-400 X 10^9/L). His mean corpuscular volume was 97 fL (80-95fL). He had severe reticulocytopenia. Reticulocyte count was 0.1% (0.5-2.5%.) Peripheral film showed marked anisopoikilocytosis, macrocytosis, and occasional ovalocytes. Liver function tests showed bilirubin of 28 umol/L (1.71-20.5 umol/L). Coombs direct and indirect

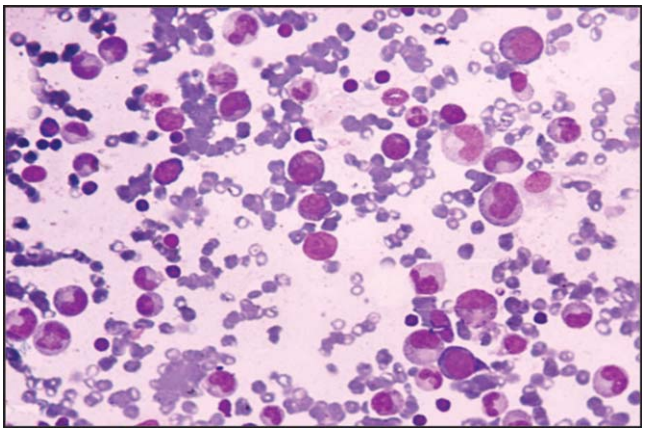

Figure-1: Bone marrow aspirate showing maturation arrest of neutrophils with a paucity of erythroid cells. Microscopic examination of the bone marrow aspirate showing giant, multinucleated erythroblasts and pronormoblasts.

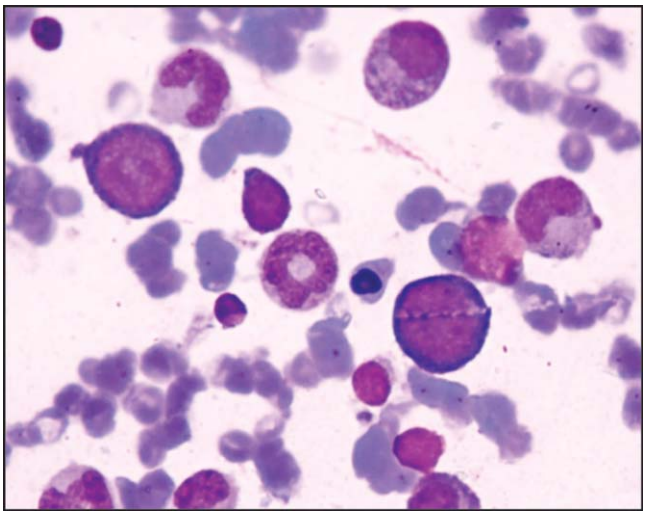

Figure-2: Bone marrow aspirate showed dysplastic myelocytes and proerythroblasts. 804Bone marrow aspirate showing dysplastic neutrophils.

tests were negative. Serum ferritin level was 204 ng/ml (20-250ng/ml). Serum B12 and folate levels were normal. Serum B12 was 289 pg/ml (190-950 pg/ml) and serum folate were 19.3 ng/ml (3-13 ng/ml). His fasting blood glucose was noted to be raised, i.e. 7.6 mmol/L (< 5.6 mmol/l) and Hb A1C of 7.8 % (<5.7%).

As serum B12 and folate levels were normal, bone marrow biopsy was conducted which revealed a hypercellular marrow. Myelopoiesis showed moderate dysplastic changes with late myeloid maturation arrest and few giant metamayelocytes as shown in Figure-1. Erythropoiesis was hypoplastic and megaloblastic. The bone marrow showed mostly proerythroblast and few intermediate erythroblasts, as shown in Figure-2, and megaloblastic erythroblasts with typical sieve-like nucleus. The percentage of total erythroid element was less than 05%. The megakaryocytes were moderately dysplastic with some showing hyperlobation and some were hypolabated. The bone marrow iron was markedly increased with moderate number of siderocytes, sideroblasts, and 8% ring sideroblasts. With a paucity of erythroid cells, occasional proerythroblast and severe reticulocytopenia serology for parvovirus b 19 was advised which turned out to be positive. Islet cell autoantibodies test was done to confirm the non-immune nature of diabetes mellitus and it was found to be negative. The classic triad of megaloblastic anaemia with bilateral sensorineural hearing loss and diabetes mellitus led to the diagnosis of TRMA with acute parvovirus infection. The patient was started on insulin, and then discharged on an oral tablet daily the composition of which was thiamine HCl (B1) 100 mg, pyridoxine HCl (B6) 50 mg, and cyanocobalamin (B12) 50 mcg, as pure B-1 preparation was not available. The patient was discharged home as his condition improved.

The patient was followed-up after six weeks of treatment and there was improvement in his clinical condition. His Hb was 13 gm/dL, and platelets and white blood cells were also within normal range. His diabetes was also ameliorated and blood glucose levels became normal. However, there was no improvement in his hearing.

Discussion

TRMA is caused by mutation of SLC19A2 gene. This gene is located on chromosome 1q 23.3 which encodes a thiamine transport protein called THTR 1 that is crucial for the uptake of thiamine by the cells.[4] Thiamine is required in high concentration in various tissues, such as islet cells of pancreas, the cochlear cells in the ear and the haematopoietic stem cells. Lack of thiamine in these cells due to defective uptake of thiamine results in cell death and, therefore, the typical manifestation of the triad of TRMA.[5]

The anaemia in TRMA could be megaloblastic, sideroblastic or aplastic. This shows that thiamine is not just required for the metabolism of DNA (megaloblastic anaemia) but is also involved at the level of haeme synthesis (ringed sideroblastic changes).[6] In a case series done on TRMA by Bergmann, all patients had megaloblastic anaemia along with ringed sideroblasts. Our patient also had megaloblastic anaemia with 8% ring sideroblasts.[6]

Faraji-Goodarzi M et al reported 15 patients with TRMA who had megaloblastic anaemia with ringed sideroblasts. Bone marrow aspirate and biopsy of these patients showed moderate dysplastic changes in all three lineages.[7] Our patient also had moderate to severe dysplastic changes in the myeloid, erythroid and

megakaryocytic lineages. There was a paucity of erythroid lineage with only proerythroblasts and dysplastic erythroid cells due to parvovirus infection. This finding further supports the fact that thiamine plays a significant role in haemopoiesis most likely at the stem cell level.[7]

For diabetes mellitus the patient was started on Insulin. His follow-up visits did show a remarkable improvement in the blood glucose levels. It has been reported that diabetes mellitus could be reversible after taking high doses of thiamine supplementation. Poggi et al reported that his patient had responded to thiamine so much so that he no longer required insulin.[8] The deafness in our patients did not improve after thiamine supplementation. It is reported that deafness is irreversible but it could be controlled to some extent by taking regular high dose supplementation as reported by Rinde at al.[9]

Parvovirus B19 is a self-remitting disease in which erythropoiesis is temporarily suppressed and may cause transient aplastic crisis (TAC) in all B19 infections[10] and the patient usually spontaneously recover from this infection but it could lead to fatal consequences in patients who already have severe anaemia.

Conclusion

The presence of megaloblastic anaemia along with deafness and diabetes mellitus should always alert the physician to consider thiamine responsive megaloblastic anaemia/Rogers syndrome as a differential diagnosis as timely and prompt treatment could possibly reverse the deafness and diabetes.

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