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Case Report

A long-term follow-up of a case of Rogers syndrome, Thiamine responsive megaloblastic anemia

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ABSTRACT

Thiamine-responsive megaloblastic anemia (TRMA) also known as Rogers syndrome is a rare autosomal recessive disorder characterized by megaloblastic anemia, diabetes mellitus, and progressive sensorineural deafness. The disease can be manifested anytime between infancy and adolescence, and all the cardinal findings may not be present at the time of the diagnosis. The main defect lies in the active thiamine uptake into cells which is disturbed. Not many cases have been reported about the long-term follow-up of children with this disorder and their associated complications. We hereby report a 14 years follow-up of a girl with Rogers syndrome diagnosed at toddler age with nonresponsive anemia and diabetes and further progressed to have sensorineural hearing loss. Her clinical exome study showed a mutation in the SLC19A2 gene. This experience illustrates the relevance of a detailed evaluation and regular follow-up to assess the progression of the syndrome till her pubertal age.

Keywords: Anemia, diabetes, Hearing loss, Thiamine responsive

INTRODUCTION

Thiamine-responsive megaloblastic anemia (TRMA) also known as Rogers syndrome is a triad of characterized by megaloblastic anemia, diabetes mellitus, and progressive sensorineural deafness. In addition to the cardinal components, other findings are also reported in TRMA syndrome including congenital heart disease, arrhythmias, cardiomyopathy, retinal degeneration, optic atrophy, situs inversus, aminoaciduria, and stroke.[1] The disease can be manifested anytime between infancy and adolescence, and all the cardinal findings may not be present at the time of the diagnosis.[2]

CASE REPORT

15-month-old female presented with severe pallor. She was born the firstborn child of a nonconsanguineous marriage via normal delivery with a birth weight of 3 kg. Since 9 months of age she had been receiving multiple oral as well as injectable hematinics, however, her pallor showed no significant improvement.

Our patient's physical examination revealed some tachycardia with hepatomegaly but no splenomegaly. Laboratory analyses showed anemia with a hemoglobin (Hb) level of 4.3gm%, white blood cell count (WBC) 6600/mm3 and thrombocytopenia (33,000/mm^3). The reticulocyte count was 3.2%. The peripheral blood smear revealed macrocytic cells with anisopoikilocytosis and mean corpuscular volume (MCV) 90fl. The bone marrow aspirate showed increased megaloblastic erythropoiesis with early-stage arrest with ringed sideroblasts >15% with no evidence of leukemic and storage cell infiltration. Her pallor persisted inspite of adequate treatment with B12 and folic acid supplementation. She even received blood transfusion a couple of times.

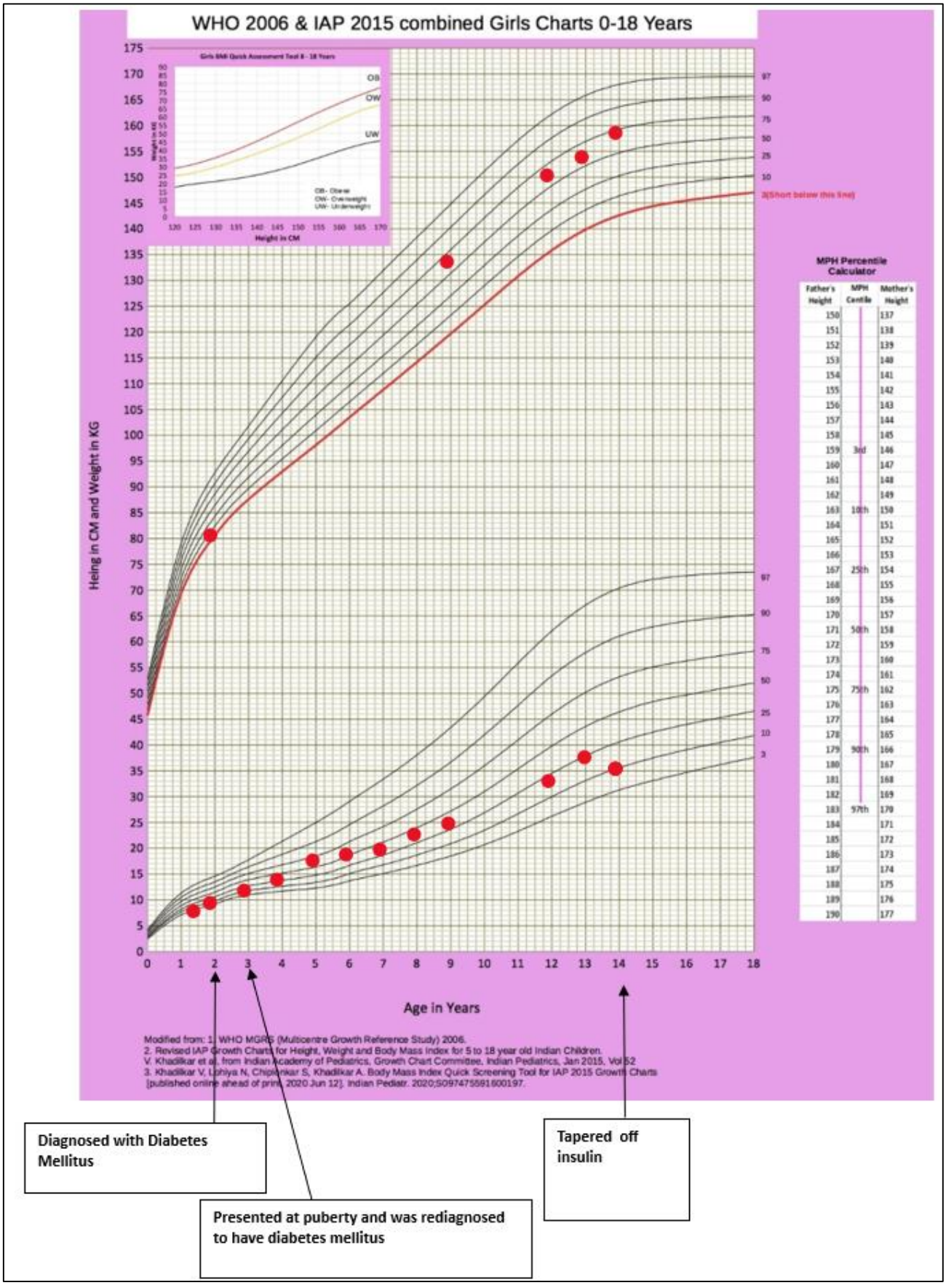

Figure 1: Anthrometric progression of our case.

Sources: https://www.iapindia.org/iap-growth-charts/

At 2 years she presented with high blood glucose level was with HbA1C of 7.7% and was diagnosed as insulin-dependent diabetes mellitus. Her GAD antibodies sent were negative. After subcutaneous insulin of roughly 1Ukg/day, normoglycemia was obtained on this basal bolus regimen. With the presence of macrocytic anemia and diabetes mellitus together, this patient was suspected to have diagnosis of TRMA. Thiamine trial was administrated at dose of 10 mg/day after diagnosis of diabetes and was gradually increased to 100mg/day. Over the period of 3-6 months insulin requirement gradually reduced and she was weaned off insulin at 3 years of age. With her ongoing thiamine treatment, anemia and thrombocytopenia improved completely. With a strong suspicion of Rogers syndrome, a brainstem auditory-evoked potentials revealed bilateral sensory neural deafness. Genetic studies sent revealed a mutation in the SLC19A2 gene which was strongly suggestive of TRMA. No congenital pathologies with regard to either the heart or the eye were present.

She was regularly followed up on an OPD basis and was assessed for growth and development as well as screening for any development of new complications. She continued to grow well with her weight centile and height centile falling in 25th to 50th centiles.

Eventually, she was lost to follow-up for a period of 3 years and then presented at 14 years when she had entered puberty and had complaints of weight loss, and polyuria since 3 months. Suspecting recurrence of diabetes mellitus she was investigated and found to have HbA1C of 8.2% with a random BSL of 300g/dl. She was restarted on insulin therapy on which her sugars were controlled. Currently she is 16 years of age with use of thiamine and there is minimal need of insulin and no further blood transfusion. Her hemoglobin concentration was 11.5g/dl, platelets were 2,04,000/mm^3, and MCV was 84fl with few macrocytes. She is growing well for her age. However, there was no improvement noted in neurosensorial deafness.

DISCUSSION

Thiamine-responsive megaloblastic anemia (TRMA) is an autosomal recessive disease whereby active thiamine uptake into cells is disturbed. At physiological concentrations thiamine is not transported normally and intracellular thiamine deficiency leads to decreased activity of enzymes associated with thiamine pyrophosphate.[3]

The clinical symptoms of TRMA are caused by a mutation in the SLC19A2 gene, which is found on the long arm of chromosome 1q23.3 which was found it our case. Mutation results in dysfunctional shorter thiamine transporter that disrupts the transportation of thiamine into the cell. Functional thiamine transporter expressed in a wide range of human tissues including bone marrow, pancreas, brain, retina, heart, skeletal muscle, kidney, liver, lung, small intestine, colon, placenta, lymphocytes, and fibroblasts hence its affection.[4]

Most of the children with TRMA syndrome may be presented with signs of profound anemia. The classical hematological finding is megaloblastic anemia with erythroblasts, which is often complicated with ringed sideroblasts which was present in our case. The megaloblastic anemia can be explained by the role of thiamine in DNA metabolism and heme synthesis.[5] A pharmacological dose of thiamine (50–100mg) can correct the megaloblastic anemia, but the macrocytic cells persist like in our case.[6]

Diabetes mellitus in TRMA patients is a consistent finding and is most likely secondary to thiamine transporter defect. Lack of thiamine in insulin-producing cells can lead to hyperglycemia (nontype 1 diabetes), and thiamine is required by pancreatic B-cells for glucose transport across the cell membrane, physiological consumption, and insulin secretion.[7] Majority of TRMA patients with DM reported in literature responded to thiamine treatment completely but some of them may need insulin treatment during puberty like in our case.[8]

The sensineural hearing loss is irreversible due to disrupted development of the inner ear parts due to thiamine deficiency during infant development. The suitable treatment is the implantation of hearing devices. [9]

In addition to the main components optic atrophy, retinal degeneration, situs inversus, cardiomyopathy, arrhythmias, congenital heart defects, and stroke have been reported in association with TRMA syndrome which were not found in our case.[1]

CONCLUSION

Very frequently anemia in diabetes is considered of autoimmune nature and remains misdiagnosed and untreated. Awareness about these associations can prove of great importance to preventing progression of diabetes as well as control of anemia. Not much information about the long-term consequences of this syndrome is available in the literature, primarily about the resurgence of symptoms. In conclusion, due to the rarity of this syndrome, many cases remain undiagnosed and are missed. Early recognition and treatment can help in aid in halting the progression of this syndrome. Carrier testing can also be undertaken for the next pregnancy with timely recognition of this syndrome.

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