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CASE REPORT

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Dyserythropoiesis and myelodysplasia in thiamine-responsive megaloblastic anemia syndrome

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Abstract

The case of thiamine-responsive megaloblastic anemia (TRMA) presented here speculates the need early diagnosis, continuous monitoring, follow-up, and regulated treatment plan for the patients. Complications and systemic manifestations are likely to enhance in otherwise circumstances.

KEYWORDS

deafness, diabetes mellitus, roger's syndrome, thiamine-responsive megaloblastic anemia syndrome

1 | INTRODUCTION

Thiamine-responsive megaloblastic anemia (TRMA) syndrome, also known as Roger's syndrome, is a rare hereditary autosomal recessive disorder characterized by a number of pathological conditions such as megaloblastic anemia, diabetes mellitus, loss of hearing, sight, and speech impairment. Although the prevalence is unknown, about 30 families have been reported to suffer from the syndrome, worldwide. Being a genetic disorder, it is expected that early diagnosis of TRMA will make the management of the resultant complications easier and minimize its impact on the patient's life and family. Herein, we present a case report of a teenage girl manifesting signs and symptoms of TRMA in Iran.

2 | CASE REPORT

A 9-year-old girl with diabetes mellitus, megaloblastic anemia, and sensorineural hearing loss, who was diagnosed with thiamine-responsive megaloblastic anemia syndrome (TRMA) or Rogers Syndrome was reported to our center. Her initial treatment included the administration of thiamine and insulin. The patient was the first child of the family who was born in a natural delivery, with a birth weight of 3500 g. At the age of 9 months, parents noticed a hearing loss in the child, which was later confirmed as bilateral sensorineural hearing loss by the means of auditory brainstem response (ABR) test. Hence a hearing aid was implanted for the child. At the age of 1 year, a funduscopic examination was performed for the patient for nystagmus in the eyes. The eye examination report is as follows: Torsional Nystagmus, optic disk pallor, salt and pepper Fundus Clear lens. No history of the similar findings was reported in the family. At 18 months of the age, she exhibited pallor, where her blood tests showed anemia and hyperglycemia, and she was admitted for further examination.

The patient did not have polyuria, polydipsia, fever, and lethargy. She had normal general appearance, and her physical examinations were normal. Blood glucose was closely monitored and checked every 6 hours. To manage hyperglycemia, NPH insulin (isophane insulin) was administered at a dose of 0.3 IU/kg. The patient was not in the diabetic ketoacidosis phase and results of laboratory assessments were as follows: ABG: (PH = 7.36, Pco2 = 35, Hco3 = 22), CBC (complete blood count): (Hb (hemoglobin) = 7.6, MCV (mean corpuscular volume) = 97.5, Plt (platelet) = 41.9 × 109/L, WBC (white blood cells) = 8.3 × 109/L, PMN (polymorphonuclear cells) = 59%, Lymph = 41%, BS = 266, (ESR (erythrocyte sedimentation rate), CRP (c-reactive protein), BUN (blood urea nitrogen), and Cr (creatinine)= Normal)).

The following tests were requested to evaluate the patient's macrocytic anemia: Serum B12: 526 pg/mL (normal range = 145-637), Serum folate = 17.9 ng/mL (normal range = 3.1-17.5), Direct coombs = negative, G6PD = Normal, Retic = 3%, TSH (thyroid-stimulating hormone) = 2 mU/L, T4 = 13.4 μg/dL, Fe(Iron)=65 ng/mL (normal = 40-100), and Liver function test = normal. CBC for Parents were normal.

In the peripheral blood smear analysis, severe anisocytosis, moderate poikilocytosis, tear drop cell, target cell, and hypersegmented neutrophils (5-6 lobes) were reported (Figure 1). WBC and platelets had normal morphology. The patient suffered from diabetes mellitus, megaloblastic anemia, and sensorineural hearing loss, and in view of possible diagnosis of TRMA, thiamine treatment (100 mg/d administered in 2 doses) was started while insulin was continued. Following 2 days, the patient's blood glucose was normalized (mean BS (blood sugar) = 95), with 8.6 hemoglobin (without transfusion) and 95 MCV.

The results of her laboratory tests after 1 month were as follows: WBC = 9.1 × 109/L, BS = 78, Hb = 10.6, MCV = 91.3, and Plt = 3 × 109/L, and hence, the amount of insulin was reduced to 0.2 lU/mg. A month later her laboratory results were as follows: WBC = 8.29 × 109/L, BS = 154, Hb = 13, MCV = 79.8, and Plt = 2.84 × 109/L. Following a month of thiamine treatment, macrocytosis persisted, which was resolved after 3 months. Consequently, the patient was asked for routine blood sugar and CBC examination every 3 months until the age of 3 years. The patient's condition remained satisfactory.

The patient had very irregular referrals and follow-up visits to the hospital. She was admitted to the hospital due to gastroenteritis at the age of 6 years. Our finding revealed that the patient had financial difficulties as such could not consistently use insulin and discontinued thiamine (for up to 2 years). Consequently, she developed speech and language disorders along with visual impairment, driving the use of spectacles. Furthermore, patients condition deteriorated to diabetic ketoacidosis (DKA) phase. She was treated with fluid and insulin therapy, and antibiotics were also administered. The results of her laboratory findings show: (BS = 320, ABG: pH = 7.07, Pco2 = 18, Hco3 = 8.8), Hb = 10, MCV = 103.3, Plt = 14 × 109/L, WBC = 6.5 × 109/L (68%), S/E: WBC: 30-35 × 109/L, RBC (red blood cells) = 18-20 × 1012/L, S/C: Shigella Flexeneri.

Three days later, the tests were repeated, and the results were as follows: WBC = 1100/μL, PMN = 45%, Hb = 5.2, MCV = 100, Plt = 6.4 × 109/L, Retic = 1.5%, ESR = 32, CRP = 24, and LDH (lactate dehydrogenase) = 540 U/L.

The patient had low levels of blood cells, pancytopenia, and dyserythropoiesis. The patient was infused with Packed Cell and subjected to G-CSF along with peripheral blood smear, bone marrow aspiration (BMA) and biopsy. BMA findings were consistent with dyserythropoiesis and myelodysplasia. Pan hypoplastic marrow was reported in bone marrow biopsy (BMB). Anti-ds-DNA, C-ANCA, and P-ANCA were normal. She was treated with the third generation of cephalosporin antibiotics and insulin. Thiamine was also given at a dose of 100 mg/d. The patient's condition improved and after a week, she was discharged with Glargine and Aspart insulin and thiamine treatment. At the time of publication, the patient was under periodic surveillance of every 3 months and her condition remain stable satisfactory (for diabetes and anemia), but she still uses hearing aids and spectacles.

3 | DISCUSSION

Thiamine-responsive megaloblastic anemia syndrome (TRMA) is also known as thiamine-responsive myelodysplasia or Roger's syndrome named after Roger et al credited for being the pioneer group to report the disorder in 1969.[1] TRMA is a rare genetic disorder caused by mutation of the *SLC19A2* gene responsible for the production a transport protein called thiamine transporter 1.[2] *SLC19A2* gene is sited on the long arm of chromosome 1q23.3 with 6 exons. Exons 1, 2, 3, and 4 are the most frequent points of mutations of the gene.[3] The genetic mutations result in the production of a defective, dysfunctional,

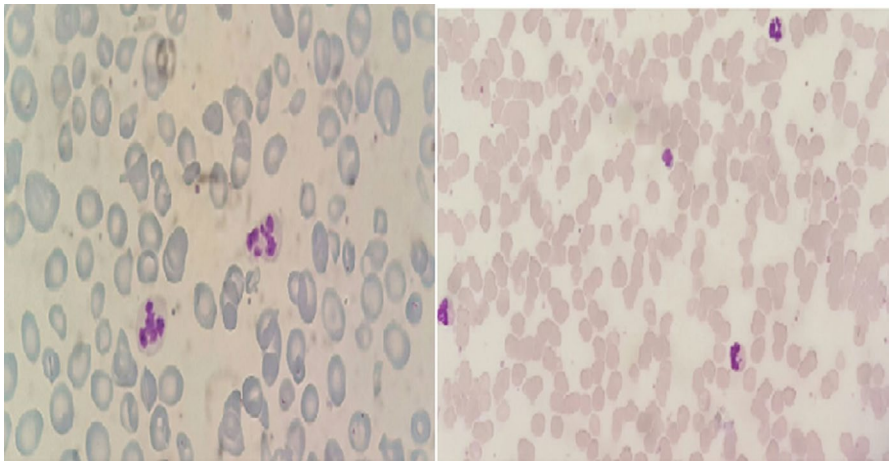

FIGURE 1 Peripheral blood slide represents severe Anisocytosis, moderate poikilocytosis, and hypersegmented neutrophil

and shorter thiamine transporter 1, which is incapable of transporting thiamine into the cell.[4,5] Although the pathophysiology of the disorder is still not completely understood, especially how the failure of the transporter leads to cascade of complications such as megaloblastic anemia, diabetes mellitus (type 1), hearing loss, and visual impairment associated with TRMA.[6] However, it has been suggested that cells usually have an alternative means of thiamine uptake, exception to which are erythropoietic cells of the bone marrow, insulin-producing cells of the pancreas and cells of the inner ear.[7] TRMA is a hereditary autosomal recessive disorder which is typically characterized by megaloblastic anemia, diabetes mellitus (type 1), hearing loss, and visual impairment in some patients. Another common trait of TRMA is the early onset of manifestations ranging from infancy to adolescent.[8]

According to Subramanian et al in a rat modeled study thiamine transport proteins THTR1 and THTR2 mediate intracellular assimilation of thiamine (vitamin B1) by the pancreatic acinar cells.[9] Following the obstruction of thiamine uptake by the pancreatic beta cells, diabetes mellitus ensues between infancy and adolescent stage. Patients often test negative to type 1 autoantibodies and insulin deficiency features prominently, therefore requiring lifelong administration of insulin to manage the blood glucose levels along with thiamine treatment. However, insulin dose can be reduced in patients where, normalization of blood glucose is achieved.[10-12] Megaloblastic anemia, another prominent clinical attribute of the syndrome, develops as a result of impaired nucleic acid synthesis due to intracellular thiamine deficiency in the erythropoietic cells. Anemia often occurs concurrently with the diabetes (hyperglycemia) but often improves with oral thiamine treatment to the point where dosage is reduced but discontinuation of the treatment triggers a relapse, as observed in our case and other known cases.[13] TRMA patients also suffer from irreversible hearing loss because of impaired development of parts of the inner ear associated with thiamine deficiency. Its precise time of onset has remained unknown as the deafness often precedes diagnosis of TRMA, but the situation is managed with implantation of a hearing device.[14] However, Onal et al reported an exceptional case where the patient at diagnosis and up to 15 months of follow-up, showed no sign of sensorineural hearing loss.[15] Visual impairment occasioned by optical atrophy and progressive retinal deterioration leading to use of spectacles by patient, as in the case under consideration, is also common as confirmed in previous publications.[4,16,17] Congenital heart defects, stroke, and arrhythmias are also reported in these patients.[16,18-20]

4 | CONCLUSION

TRMA syndrome patients, if well managed, can lead a normal life but may prove deadly owing to financial burden or obstruction of the treatment. Genetic counseling remains the most effective strategy to prevent the occurrence of the disease. People from families with the history of TRMA syndrome should undergo genetic (carrier) screening with their prospective life partners to investigate the possibilities of infants with the mutated homozygous gene. Prenatal screening is also advised for suspected pregnant women perhaps thiamine administration during pregnancy could help minimize or delay onset of some of TRMA symptoms.

CONFLICT OF INTEREST

The authors deny any conflict of interest in any terms or by any means during the study. All the fees provided by research center fund and deployed accordingly.

AUTHOR CONTRIBUTIONS

MFG: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript. NT: designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript. FT: coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors: approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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