ROGERS SYNDROME-THIAMINE RESPONSIVE MEGALOBLASTIC ANEMIA SYNDROME: CASE REPORT

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ABSTRACT

Thiamine responsive megaloblastic anemia (TRMA) encompasses a complex syndrome of anemia, sensorineural hearing loss and Diabetes Mellitus. We report a 06 years old male child with pallor, bilateral sensorineural hearing loss, Diabetes Mellitus, megaloblastic anemia, retinitis pigmentosa and a normal response to water deprivation test. Child responded well to high doses of thiamine treatment. Rogers Syndrome, a spectrum disease, should be kept in mind in differential diagnosis of Diabetes Mellitus and megaloblastic anemia in population with frequent consanguinity. Thorough medical and family history and physical examination are vital for diagnosis. Prompt diagnosis, use of careful clinical monitoring and supportive care can relieve the debilitating symptoms.

Key Words: Diabetes Mellitus, Megaloblastic anemia, Sensorineural hearing loss, Rogers syndrome.

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INTRODUCTION

Rogers syndrome also called “Thiamine responsive megaloblastic anemia” (TRMA) results due to loss of function mutation of transporter (THTR1). It has triad features of monogenic Diabetes Mellitus with contemporaneous existence of thiamine responsive megaloblastic anemia and sensorineural hearing loss [1]. Individuals with TRMA syndrome begin to express symptoms between infancy and adolescence. In addition to cardinal findings, congenital cardiac malformations [2], optic nerve atrophy and cerebrovascular accidents [3] have also been reported. This syndrome is called "thiamine-responsive" because high dosage of vitamin B1 (50-100mg/day) can treat anemia and reappear after thiamine therapy has been stopped. Sensorineural hearing develops during early years, evolves over the period and become permanent. Diabetes Mellitus is monogenic, non-type-I in nature and patients require insulin treatment.

Rogers Syndrome occurs approximately < 1 in 1000,000 live births. It has been reported frequently in populations with an increased frequency of consanguinity [4,5].

CASE REPORT

A 06 years old boy, resident of Kohat, was brought to child OPD of Military Hospital, Rawalpindi Pakistan, by his parents with seven days history of lethargy and dizziness. He also had complaints of increased thirst and passage of large volumes of urine for the past 6 months. He drinks more than 3 liters of water just over night. There was no associated history of fever, cough, fits altered consciousness, head trauma and altered bowel movements. The patient was delivered through spontaneous vaginal delivery in hospital settings. He was noticed to be deaf-mute during first year of life. With further work up, it was found to be bilateral sensorineural. From the age of one year onwards he had recurrent episodes of respiratory tract infections and was found to be severely anemic with hemoglobin dropping down to a level of 3 g/dl for which he was transfused with red cell concentrates multiple times. An extensive work up could not identify the cause and he was initially labeled as a case of transfusion-dependent anemia, which later was diagnosed after bone marrow biopsy as megaloblastic at 4 years of age. As he turned 5, he was noticed to be lethargic with poor feeding and frequent vomiting. At that time, he was found to have high blood glucose of around 14 mmol/l but without ketoacidosis. Patient was eventually diagnosed to have Diabetes Mellitus and started on insulin but had poor glycemic control. The child then developed decreased vision which was more during the day.

He was born to parents with consanguineous marriage with two healthy elder sisters. General physical examination revealed a conscious and co-operative child with normal vital signs. He had pallor

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and profound hearing loss with no speech development and was communicating via gestures. Normal cognitive skills were observed. His weight was 20kgs and height 115cm both below 50th percentile, while rest of the general physical examination was unremarkable. Upon examining the central nervous system, he was found to have bilateral sensorineural hearing loss. Rest of the systemic examination was not significant. A differential diagnosis of Rogers syndrome and DIDMOAD syndrome was made. Working on the lines of differential diagnosis child was thoroughly investigated. His hematological workup e.g., CBC showed decreased hemoglobin levels with macrocytosis and anisocytosis with normal total leukocyte and platelet count. Bone marrow aspiration and biopsy revealed a hypercellular bone marrow with dyserythropoietic, megaloblastic changes and > 15% ringed sideroblasts (Figure-I). Both Direct and Indirect Coombs test were negative. Patient's biochemical profile was done which revealed a markedly raised Fasting plasma glucose:10mmol/l (3.3-5.6) and HbA1C:10.7% (<6.5) levels. Serum Lactate dehydrogenase was 773U/l (230-460) which was quite raised. Serum urea: 4.2 mmol/l (3.3-6.7), Serum creatinine:52µmol/L(27-62),serum electrolytes {sodium 138 mmol/L (136-149) and potassium: 4.2 mmol/L (3.5-5.0)} along with plasma:288 mOsmol/kg (275-295) and urine: 711 mOsmol/Kg (100-1200) osmolality were within normal limits. Plasma Ammonia levels: 105 mmol/L (12-47) and Lactate: 3.0 mmol/l (0.5-2.22) were also raised. Urine for ketone bodies was negative. Plasma amino acid analysis done on High performance liquid chromatography was within normal intervals. Serum Folate: 11.4 nmol/l (6.25-45.3) and Vitamin B12: 352 pmol/l (176-686) were in normal range. While Ferritin levels: 475 ng/ml (20-250) were raised. Hormonal profile including morning serum Cortisol levels (0800 hrs): 258 nmol/L (138-690) were within reference interval. Immunological investigations including EBV IgM, Parvovirus B19 IgM, Anti tissue transglutaminase and Gastric Parietal cell antibodies, Anti Islet Cell and Glutamic Acid Decarboxylase antibodies all were negative. Patient had a normal response to Water Deprivation Test ruling out presence of Diabetes Insipidus. Ophthalmological Workup revealed bilateral leukocoria. Examination under anesthesia was performed which revealed salt and pepper appearance of fundus and an impression of retinitis pigmentosa was made. Findings of radiological investigations including chest X-ray, abdominal ultrasonography, ECG, echocardiography and CT scan were unremarkable. Thus, a final diagnosis of Rogers syndrome was made.

Patient was advised subcutaneous insulin (70/30), 28 units in morning and 8 units in evening, thiamine 75 mg one tablet OD, vitamin B Complex syrup and sodium feredetate syrup one teaspoonful OD, folic acid half tablet OD and blood glucose monitoring. Presently patient's anemia has improved with a haemoglobin of 12 g/dl and has good glycemic control (HbA1c:7%).

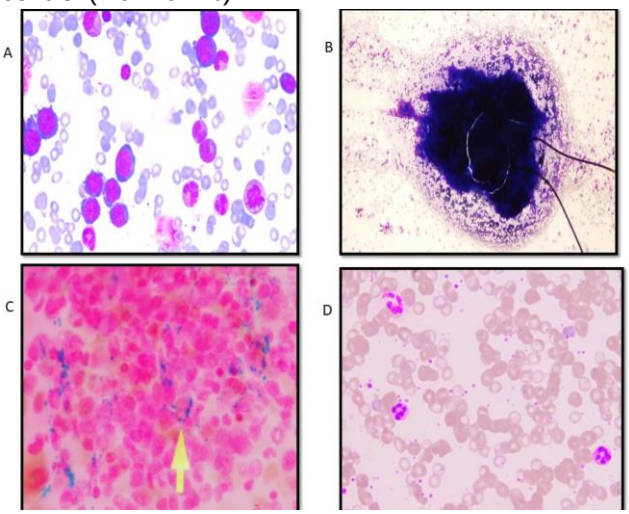

Figure-I: (A) Bone marrow aspiration biopsy showing megaloblastic changes in erythropoiesis; (B) Hyper cellular Fragments with trails; (C) Perls staining of bone marrow aspirate showing more than 15% ring sideroblast; (D) Hyper segmented neutrophils seen on Giemasa stain.

DISCUSSION

Our patient had insulin dependent Diabetes Mellitus with negative Anti Islet Cell and Glutamic Acid Decarboxylase antibodies. It is a characteristic finding in patients of Rogers syndrome resulting due to defective function of islet cells contributed by deficient intracellular thiamine concentration (Figure-II). Impaired oxidative phosphorylation and intracellular energy deficit limits the capacity of pancreatic beta cells to produce insulin in response to increased blood glucose levels [6]. Specific autoantibodies of type I Diabetes Mellitus are absent in TRMA patient as seen in our patient as well [7]. Hematological workup of our patient revealed megaloblastic anemia. Classical findings seen in Rogers Syndrome are of megaloblastic anemia with erythroblasts and ringed sydroblast. It has been postulated that decreased nucleic acid production due to defective transketolase catalysis leads to cell cycle arrest or apoptosis in bone marrow cells resulting in profound megaloblastic anemia [8].

TRMA patients have progressive and irreversible hearing loss, owing to increased energy requirement of acoustic nerve cells. Cellular energy deficit leads to cell death. Even pharmacologic doses

of thiamine do not put off sensorineural deafness in such patients. However, substantial improvement has be seen by introduction of cochlear implants [9]. Optic nerve atrophy and retinal dystrophy has been seen in TRMA. Rhodopsin dysfunction with Retinitis Pigmentosa as seen in our patient has also been reported [10]. Intracellular thiamine deprivation leads to a disruption of the Citric acid cycle and impaired energy generation by mitochondria, thus causing apoptotic cell death of retinal ganglionic cells and photoreceptors. Clinical features (Figure-III) overlap in Rogers syndrome and DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, optic atrophy, and deafness).

Pakistan being a developing country, availability of genetic analysis is limited in our health care set ups. However, a comprehensive history and thorough workup helps in differentiation as done in our patient.

Management involves multidisciplinary approach including lifelong use of pharmacologic doses (50-100 mg/day) of oral thiamine. Pharmacological dose of thiamine results in significant hematological response and improved glycemic control but has no effect on hearing loss. Red blood cell transfusion may be required for treatment of severe anemia. Insulin therapy is required for management of Diabetes Mellitus [11]. Genetic counseling and family planning should be made available to families who have children with TRMA.

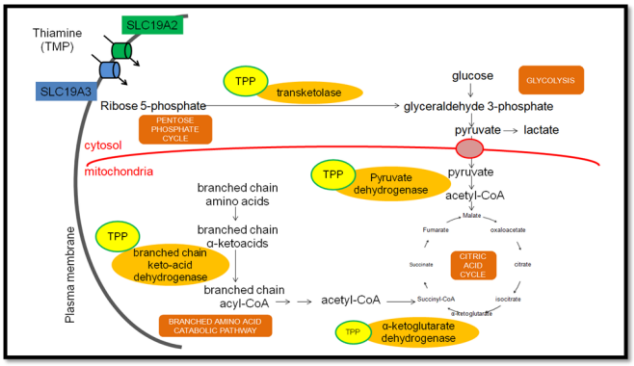

Figure-II: Metabolic pathways requiring thiamine pyrophosphate.

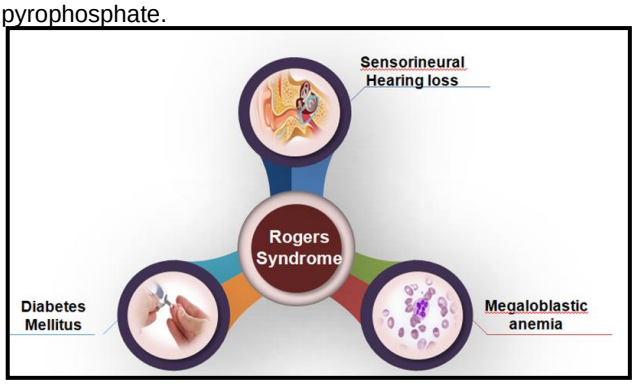

Figure-III: Triad of Rogers syndrome.

CONCLUSION

Rogers Syndrome, a spectrum disease, should be kept in mind in differential diagnosis of Diabetes Mellitus and megaloblastic anemia in population with frequent consanguinity. Thorough medical and family history and physical examination are vital for diagnosis. Prompt diagnosis, use of careful clinical monitoring and supportive care can relieve the debilitating symptoms.

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AUTHORS CONTRIBUTION

Alveena Younas: Conception of the work, Acquisition and review of data, Manuscript writing, Final approval of the version to be published

Mohsin Younas: Literature review, manuscript review, final approval of the version to be published

Aamir Ijaz and Zujaja Hina Haroon: Conception of work, Manuscript review, Literature review

Nida Basharat: Data collection, Manuscript drafting

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