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A RARE CASE OF THIAMINE RESPONSIVE MEGALOBLASTIC ANEMIA PRESENTING WITH SEIZURES

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ABSTRACT:
Thiamine responsive megaloblastic anemia (TRMA) also known as Rogers syndrome is a rare entity inherited as an autosomal recessive disorder. It consists of a pentad of diabetes-mellitus, megaloblastic anemia, thrombocytopenia, leukopenia and sensory-neural hearing loss. The defect occurs due to mutations in SLC19A2 gene resulting in the deficiency of a thiamine transporter proteins which prevents the transport of thiamine in to the cells and tissues. Here we report a 13 year old boy with megaloblastic anemia, sensory-neural deafness and young onset diabetes mellitus who presented with generalized tonic-clonic seizures. Diagnosis was based on clinical features and a rapid response to thiamine replacement with adequate control of seizures. This clinical entity and its association with epilepsy is extremely rare and must be thought of amongst the differentials of megaloblastic anemia and epilepsy. This rare case emphasizes the unique association of TRMA with epilepsy. Early diagnosis and management with thiamine drastically improves anemia, seizure control and blood glucose levels. To the best of our knowledge, it is the first case report of TRMA with epilepsy from Pakistan.

KEYWORDS: TRMA, Rogers syndrome, SLC19A2 mutation, Megaloblastic anemia, Epilepsy

INTRODUCTION:

In 1969 this rare clinical entity thiamine responsive -megaloblastic-anemia (TRMA) or Rogers syndrome was first penned down by Rogers,et al with clinical triad of megalo-blastic anemia, diabetes-mellitus and sensory-neural hearing-loss showing remarkable response to thiamine supplementation [1]. Its genetic predisposition is due to mutation of SLC19A2 which is used for the high-affinity-thiamine-transporter-1 (h-THTR1), through this route thiamine is delivered to different cells and tissues e.g. ß-cells of pancreas, cochlear-cells, haemopoietic tissues, and retinal-epithelial cells [2]. Due to this deficiency of thiamine-transport system the cells and tissues are unable to utilize thiamine from the diet for their normal functioning thus causing low concentrations of thiamine in the body and eventually cell death. TRMA is a very rare entity with only a few well documented cases worldwide. [3]. Thiamine's active form is thiamine-diphosphate which acts as a co-factor for enzymes like pyruvate-dehydrogenase, transketolase and alpha-ketoglutarate all of which contribute in the hexose-monophosphate cycles which generate nicotinamide-adenine-dinucleotide-phosphate for nucleic-acid-synthesis. These enzymes are needed for catabolism of carbohydrates and thiamine is needed for the production of acetylcholine and gamma-amino-buy ric-acid which act as neuro-transmitters [4]. The onset of TRMA is usually at infancy or childhood. Megaloblastic anemia is usually corrected with life-long use of thiamine at 25-75mg/day rather than recommended daily dosage of thiamine 1.5mg/day; it is important to note that anemia can persist once thiamine is stopped. Sensory-neural deafness is reported to be permanent and does not resolve with thiamine supplementation since h-THTR1 is located on cochlear cells and the mutation results in permanent cochlear neuropathy [5]. Thiamine has been proposed to cause remission of diabetes in such patients with less insulin requirement but some reports have also described keto-acidosis with TRMA due to apoptosis of beta cells of pancreases thus requiring insulin with thiamine to control diabetes [6]. In normal population where no genetic mutation is seen but they have thiamine deficiency due to severe mal-nourishment their clinical features consist of lethargy, easy fatiguability, mild neurological and gastro-intestinal symptoms. Later in life they can suffer from beriberi, peripheral neuropathy, absent position and vibration sense, absent deep-tendon reflexes, muscle cramps, cardiomyopathy and psychological manifestations [7]. It could also be complicated with optic-nerve atrophy,

ptosis, hoarseness of voice, muscular atrophy, meningismus, ataxia, loss of deep sensations and sometimes coma [7]. In patients with TRMA due to genetic mutations there is decreased production of nucleic-acids thus causing molecular and biochemical disturbances leading to cell arrest and apoptosis inside bone marrow thus depicting manifestations of TRMA.
Other associated manifestations of TRMA include myelodysplasia, congenital heart defects (patent ductus arteriosus), arrhythmias, ischemic stroke and retinal abnormalities e.g. retinitis pigmentosa, cone-rod dystrophy and optic atrophy etc[8].We report a rare case of a 13 year old boy who presented with seizures and was later diagnosed to have TRMA. Seizures with TRMA are rare and an unusual manifestation of Rogers syndrome. To our knowledge this is the first case of TRMA with epilepsy from Pakistan.

CASE PRESENTATION:

A 13 year old boy came to Neurology out patient department with history of loss of consciousness succeeded by frothing from mouth, abnormal jerking of the body and sphincter incontinence for the past 6 months. Initially he was taken to a local spiritual healer by his parents but no improvement was seen in his symptoms, then he was taken to a Pediatrician who eventually referred him to us for the evaluation of seizures. Upon inquiring his mother, they had a single child with a consanguineous marriage. He was born at a local dispensary through normal vaginal delivery with normal cry at birth. Being a new born, he was noted to have lethargy, generalized weakness and extreme pallor for which frequent help was sought. At that time based on his blood peripheral film and bone marrow biopsy he was diagnosed to have megaloblastic anemia and received his first blood transfusion at the age of 12 months. Since then he would require monthly blood transfusions with red cell concentrates. At the age of 2.5 years his parents noted hearing impairment and lack of attention when confronted, medical help was sought and he was diagnosed to have a sensory-neural deafness. Therefore, he received his early education at a special children school. At the age of 13 years, he started having episodes of loss of consciousness with post-ictal confusion and sphincter disturbance. On general physical examination he had normal vital signs. He looked extremely weak and pale but no cyanosis, jaundice, clubbing, leukonychia or koilonychias was seen. His height and weight was well below third percentile and his body mass index was 16.2 signifying being underweight. Tuning fork test showed a bilateral sensory-neural deafness while all other systemic examination showed no abnormality. During further inquiring his father provided with a lead that one of his son's paternal-cousins had the same disease. Therefore, considering his past history and examination we put TRMA as the top clinical differential and investigated him. Upon investigations his blood picture showed a hemoglobin of 9g/dl (normal range: 14-18), blood indices showed mean-corpuscular-volume MCV was 106 fl (normal range:82-90), mean-corpuscular hemoglobin was 34.3 pg(normalrange:27-32) ,mean-corpuscular-hemoglobin concentration was 32.5g/dl (normal range:32-36). White blood cells were 9x109/L and platelet count 394x109/L. Erythrocyte-sedimentation rate was 11mm/1st hour. Peripheral blood film showed macrocytosis with hyper segmented neutrophils. Serum ferritin was 380 ng /ml (normal range:10-308 ng/ml), Total iron-binding-capacity was 42.2 umol/L (normal range:42.96-80.55 umol/L), serum iron was 161 ug/dL (normal range:30-159), reticulocyte count showed 0.6% retics and hemoglobin electrophoresis showed no abnormality. Serum Vitamin B12 levels were 550 pg./mL (normal range: 221-920) while serum folate levels were 18 ng/ mL (normal range: 4-17). Bone marrow aspiration with trephine biopsy showed normo-cellular bone marrow with megaloblastic changes (Figure A). Osmotic fragility showed no abnormality and Coomb's direct and indirect test was negative. Fasting blood glucose levels were 230 mg/dL while hemoglobin A1c was 11%. Liver and renal functions were normal. Serum levels of Vitamin-D, calcium and thyroid profile was normal. Hepatitis B and C serologies were negative. Arterial blood gases showed no abnormality and urinary/serum ketones showed no evidence of keto-acidosis. Fundoscopy and slit lamp examination showed no retinal abnormality. Electrocardiogram and echocardiogram showed no valvular abnormality with sinus rhythm. Ultrasound abdomen showed no organomegaly or ascites. Chest Xray was unremarkable. maging of the brain (MRI brain) was done which showed no acute or chronic pathology while electroencephalogram (EEG) hyper-ventilation induced generalized spike burst 1-2 sec with normal background rhythm (Figure B).On the basis of significant history, clinical examination and laboratory findings he was diagnosed to have Rogers syndrome/TRMA. Oral thiamine supplementation was started at 250 mg daily with multi-vitamin supplementation. Insulin was started at 0.7units/kg subcutaneously. For seizures he was started on carbamazepine 200mg twice daily. After four weeks of follow up he remained seizure free on carbamazepine, hemoglobin level

increase from 9 to 12g/dl while MCV dropped from 105 to 99 fl. After 12 months of follow up his hemoglobin levels remained static at 12g/dl with no transfusions. His weight and height reached third centile for his age. HbA1c levels dropped from 12 to 8.5%. Patient's insulin dose was reduced and continued with carbamazepine 200mg twice daily, thiamine 100mg daily, multi-vitamins and dietary/life style modifications were explained to family regarding his diabetes. Unfortunately, there was no improvement in his hearing for which he was referred to ENT specialist for cochlear implants.

Figure A: Normo-cellular bone marrow with megaloblastic erythropoiesis

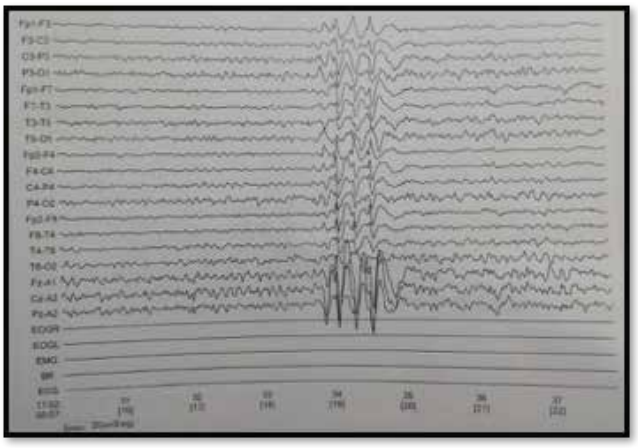

Figure B: Hyper-ventilation induced generalized spike and wave discharges with normal background rhythm.

DISCUSSION:

Rogers syndrome or TRMA is an autosomal recessive disorder with clinical constellation of sensory-neural deafness, megalo-blastic anemia and diabetes mellitus. It occurs due to mutation of SLC19A2 gene which is responsible for the high-affinity-thiamine-transporter-1 (h-THTR1) used for transporting thiamine to tissues [9]. Our 13 year old patient had persistent anemia since early life with deafness and required blood transfusions due to megaloblastic picture with normal B12/folate levels. In TRMA megaloblastic anemia must be differentiated from other common causes like B12/folate deficiency and some rare causes like orotic-aciduria. Orotic-aciduria causes megaloblastic anemia due to deficient pyrimidine synthesis leading to reduced lipid co-factors required for red cell membrane synthesis; it also shows mental retardation, growth-failure and raised urinary orotic acid [10]. Other differential diagnosis with similar phenotype include DIDMOAD syndrome (diabetes-insipidus, diabetes-mellitus, optic-atrophy, and deafness) showing diabetes insipidus a clue to diagnosis without anemia; Kearns Sayre syndrome has chronic progressive external ophthalmoplegia with retinopathy and deafness and Pearson syndrome has persistent sideroblastic pancreatic insufficiency and pancytopenia both classifying as mitochondrial disorders which don't exhibit megaloblastic anemia, bone marrow biopsy is normal and do not show response to thiamine therapy. The pattern of mitochondrial disorders is maternal while TRMA is autosomal recessive. In our patient bone marrow showed a normo-cellular picture with megaloblastic changes in erythropoiesis but TRMA can be confused with myelodysplasia of pre malignancy [11]. Our patient was started on daily thiamine supplementation of 250mg daily which was the only high dose formulation available. His hemoglobin levels improved drastically over a period of four weeks. Although in our case anemia showed response to thiamine supplementation but the macrocytosis did not revert indicating that the red cells maintain their macrocytic ability due to permanent erythropoietic aberration and anemia can recur once thiamine is stopped. Diabetes in this disease is non-autoimmune type and may start as type 2 and then gradually progress to insulin-dependency due to insulin deficiency secondary to dysfunction of islet cells [12]. TRMA patients show normal insulin secretion to glucose intake and have normal C-peptide-secretions. Such patients respond to thiamine supplementation thus reducing the dose of insulin but most patients require insulin for life time after puberty [12]. Diabetic keto acidosis could be the very first presentation of such patients or once thiamine therapy is stopped [12]. Thiamine shows a remarkable response to disturbed hematological parameters with improvement in diabetic control but deafness is permanent with no response to thiamine treatment however some studies suggest that early diagnosis and treatment could partially reverse sensory-neural deafness in humans [13]. Our patient's HbA1c dropped from 12 to 8.5% after 12

months of thiamine therapy with decline in insulin dose which is remarkable improvement in glycemic control. Insulin dependence could be due to high insulin requirement during puberty and late diagnosis thus late thiamine initiation which did not reverse his glycemic indices to normal. Our patient started experiencing seizures and showed reduction in seizure frequency with carbamazepine thus was diagnosed TRMA with epilepsy because his seizures were not hypo-glycemic or metabolic. They represent an un-usual manifestation of this disease. Treatment of TRMA is life long thiamine therapy at 25-75mg/day. Patients should be followed up to see compliance to oral thiamine as well as to see disease progression with yearly blood counts, retic count, glucose intolerance tests, urine analysis, hearing, cardiac and ophthalmological evaluations [14].

CONCLUSION: Rogers syndrome must be thought of amongst the differentials of megaloblastic anemia, diabetes and hearing loss just like our patient who was suspected on clinical acumen including laboratory tests, thiamine responsive anemia and decrease in HbA1c with reduction in insulin dose signifies the effects of thiamine on glycemic control. Deafness showed no response while epilepsy showed partial response to thiamine and complete response to anti-epileptic drugs. Based on clinical diagnosis thiamine should be given prophylactically in all such patients presenting with clinical triads and non-availability of genetic analysis. Thiamine has an economical price and response can easily be observed after its initiation. This clinical entity and its association with epilepsy is extremely rare and must be thought of amongst the differentials of megaloblastic anemia and epilepsy specially in countries like Pakistan where there is a high background of consanguinity.

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Waleed Shahzad; data collection, data analysis, manuscript writing, manuscript review
Tehmina Inayat; data analysis, manuscript writing, manuscript review
Mansoor Iqbal; data analysis, manuscript review
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Fibhaa Syed; manuscript writing, manuscript review
Naveedullah Khan; manuscript writing, manuscript review
Mazhar Badshah; data analysis, manuscript review
Misbah Malik; data analysis, manuscript writing, manuscript review