International Journal of Contemporary Pediatrics
Kataria B et al. Int J Contemp Pediatr. 2023 Jun;10(6):962-965
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20231510

Case Report

Roger's syndrome presenting with stroke

Bhavya Kataria[1], Bijoy Patra[2], Shishir Chumber[3], Kavita Vani[4]*

[1]Department of Radiology, [2]Department of Pediatrics, [3]Department of Neurology, [4]Department of Radiology, ABVIMS and Dr. RML Hospital, Delhi, India

Received: 19 April 2023
Accepted: 12 May 2023

***Correspondence:**
Dr. Kavita Vani,
E-mail: kavitavani03@gmail.com

ABSTRACT

Rogers syndrome (Thiamine responsive megaloblastic anaemia-TRMA) occurs due to defect in the SLC19A2 gene. SLC19A2 and SLC19A3 genes encode THTR1 and 2 respectively, which are thiamine transporter proteins. The SLC19A2 gene is expressed in the inner ear cells, β-islet cells, and hematopoietic stem cells; consequently, the typical clinical trial of TRMA is diabetes, TRMA, and sensorineural hearing loss. This syndrome, eponymously called Roger's syndrome is rare. Mode of inheritance of TRMA is autosomal recessive. Clinical presentation as recurrent stroke is extremely rare. We present a case of a five-year-old boy who had recurrent large artery territory cerebral infarcts, with no other identifiable underlying cause of stroke. During current admission, no underlying etiology could be identified for cerebral infarct. On workup, a preliminary diagnosis of TRMA was made and thiamine supplementation was instituted. Gene analysis confirmed the diagnosis. The child was a product of non-consanguineous marriage. There was history of early childhood demise of two older siblings within five years of age due to diabetic ketoacidosis (DKA). TRMA is a rare autosomal recessive syndrome that manifests as a typical triad with diabetes, hearing loss and megaloblastic anaemia. The treatment is with high dose thiamine supplementation that can alleviate symptoms of diabetes and megaloblastic anaemia. Onset and progression of hearing loss may be delayed with treatment. Some cases may present with recurrent stroke as in the proband.

Keywords: SLC19A2 gene mutations, Deafness, Non-type 1 diabetes, TRMA syndrome, Thiamine transporter THTR1

INTRODUCTION

Rogers syndrome (Thiamine responsive megaloblastic anemia-TRMA) occurs due to a defect in the SLC19A2 gene. SLC19A2 and SLC19A3 genes encode THTR1 and 2 respectively, which are thiamine transporter proteins. The SLC19A2 gene is expressed in the inner ear cells, β-islet cells, and hematopoietic stem cells; consequently, the typical clinical trial of TRMA is diabetes, megaloblastic anaemia, and sensorineural hearing loss.[1] Additional findings that are associated include optic atrophy, congenital heart disease, and short stature. Presentation of this disorder as ischemic episodes of stroke has been reported in 4 cases in literature so far. This syndrome, eponymously called Roger's syndrome is rare. Mode of inheritance of TRMA is autosomal recessive. Clinical presentation as recurrent stroke is extremely rare. Here we present a case of a 5-year-old boy who had recurrent large artery territory cerebral infarcts, with no other identifiable underlying cause of stroke.

CASE REPORT

A 5-year-old boy presented to the emergency on 04/10/2020 with altered sensorium and right hemiparesis of over 24 hours duration.

Birth history of the child was uneventful. The child was a product of non-consanguineous marriage. Developmental history of the proband was normal except for impaired speech. The child had been admitted to various hospitals

on several occasions earlier. At the age of 11 months, the child had acute onset left hemiparesis. MRI brain done at the time revealed right MCA territory infarct. The patient had been evaluated for common causes of pediatric stroke. No underlying etiology had been identified.

Around 2 years later, child had suddenly developed altered sensorium. During this admission, he was diagnosed to be suffering from type 1 diabetes mellitus and was in DKA at the time. He was also found to have bilateral sensori-neural deafness. The speech impairment of the patient was attributed to sensori-neural deafness. Child had been managed with insulin and anti-epileptics.

About a year later, when the child was around four years old, he was again hospitalised; this time with complaints of generalized weakness and altered sensorium. During this admission, the child was in DKA and was also found to have megaloblastic anemia.

There was a history of early childhood demise of two older siblings within 5 years of age due to DKA.

During the current admission, workup revealed: Heart rate of 130 beats per minute, respiratory rate of 32 beats per minute, severe dehydration (BP-100/60 mm Hg and capillary refill time less than 3 sec, with cold extremities) and RBS-350 mg/dl. Urine ketones were positive.

The muscular power in the right upper and lower limbs was 2/5. BERA revealed bilateral sensorineural hearing loss. Serum homocysteine levels were 6.98 micromoles/L (normal). HbA1c was 13% (high). Serum lactate levels were normal and CRP levels were normal-2.8 mg/dl. There was megaloblastic anaemia on peripheral smear. Bone marrow examination showed megaloblastic cells. The levels of folate and vitamin B12 were found to be normal. Retina and Cardiovascular system examination were normal.

MRI scan was as in Figures 1 and 2.

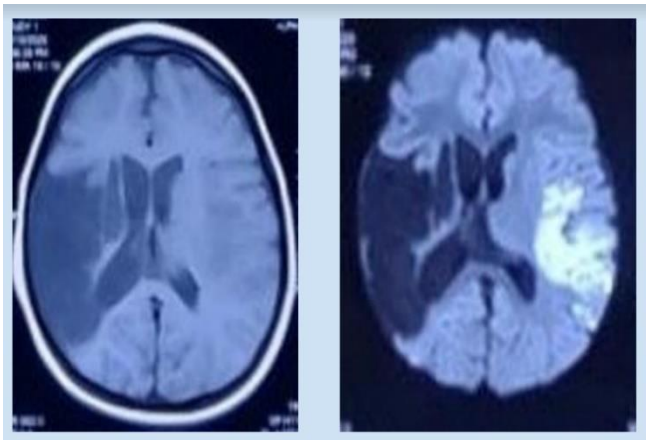

Figure 1: MRI scan showed large right MCA territory encephalomalacia on T1WI (left image) and large left MCA territory acute infarct on DWI (right image).

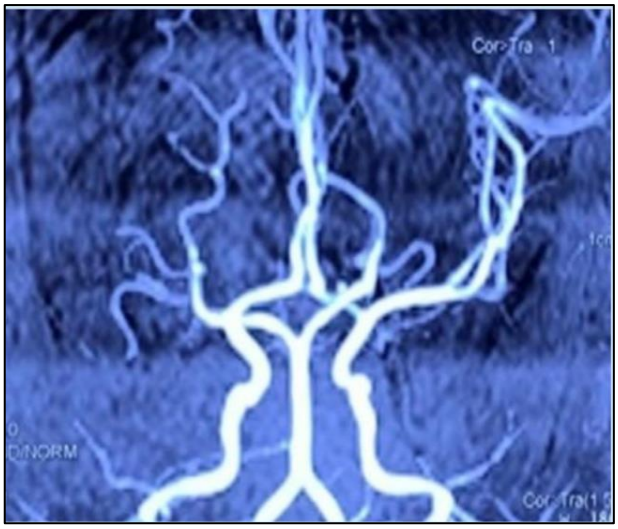

Figure 2: MRA revealed attenuated RICA and its branches, likely related to old infarct, as a cause or consequence. There was no abnormality of the remaining intracerebral arteries including LICA and LMCA, hence no evidence of large vessel occlusion to explain current infarct could be found.

Common causes of pediatric stroke include sickle cell disease, cardiac disease, Moya-Moya syndrome, cervical arterial dissection, steno-occlusive cerebral arteriopathy, coagulopathy and infectious vasculitis. These were ruled out by laboratory tests, echo, MRI brain and doppler of neck vessels. The possibility of endocrine and metabolic abnormalities was considered. A provisional diagnosis of mitochondrial disorders (Kearns-Sayre syndrome, Leigh disease) and TRMA was kept. Kearns-Sayre syndrome and Leigh disease show typical MRI findings: T2 subcortical hyperintensities with areas of calcifications with or without basal ganglia sidero-calcific deposits. The brainstem, medulla, putamen, periaqueductal grey matter, corpus striatum, thalami and substantia nigra are the characteristic areas of involvement. Diffuse supra and infratentorial atrophy are occasionally seen.

Hence, TRMA was considered to be the diagnosis. The patient was started on Pyridoxine and Thiamine supplements and blood sample was sent for gene analysis.

The patient showed improvement post Thiamine supplementation and the gene analysis revealed a homozygous mutation of the pathogenic variant of SLC19A2 on chromosome 1.

Thus, the diagnosis of Roger's syndrome (TRMA) was confirmed.

High dose thiamine supplementation was started (50 mg/day) in this patient which led to improvement in blood sugar levels and anemia. Hearing loss remained unaffected. With time, symptoms of stroke showed mild improvement.

Lifelong therapeutic use of thiamine in the range of 25-75 mg/day was recommended and parents were advised to remain vigilant about the development of paretic symptoms to facilitate early diagnosis and treatment of stroke.

DISCUSSION

The typical constellation of findings, viz, diabetes, hearing loss and megaloblastic anaemia, was first described by LE Rogers in 1969. The diagnosis of TRMA is established in a proband (with or without diabetes or hearing loss):1) With megaloblastic anemia and normal vitamin B12 & folic acid levels in whom there is a response to oral thiamine; and/ or 2) By identification of biallelic pathogenic variants in SLC19A2 by molecular genetic testing.

Under physiological concentrations, thiamine is transported into the cell mainly by saturable, high affinity and low adhesion transporters THTR-1 and THTR-2, which are encoded by the SLC19A2 and SLC19A3 genes, respectively.[1] SLC19A2 gene encodes a transmembrane protein of 497 amino acids called THTR. TRMA is characterized by mutation of this gene located on 1q23.3. Intracellular thiamine is converted into thiamine pyrophosphate (TPP), which is incorporated into mammalian enzymes involved in the pentose phosphate shunt pathway and oxidative decarboxylation reactions. The SLC19A2 gene is expressed in the inner ear cells, β-islet cells, and hematopoietic stem cells; consequently, the typical clinical trial of TRMA, that is, diabetes, megaloblastic anemia and sensorineural hearing loss, develops. TRMA patients can also show visual impairment, congenital heart disease, arrhythmia, short stature, cerebrovascular events, thrombocytopenia, and leukopenia.[2,7]

The β-islet cells in patients with TRMA cannot transport thiamine effectively, leading to decreased insulin and type-1 diabetes. Development of diabetes into ketoacidosis is rare in patients with TRMA; however, in thiamine shortage, ketoacidosis may also appear before puberty.[3] The activity of transketolase in hematopoietic cells in the bone marrow decreases in patients with TRMA syndrome causing several cellular abnormalities, immature DNA synthesis, and anaemia along with the formation of ring sideroblasts. Thiamine therapy is shown to alleviate symptoms of anemia and diabetes. Hearing loss in these patients is attributed to atrophy of the cochlear inner hair cells due to deficiency of thiamine. Majority of patients with TRMA syndrome have deafness, even with thiamine therapy. Therefore, it is generally believed that thiamine therapy cannot alleviate deafness but can decelerate its progression.

Currently, 45 different mutations are documented in the SLC19A2 gene from TRMA patients according to the Human gene mutation database, for example, in one case, comprising a single nucleotide deletion (c.791delG).[1] Most patients are from consanguineous backgrounds.[4,5] The patient presented here is a product of non-consanguineous marriage and seen to have a homozygous mutation in the SLC19A2 gene.

No data is available to date, in patients with the TRMA syndrome where evidence of a causal relationship between Stroke and TRMA has been shown. A new insight into the genetic mapping of the human coagulation factor V and anti-thrombin III precursors could pave the way for understanding the disturbed coagulation cascade leading to susceptibility to thrombosis and recurrent attacks of stroke in TRMA patients.[6]

Multiple recurring infarcts could occur due to changes in the thrombotic cascade but need further analysis of the coagulation pathway genes to establish a causal relationship.

In 2002, Oishi published the report of their work wherein they produced mice with a defect in SLC19A2 gene. These mice developed diabetes, hearing loss and megaloblastic anemia. Diabetes and megaloblastic anemia improved on institution of therapeutic doses of Thiamine; hearing loss did not improve. The control group consisted of wild type mice, kept in identical conditions, who did not develop diabetes, hearing loss or megaloblastic anemia.[8]

CONCLUSIONS

In patients who have diabetes, hearing loss and megaloblastic anaemia, the possibility of Rogers syndrome, should be considered and high dose thiamine supplementation started pending confirmation by gene analyses. Presentation of the clinical trial, as well as laboratory examination and genetic analysis, are instrumental in confirming the diagnosis of such patients.

These patients may have other associated problems such as visual impairment and cardiac arrhythmias. In our case, at least two episodes of large artery cerebral infarctions had occurred.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Li X, Cheng Q, Ding Y. TRMA syndrome with a severe phenotype, cerebral infarction, and novel compound heterozygous SLC19A2 mutation: a case report. BMC Pediatr . 2019;19:233.
2. Ortigoza-Escobar JD, Molero-Luis M, Arias A, Martí-Sánchez L, Rodriguez-Pombo P, Artuch R et al. Treatment of genetic defects of thiamine transport and metabolism, Expert Review of Neurotherapeutics, 2016;16(7):755-63.

3. Ricketts CJ, Minton JA, Samuel J, Ariyawansa I, Wales JK, Lo IF et al. Thiamine- responsive megaloblastic anemia syndrome: long-term follow-up and mutation analysis of seven families. Acta Paediatr. 2006;95:99-104.
4. Mikstiene V, Songailiene J, Byckova J. Thiamine responsive megaloblastic anemia syndrome: a novel homozygous SLC19A2 gene mutation identified. Am J Med Genet A. 2015;167(7):1605-9.
5. Pichler H, Zeitlhofer P, Dworzak MN, Diakos C. Thiamine-responsive megaloblastic anemia (TRMA) in an Austrian boy with compound heterozygous SLC19A2 mutations. Eur J Pediatr. 2012;171(11):1711-5.
6. Villa V, Rivellese A, Di Salle F, Iovine C, Poggi V, Capaldo B. Acute ischemic stroke in a young woman with the thiamine-responsive megaloblastic anemia syndrome. J Clin Endocrinol Metabol. 2000;85:947-9.
7. Zhao R, Goldman ID. Folate and thiamine transporters mediated by facilitative carriers (SLC19A1-3 and SLC46A1) and folate receptors. Molecular Aspects Med. 2013;34(2-3):373-85.
8. Oishi K, Hofmann S, Diaz GA, Brown T, Manwani D, Ng L et al. Targeted disruption of Slc19a2, the gene encoding the high-affinity thiamin transporter Thtr-1, causes diabetes mellitus, sensorineural deafness and megaloblastosis in mice. Human Molecular Genetics. 2002;11(23):2951-60.

Cite this article as: Kataria B, Patra B, Chumber S, Vani K. Roger's syndrome presenting with stroke. Int J Contemp Pediatr 2023;10:962-5.