

Stroke as an Initial Manifestation of Thiamine-Responsive Megaloblastic Anemia

Sir,

Pediatric arterial ischemic stroke (AIS) is relatively uncommon and often under-recognized. It comprises 5%-10% of all strokes.^[1] Pediatric stroke is an entity with diverse etiologies varying from cardiac diseases, hematological disorders, vasculopathies to malformations or genetic defects. Multiple risk factors might be contributory in a single patient. Despite

extensive evaluation, no associated risk factor is identified in 25% cases of childhood stroke.^[2]

Among hematological diseases, sickle cell disease is one of the most common and most studied disorder associated with pediatric ischemic stroke.^[3] Literature regarding other hematological disorders such as megaloblastic anemia is scarce. Hereby we report an infant with acute-onset hemiplegia

with left middle cerebral territory infarction associated with an underlying rare hematological and genetic disorder: Thiamine-responsive megaloblastic anemia (TRMA). TRMA is a clinical triad of megaloblastic anemia, diabetes mellitus and sensorineural hearing loss.^[4] Among these manifestations, sensorineural hearing loss presents in toddlers while rest can manifest anytime till adolescence.^[5] AIS in the index child is an atypical presentation of TRMA.

CASE REPORT

A 10-month-old developmentally normal boy, second born of third degree consanguineous parents, presented with right focal seizures. Postictally, the child had altered sensorium along with right hemiparesis. He was hospitalized for the same and was later referred to us on day 6 of illness.

At admission, the child was in altered sensorium with a Glasgow coma score (pediatric) of 12. He had significant pallor but was hemodynamically stable. All peripheral pulses were well-palpable. Clinical diagnosis of left middle cerebral artery territory AIS was kept and MRI brain confirmed the same [Figure 1a]. MR angiography revealed a sudden cut-off in left internal carotid artery just after the origin with complete occlusion of the same but dissection could not be ruled out. Intracranial left internal carotid artery and its branches were also not visualized and there were no significant collaterals [Figure 1b]. On sonography and Doppler of neck vessels, left internal carotid artery could not be visualized. Echocardiography was essentially normal.

The child was extensively evaluated for all possible risk factors contributing to stroke, detailed in Supplementary Table 1. His blood investigations revealed a normocytic normochromic anemia (MCV = 94 μ l) with a normal platelet and total leucocyte count. By the fourth day of hospitalization, he developed thrombocytopenia with elevated lactate dehydrogenase (LDH). Peripheral smear examination showed schistocytes (4%-5%) with a low reticulocyte count. His serum vitamin B12, folate, plasma homocysteine, and C₃ levels were within normal limits. Subsequently, a gradual decline of hemoglobin levels and platelet count was noted. In addition to the evolution of bicytopenia, he also developed facial puffiness with hypertension. A working diagnosis of congenital thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome (HUS) was considered and clinical exome sequencing was ordered. He was started on daily fresh frozen plasma transfusion followed by Plasma Exchange (PEX). Once platelet counts improved to >1 lac/mm³ with normalization of blood pressure records, the child was switched to oral steroids which were continued for about a month and gradually tapered monitoring the platelet count.

Exome sequencing revealed a novel homozygous nonsense variation in exon 2 of the *SLC19A2* gene (*chr1:169446604; G>C; Depth: 119x*) that results in a stop codon and premature truncation of the protein at codon 199 (*p.Ser199Ter; ENST00000236137*). The region is conserved across species.

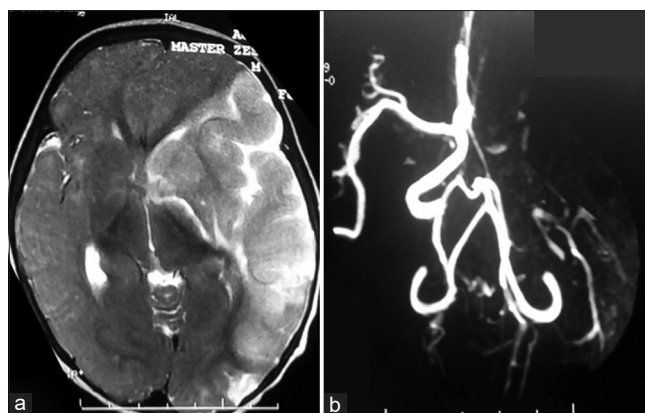


Figure 1: (a and b) MRI brain and MR angiography of the index case. (a) MRI brain (T2-weighted axial section) of the index case revealing left middle cerebral artery territorial infarct. (b) MR angiography of the index case at the time of presentation reveals an absent flow in the left internal carotid artery and the distal vessels and absence of collaterals

The detected variant was predicted to be damaging by SIFT, LRT and Mutation Taster and was likely pathogenic.

At 3-month follow-up, the child developed sensorineural hearing loss. Bone marrow aspirate revealed cellular marrow with adequate megakaryocytosis and erythroid series showed megaloblastic maturation. HbA1c was 6.7 g/dl (normal <6.5%). Child was initiated on thiamine in suprathreshold doses (500 mg/day). Currently, at 2-year follow-up, hematological parameters are within normal limits. There has not been any recurrence of stroke. He failed a hearing-aid trial and has been planned for cochlear implant surgery. Informed consent was obtained from parents for publication.

Thiamine responsive megaloblastic anemia (Roger syndrome) is characterized by a clinical triad of megaloblastic anemia, deafness, and diabetes. Megaloblastic anemia and diabetes may manifest from infancy to adolescence while deafness usually manifests in the toddler age group. This entity was first described in 1969 by Roger *et al.*^[4] It is caused by a mutation in *SLC19A2* gene, which encodes the high-affinity thiamine transporter. Besides classical triad, other features include abnormalities of retina and optic nerve, stroke-like episodes, congenital heart disease, arrhythmias, aminoaciduria, tri-lineage myelodysplasia, short stature, and situs inversus.

Thiamine deficiency is known to affect respiratory chain complex I activity. The neurological features of TRMA, resembling those of mitochondrial complex I deficiency, may be caused due to a secondary defect in mitochondrial energy production.^[6] But, the association with stroke and pathophysiology of stroke in TRMA is unclear.

Till date, there are two patients with TRMA reported with AIS and one with cerebral sinus thrombosis.^[7-9] Possible pathogenic mechanisms include: Mapping of human coagulation factor V and antithrombin III precursor to nearby

region as SLC19A2 gene (a complex mutational event in this region may also involve coagulation cascade genes, causing susceptibility to thrombosis)^[6] and prothrombotic tendency due to hyperglycemic state (increased levels of plasminogen activator inhibitor-1 and the decreased endogenous fibrinolysis activity).^[7] Besides these, the clinical spectrum of TRMA is still evolving due to the rarity of this disorder; microvascular and coagulation pathway affection are still ambiguous. Also, the role of a particular genotype causing disease and stroke as a presenting feature is also unclear.

Our initial clinical possibility in the index patient was congenital HUS/TTP in view of thrombocytopenia, hypertension, consanguinity and early infantile onset, and exome sequencing was done suspecting the same. But it revealed a likely pathogenic variation in the gene for TRMA. Anecdotal reports suggest that TRMA may be associated with stroke however its association with TTP/HUS is speculative. There have been rare reports of atypical HUS associated with cobalamin C defect which presents with megaloblastic anemia, methylmalonic acidemia, and homocystinuria.^[10,11] However, no direct link between TRMA and HUS/TTP have been mentioned. Both acquired HUS and TRMA seem to have coexisted in the index case and this probable unusual association merits documentation.

The basis for responsiveness of thrombocytopenia to plasma exchange in the index case is uncertain. Possibilities include superadded consumption coagulopathy, acquired hemolytic uremic syndrome/TTP, thiamine repletion, and prothrombotic state due to disease per se which also might have responded to plasma exchange.

This patient had two uncommon manifestations of this rare disorder: AIS and thrombocytopenia. Also, the child had a novel nonsense mutation in *SLC19A2* gene. History of consanguinity, in this case, was another pointer towards a genetic disorder. Later, clinical features such as sensorineural hearing loss and slightly elevated HbA1c confirmed the clinical phenotype.

This case brings forth association between TRMA, prothrombotic state, and AIS; although the exact physiological basis still remains indeterminate. TRMA as a possible risk factor for stroke still remains a mystery. Evolving phenotypic spectrum of this disease might make the intricate pathways more lucid.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgements

Authors are grateful to the patient and his family.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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DOI: 10.4103/aian.AIAN_166_19