pediatric stroke

Case Report

Arterial Ischemic Stroke as Initial Presentation of a Congenital Disorder of Glycosylation

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Abstract:

A 2-year-old male presented with acute onset of right face, arm, and leg weakness and paucity of speech. Imaging demonstrated occlusive thrombus in the left M1 segment and consequent left MCA infarct. He was found to be in heart failure in addition to having multiple prothrombotic abnormalities. The patient was diagnosed with phosphoglucomutase-1 deficiency, a congenital disorder of glycosylation associated with a range of phenotypes. Although rare, some metabolic disorders are associated with increased risk for arterial ischemic stroke and should be on the differential in patients with multisystem involvement.

Introduction:

Pediatr Stroke. 2023;6: 51-59

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Case Report

Childhood arterial ischemic stroke (CAIS) has many different risk factors and can occur both in isolation or as sequela of systemic disease. While the most common risk factor present in about 50% of cases of CAIS is arteriopathy, the second most common cause is cardioembolism, accounting for about 30% of all cases.1 Prothrombotic states are also an important risk factor present in 13% of CAIS, and over half of all children will have multiple risk factors.1

Metabolic diseases are traditionally associated with “metabolic stroke”, rather than CAIS. However, there are some metabolic diseases that also increase risk for arterial ischemic stroke because they are associated with cardiac disease, arteriopathy, or coagulopathies.2 Phosphoglucomutase-1 deficiency (PGM1-CDG) is a rare congenital disorder of glycosylation caused by biallelic mutation in the gene encoding phosphoglucomutase-1. Arterial ischemic stroke has not been described previously in this population. However, it is well known that patients with PGM1-CDG can develop cardiomyopathy and heart failure, as well as coagulation abnormalities,3 thereby putting them at risk for thrombus formation and stroke. We present the case of a pediatric patient with acute arterial ischemic stroke as the presenting symptom of PGM1-CDG.

Case:

A 2-year-old male with a history of speech delay presented with sudden onset right face, arm and leg weakness, and paucity of speech. The week prior, he had symptoms of cough and congestion and was evaluated by his pediatrician and prescribed dexamethasone for presumed croup. The cough did not improve. On the day of admission, he was last seen normal at about 3 am when his mother woke him to feed him. Later that morning, upon awakening again around 9 am, he was noted to have a right facial droop and was not able to sit up or walk. He was also irritable and crying and was not speaking.

He presented to the emergency department at 11:20 am, and his initial examination was notable for a right lower facial weakness and mild right arm weakness. PedNIHSS4 was 5 (2 for

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facial palsy, 1 for right upper extremity, and 2 for language). At the time of presentation he was 8 hours from the time last known normal and had a mild deficit, thus, was deemed to not be a candidate for thrombolysis or thrombectomy. Rapid protocol MRI was obtained and showed an acute left middle cerebral artery infarct (Figure 1A and B).

Initial laboratory studies were notable for mild anemia (10.4 g/dL; normal 11.5-13.5 g/dL), elevated INR (1.8, normal 0.92-1.14), lactatemia (3.1 mmol/L, normal 0.5-2.2mmol/L), mild elevation in liver enzymes with AST 185 U/L (normal 20-60 U/L) and ALT 55 U/L (normal 10-30 U/L), hyponatremia to 134 mmol/L (normal 138-145). There were no other electrolyte or hematologic abnormalities, including normal platelets at 371 x103/uL (normal 150-400 x103/uL), normal PT (14.3 units, normal 12.1-14.5 units), normal aPTT 24.4 (normal 33.5-43.8) and normal alkaline phosphatase 170 U/L (normal 145-320 U/L). He was admitted to the pediatric intensive care unit for monitoring and further work-up.

CTA head was completed after admission to the pediatric intensive care unit. This was chosen over MRA to avoid additional sedation, and demonstrated a corresponding vessel occlusion, in the left M1 segment, consistent with a thrombus (Figure 1C). Echocardiogram demonstrated severely diminished left ventricular function with an ejection fraction (EF) estimated at 28% and moderate to severe mitral regurgitation. He was transferred to the cardiac intensive care unit for management of heart failure with a milrinone infusion and diuretics. Given concern for a cardioembolic source, he was started on anticoagulation with enoxaparin. Thrombophilia work-up also demonstrated multiple pro-thrombotic factors including low antithrombin III activity (79%, normal 87-145%), protein C deficiency (41%, normal 81-150%), elevated factor VIII (374.3%, normal 49-191%), and elevated factor IX (144.8%, normal 52-112%).

The patient's brother was known to have PGM1-CDG, although with a more classic presentation of persistent hypoglycemia and congenital malformations from Pierre Robin sequence. In light of this family history, and the patient's presentation with heart failure, multiple coagulopathies,

and speech delay, we had a high suspicion for the same disorder in this patient. Carbohydrate Deficient Transferrin and N-Glycan assays were sent showing mixed-type transferrin glycosylation defect and under-galactosylated glycans were markedly elevated, with A-Gal glycan at 3.43% (normal 0-0.42%) and Mono-gal at 3.69% (normal <1.88%), demonstrating hypogalactosylation consistent with PGM1-CDG. Genetic testing later confirmed a homozygous pathogenic PGM1 variant c.1544G>A; p.Arg515Gln, which is the same variant in the patient's brother. His two sisters were also tested and found to be unaffected carriers for this variant.

He was started on enteral D-galactose supplementation and Enoxaparin sodium with subsequent transition to warfarin. At 6 months post-stroke, he continues to have severe dilated cardiomyopathy, moderate to severe mitral valve regurgitation, and severe left ventricular systolic dysfunction with an EF of approximately 30%. He is maintained on a cardiac regimen of furosemide, spironolactone, carvedilol, and enalapril. He was also continued on warfarin for secondary stroke prevention. He had moderate residual impairment at 6-month follow up, with a Pediatric stroke outcome measure5 score of 1.5 (maximum score = 10) with 1 for right sensorimotor deficit, and 0.5 for expressive language deficit.

Discussion:

PGM1-CDG is rare, with under 60 genetically-confirmed cases in the literature.3 It was initially described as a glycogen storage disorder (GSD XIV) and later was determined to also be a congenital disorder of glycosylation (CDG).3 PGM1-CDG is caused by mutations in PGM1 which results in phosphoglucomutase 1 enzyme (PGM1) deficiency. PGM1 catalyzes the interconversion of glucose 1-phosphate and glucose 6-phosphate and is involved in multiple important metabolic pathways including glycolysis, glycogenolysis, glycogenesis, and N-linked glycosylation.3,6

PGM1-CDG encompasses a wide range of phenotypes and has multisystemic involvement. Interestingly, genotype and enzyme activity are not entirely correlated with severity of disease.6 This is hypothesized to be due to differences in compensatory activation of phosphoglucomutase-2 (PGM2). The most common features are rhabdomyolysis, increased transaminases, hypoglycemia, and hematologic abnormalities that are both pro- and anti-thrombotic (antithrombin III, factors XI, VII, IX, X, and XI deficiencies low proteins C and S), which are present in over 50% of cases.3 Patients may also have congenital malformations including cleft palate, bifid uvula, anal atresia, vertebral malformations, and Pierre Robin sequence.3,6 Other features include developmental delays and intellectual disability, dilated cardiomyopathy, exercise intolerance, myopathy, strabismus, and malignant hyperthermia.3 Features present in this patient were a history of hypoglycemia as a neonate, developmental delay, hepatopathy, dilated cardiomyopathy, low antithrombin III activity, protein C deficiency, , and subtle dysmorphic features including a small chin and high-arched palate. Although patients with PGM1-CDG have multiple risk factors for CAIS due to cardiac and hematologic abnormalities, stroke has not been previously reported in this population.

PGM1-CDG is one of the few congenital disorders of glycosylation that has an accepted treatment.3 Enteral D-galactose supplementation improves the biochemical profile of patients with PGM1-CDG, including correction of hematologic pro and anti-thrombotic abnormalities3. D-galactose restores glycosylation by replenishing nucleotide sugar pools UDP-glucose and UDP-galactose necessary for ER-linked glycosylation and Golgi-linked glycosylation, respectively. It can take weeks to months for biochemical treatment efficacy to occur.7 Importantly, D-galactose therapy can correct coagulopathies and thereby likely decrease the risk of future thrombotic events. However, D-galactose therapy has not been proven to be efficacious in treating cardiomyopathy.8

There are multiple other metabolic disorders that are associated with increased risk for ischemic stroke. Homocystinuria and methylenetetrahydrofolate reductase (MTHFR) deficiency both result in hyperhomocysteinemia, which is prothrombotic.2 Fabry disease is most often associated with subtle white matter lesions that accrue gradually over time due to progressive

accumulation of globosotriaosylceramide in endothelial and vascular smooth muscle cells.2,9 However, globosotriaosylceramide accumulation can also result in abnormalities in larger vessels, predisposing patients to artery-to-artery embolization events. Patients with Fabry disease can also have cardiac valve disease, left ventricular hypertrophy, arrhythmias, and hypertension, increasing risk for cardioembolic strokes.9 Similarly, ischemic stroke has been reported rarely in patients with Pompe disease (another glycogen storage disease), both due to intracranial artery abnormalities such as aneurysms and dilative arteriopathy, and cardiac disease.10,11

This case highlights the importance of integrating clinical history (e.g., history of neonatal hypoglycemia and speech delay, and family history) with abnormalities on the CAIS work-up (e.g., cardiomyopathy, coagulopathies). Though rare, children with metabolic diseases can have CAIS rather than "metabolic strokes" due to energy failure. Careful attention to case details can lead to additional work-up for such metabolic diseases. Any child with cardioembolic CAIS due to a dilated cardiomyopathy should be considered for additional metabolic and mitochondrial testing.

Key points:

1. Providers should have high index of suspicion for stroke in all pediatric patients with focal deficits, no matter how subtle. Irritability and crying could be a sign of frustration due to aphasia in very young patients.

2. Cardiac disease and hypercoagulable state are both common risk factors for stroke in pediatric patients. In most cases, further investigation may be warranted to determine the cause of these abnormalities.

3. Metabolic disease is traditionally associated with “metabolic stroke”; however, some metabolic diseases also increase risk for CAIS due to cardiomyopathy and/or coagulopathies.

4. Patients with PGM1-CDG are at risk for CAIS due to both heart failure and coagulopathies. Coagulopathy may be mitigated with D-galactose treatment, but cardiomyopathy may persist despite improvements in the biochemical profile. Patients with CAIS due to PGM1-CDG may require long-term antithrombotic medications.

References:

1. MacKay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA, Ganesan V. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. Ann Neurol. 2011;69(1):130-140. doi:10.1002/ANA.22224

2. Tabarki B, Hakami W, Alkhuraish N, Graies-Tlili K, Nashabat M, Alfadhel M. Inherited Metabolic Causes of Stroke in Children: Mechanisms, Types, and Management. Front Neurol. 2021;12. doi:10.3389/FNEUR.2021.633119

3. Altassan R, Radenkovic S, Edmondson AC, et al. International consensus guidelines for phosphoglucomutase 1 deficiency (PGM1-CDG): Diagnosis, follow-up, and management. J Inherit Metab Dis. 2021;44(1):148-163. doi:10.1002/JIMD.12286

4. Ichord RN, Bastian R, Abraham L, et al. Interrater reliability of the Pediatric National Institutes of Health Stroke Scale (PedNIHSS) in a multicenter study. Stroke. 2011;42(3):613-617. doi:10.1161/STROKEAHA.110.607192

5. DeVeber GA, MacGregor D, Curtis R, Mayank S. Neurologic outcome in survivors of childhood arterial ischemic stroke and sinovenous thrombosis. J Child Neurol. 2000;15(5):316-324. doi:10.1177/088307380001500508

6. Yan-Wai Wong S, Beamer LJ, Gadomski T, et al. Defining the Phenotype and Assessing Severity in Phosphoglucomutase-1 Deficiency. J Pediatr. 2016;175:130-136.e8. doi:10.1016/j.jpeds.2016.04.021

7. Radenkovic S, Bird MJ, Emmerzaal TL, et al. The Metabolic Map into the Pathomechanism and Treatment of PGM1-CDG. Am J Hum Genet. 2019;104(5):835-846. doi:10.1016/J.AJHG.2019.03.003

8. Donoghue SE, White SM, Tan TY, Kowalski R, Morava E, Yaplito-Lee J. Galactose treatment of a PGM1 patient presenting with restrictive cardiomyopathy. JIMD Rep. 2020;57(1):29-37. doi:10.1002/JMD2.12177

9. Testai FD, Gorelick PB. Inherited metabolic disorders and stroke part 1: Fabry disease and mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes. Arch Neurol. 2010;67(1):19-24. doi:10.1001/ARCHNEUROL.2009.309

10. Montagnese F, Granata F, Musumeci O, et al. Intracranial arterial abnormalities in patients with late onset Pompe disease (LOPD). J Inherit Metab Dis. 2016;39(3):391-398. doi:10.1007/S10545-015-9913-X

11. Quenardelle V, Bataillard M, Bazin D, Lannes B, Wolff V, Echaniz-Laguna A. Pompe disease presenting as an isolated generalized dilative arteriopathy with repeated brain and kidney infarcts. J Neurol. 2015;262(2):473-475. doi:10.1007/S00415-014-7582-6/METRICS

Figure 1. DWI (A), ADC (B), and CTA (C) showing acute left MCA infarct with occlusive thrombus in left M1 segment (red arrow).

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