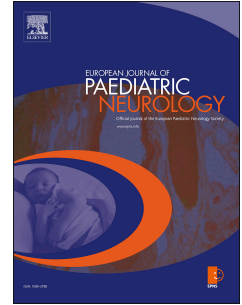


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Transient regional cerebral hypoperfusion during a paroxysmal hemiplegic event in GLUT1 deficiency syndrome

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Title: Transient regional cerebral hypoperfusion during a paroxysmal hemiplegic event in GLUT1 deficiency syndrome

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Abstract:

GLUT1 deficiency syndrome (GLUT1DS) is a well described neurometabolic disorder that results from impaired glucose transport into the central nervous system. GLUT1DS classically presents with infantile-onset epilepsy, progressive microcephaly, developmental delay, ataxia, dystonia, and spasticity, but a minority of patients may manifest with paroxysmal non-epileptic phenomena including hemiparesis (Wang et al., 2002). We report for the first time cerebral perfusion changes during an acute episode of hemiparesis in a 9 year old child with GLUT1DS. The patient presented as a code stroke with her second episode of acute-onset left hemiparesis and altered mental status. Emergency MRI of brain demonstrated normal diffusion-weighted imaging, but arterial spin label perfusion weighted imaging (ASL-PWI) showed regional hypoperfusion of the right cerebral hemisphere and magnetic resonance angiography (MRA) revealed distally restricted flow related enhancement in the right MCA. The patient's deficits resolved entirely within several hours from onset. Repeat MRI one month later was normal. Our

report suggests that GLUT1DS-related hemiplegic events are associated with transient lateralized cerebrovascular hypoperfusion similar to that described in hemiplegic migraine and other pediatric stroke mimics. The underlying pathophysiology for this phenomenon in GLUT1DS is not known, but may relate to cortical energy failure or abnormal cerebral microvasculature.

Keywords:

GLUT-1 deficiency, hemiplegia

1.0 Introduction

GLUT 1 deficiency syndrome (GLUT1DS) is a genetic disorder resulting in impaired glucose transport across the blood-brain barrier. It is caused by heterozygous pathogenic variants in the SLC2A1 gene; 90% of cases occur *de novo*. Commonly, this condition manifests as infantile-onset epilepsy, progressive microcephaly, global developmental delay, spasticity, dystonia, and ataxia (De Vivo et al., 1991). In approximately 10% of cases, GLUT1DS presents with a non-epileptic phenotype associated with a paroxysmal motor disorder, classically exercise-induced dystonia or hemiparesis (Schneider et al., 2009). The disorder can be treated with the ketogenic diet. Cerebrovascular changes during an acute hemiplegic event in GLUT1DS have not been previously described. We report for the first time regional cerebral hypoperfusion during a paroxysmal hemiplegic event in a 9 year old child with GLUT1DS.

2.0 Case Study

The subject is a 9-year-old female with genetically confirmed GLUT1DS. She was born at term without complication. At the age of five months, she developed head bobbing episodes and her development plateaued. Following her first tonic-clonic seizure at 16 months, prolonged video EEG demonstrated that her recurrent head drops were also seizures. She was initially treated with levetiracetam, but this was discontinued due to behavioral side effects. Sodium valproate was effective in controlling her seizures, and she remained seizure-free until she broke through at 6 years of age, when her dose was lowered in an attempt to wean her off. She was subsequently started on zonisamide, which is the only anticonvulsant she remains on to date, and has remained seizure-free since.

Her diagnostic evaluation included normal acylcarnitine profile, plasma amino acid, urine organic acid, urine acylglycine, and chromosomal oligo-microarray. An Epilepsy gene panel demonstrated a *de novo* heterozygous missense variant in the SLC2A1 gene, c.79G>A/p.Gly27Ser. This is a non-conservative amino acid substitution at a highly conserved location, and is not found in the gnomAD database. CSF glucose was not measured. A clinical diagnosis of GLUT1DS was made.

At the age of 6 years, the subject presented with an episode of altered mental status and acute left hemiparesis lasting approximately half a day. EEG demonstrated interictal 3 hz generalized spike and wave discharges, but no seizures. Brain MRI with MRA was performed when her deficits had resolved and was normal.

She was started on the ketogenic diet (2:1) at the age of 7 years to treat her underlying disorder, and has remained on it to date. Her baseline beta-hydroxybutyrate levels are generally in the range of 1-2 mmol/L. She has mild intellectual disability and ADHD.

At the age of 9 years, the subject presented with a second episode of altered mental status and acute-onset left sided hemiplegia involving face, arm and leg. She also reported headache and had several episodes of emesis. EMS was called and she was brought to a local hospital, where non-contrast head CT was normal. The patient was treated with 10mg of IV ketorolac, given a normal saline bolus, and then transferred to our hospital for further evaluation. On arrival at our institution approximately 3 hours after symptom onset, her deficits had resolved with a pedNIHSS score of 0. At this time, serum beta hydroxybutyrate level was 0.58 mmol/L, lower

than her typical levels. Blood glucose was 77 mg/dl. The patient and family denied any intentional non-adherence to her ketogenic diet. Brain MRI/MRA (Figure 1) demonstrated mild attenuation of the distal cortical right MCA branches with corresponding increase in oxygen extraction on susceptibility weighted imaging (SWI). ASL demonstrated decreased perfusion in the right hemisphere (delayed arterial transit, apparent cortical hypoperfusion). There were no diffusion abnormalities, or areas of abnormal T2 signal. The patient was discharged from the ED later that day. Repeat MRI/MRA brain one month later was normal (Figure 1).

3.0 Discussion

Various non-epileptic, paroxysmal events have been reported in patients with GLUT1DS, including exercise induced dystonia, paroxysmal non-kinesigenic dyskinesia, alternating hemiplegia of childhood, and hemiplegic migraine. A recent report described the EEG changes during an acute episode of reversible hemiparesis associated with confusion and aphasia in a GLUT1DS patient consisting of contralateral hemispheric slowing (Pellegrin et al., 2017). The neuroimaging correlate of acute hemiplegic phenomena in GLUT1DS has not been previously described.

We report for the first time transient imaging abnormalities during an acute episode of hemiplegia in a patient with GLUT1DS. Imaging in our patient demonstrated unilateral attenuation of distal cortical MCA branches on MRA, corresponding increase in oxygen extraction on susceptibility weighted imaging (SWI), and decreased hemispheric perfusion on ASL. There were no diffusion abnormalities, or areas of abnormal T2 signal. These abnormalities were not seen on repeat imaging one month later. These perfusion abnormalities are similar to those reported in patients with non-GLUT1DS associated hemiplegic migraine, and may suggest a common pathophysiology (Bosemani et al., 2014; Prodan, Holland, Lenaerts, & Park, 2002; Safier et al., 2014). Similar, transient perfusion abnormalities have also been recently reported in a pediatric cohort of otherwise healthy children presenting with acute, reversible stroke-like events. Imaging findings in the latter study included evidence of lobar or hemispheric hypoperfusion by susceptibility-weighted imaging and/or arterial spin-labeled perfusion imaging and presence of arterial pruning without occlusion on MRA. Subsequent imaging confirmed normalization of vascular and perfusion findings without infarction (Lehman et al., 2017).

The underlying pathophysiology for such episodes of transient neurological symptoms in association with focal cerebral hypoperfusion is not certain. In the context of hemiplegic migraine, cortical spreading depression and associated decrease in cerebral perfusion related to neurovascular coupling has been implicated. In the case of GLUT1DS, it is possible that cortical hypometabolism related to insufficient glucose supply in the CNS serves as the trigger for these episodes, with secondary decreased regional cerebral perfusion (related to neurovascular coupling). This is supported by the onset of symptoms in our patient in association with a loss of ketosis, our patient's primary source of energy for the CNS. Alternatively, the GLUT1 transporter is particularly abundant in cerebral vessel endothelial cells, and angiogenesis is highly reliant on glycolysis. This raises the possibility of whether failure of glucose metabolism in the CNS may result in abnormality of cerebral blood vessels or dysregulation of vasomotor tone that make these individuals more susceptible to episodes of transient vasospasm, wherein the hypoperfusion itself is the cause rather than effect of the neuronal dysfunction. A primary effect on cerebral vasculature is supported by the mouse SLC1A2 haploinsufficiency model, which demonstrates impaired angiogenesis and a profound diminution of brain microvasculature

resulting from impaired glycolysis and decreased levels of the vascular growth factor, Vegfr2 (Tang et al.,2017).

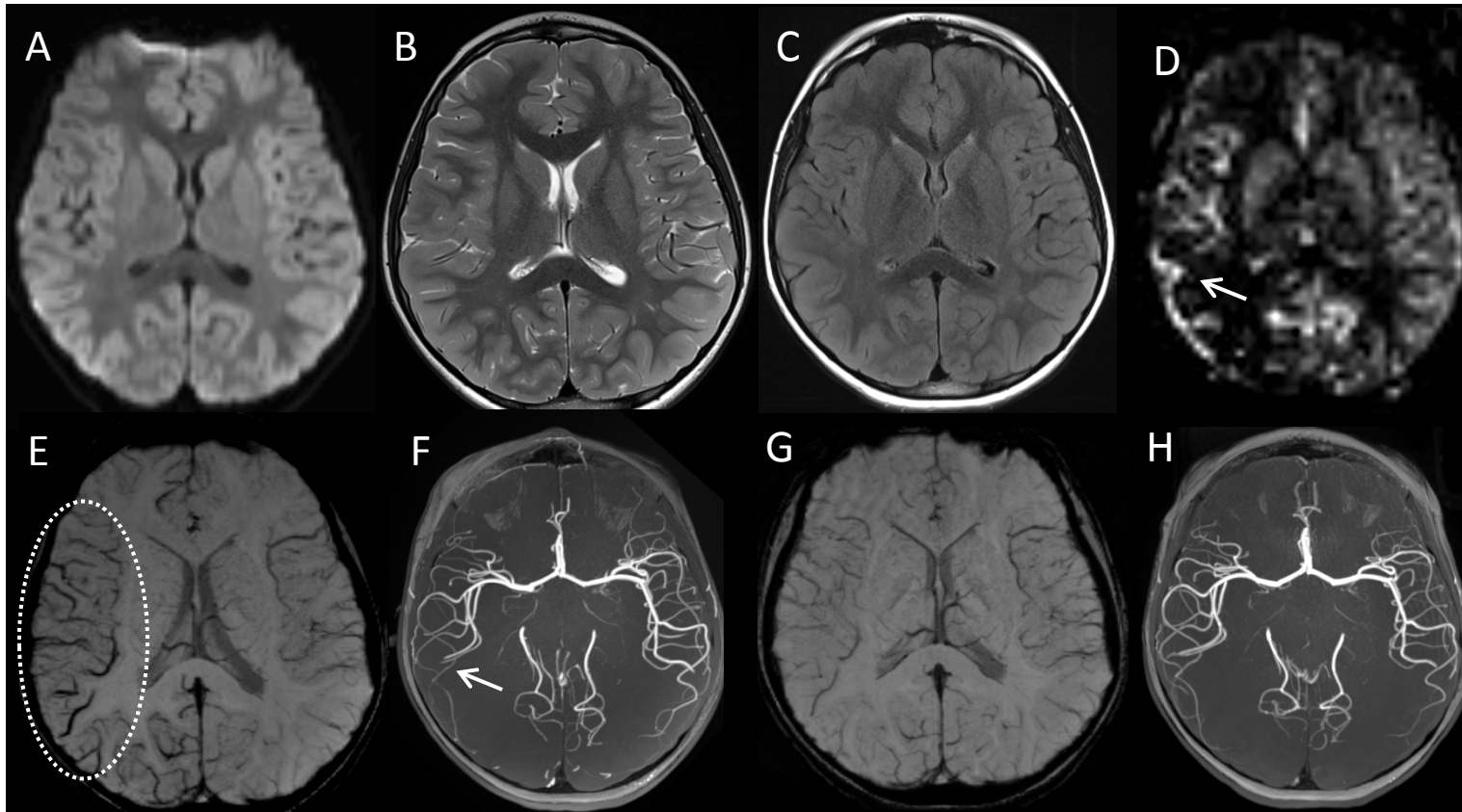
In conclusion, we report for the first time transient perfusion abnormalities associated with reversible neurological deficits in a patient with GLUT1DS. This imaging is reminiscent of the pattern seen in hemiplegic migraine, and in children with idiopathic transient focal neurological symptoms, suggesting a possible common pathophysiology. GLUT1DS should be added to the list of pediatric stroke mimics.

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Conflict of Interest

Dr. Mohammed Almuqbil declares no conflict of interest or competing interest.

Dr. Michael Rivkin declares no conflict of interest or competing interest.

Dr. Lance Rodan declares no conflict of interest or competing interest.

Dr. Edward yang served as a consultant for Corticometrics LLC which develops software for computer aided diagnosis of cortical.

Dr. Masanori Takeoka declares no conflict of interest or competing interest.