GLUT-1 deficiency presenting with a reversible leukoencephalopathy

Naila Ismayilova[1], Yael Hacohen[1], Andrew MacKinnon[2], Frances Elmslie[3], Antonia Clarke[1]

[1]Department of paediatric neurology, St. George's Hospital NHS Trust, London

[2]Department of Neuroradiology, Atkinson Morley Regional Neuroscience Centre, St. George's Hospital NHS Trust, London

[3]Department of medical genetics, St George's Hospital NHS Trust London

Running head: Leukoencephalopathy in GLUT1 deficiency

Word Count: 685

Title: 64 characters

References: 10; Figures: 1

Addresses for correspondence:

Dr Antonia Clarke

St George's Hospital. Blackshaw Road, Tooting, London SW17 0QT.

Antonia.Clarke@stgeorges.nhs.uk

+44 (0) 20 8672 2931

Introduction

Glucose transporter type 1(GLUT1) deficiency syndrome is a treatable genetic neurometabolic disorder due to a mutation in the GLUT1 (encoded by the SLC2A1 gene) which results in an impaired glucose transport across the blood-brain barrier with associated low cerebrospinal fluid glucose levels[1-3]. This syndrome was initially reported in infants with progressive encephalopathy, acquired microcephaly and drug-resistant epilepsy that can be treated with the ketogenic diet. Increase awareness and advance in genetic diagnoses resulted in expansion of the phenotype to include milder presentations with epilepsy, movement disorders, cognitive impairment which may occur in both in combination or isolation[2]. Conventional neuroimaging is uninformative in the majority of patients[2]. Here we describe a case of an infant with GLUT1 deficiency and extensive bilateral predominantly frontal white matter changes mimicking Alexander's disease. He improved both clinically and radiologically on the ketogenic diet.

Case

A 5-month old boy presented with a 2-week history of myoclonic jerks (up to 100 jerks a day) which occurred predominantly in the morning. He was the first child of healthy non-consanguineous Caucasian parents. There was no significant family history and he had an unremarkable antenatal, perinatal and postnatal history. His development at presentation was delayed. There were no concerns regarding his hearing and vision.

On examination, he was normocephalic (43.5 cms – 50th -75th centile) and had no dysmorphic features. He was only intermittently fixing and following. He had truncal hypotonia with significant head lag. Tone, power and reflexes in the limbs were normal. Electroencephalogram (EEG) revealed irregular generalised spike and slow wave epileptiform discharges on the background of multifocal spikes with no hypsarrhythmia. MRI brain showed a confluent symmetrical T2 hyperintense signal abnormality in both anterior frontal lobes involving periventricular, deep and juxtacortical white matter (Figure 1A). The myelination elsewhere was delayed with normal N-acetylaspartate and choline peaks. The myelination elsewhere was delayed. He was treated empirically with Pyridoxine and Biotin. Extensive neurometabolic and genetic screen revealed low CSF glucose of 1.2mmol/L, CSF/serum ratio 0.24 and a CSF lactate of 0.8mmol/L. *GFAP* mutation was negative. No other cause of his white matter disease was identified. A provisional diagnosis of GLUT1 deficiency was made. This was subsequently confirmed by finding a pathogenic *de novo* heterozygous mutation in *SLC2A1* (c.275+1G>A). Treatment with the ketogenic diet on a 2:1 ratio was commenced with a dramatic termination of seizures at 72 hours. Repeat imaging at the age of 11-months revealed significant resolution of the previously seen white matter changes; with age appropriate myelination and improvement in white matter bulk (Figure 1B). At 15-months, he continued to be seizure-free with marked developmental catch up although still delayed (level of 8-month old). He is maintained on the ketogenic diet.

Discussion

Identification of distinct white matter changes on MRI, typically suggests a diagnosis of a leukodystrophy or a genetic leukoencephalopathy. In the majority of these disorders no established treatment are available[6]. The neuroimaging finding in our case has made us look for an additional diagnosis such as Alexander's disease but the temporal improvement both clinically and developmentally on the Ketogenic diet and the reversibility of the radiological changes suggests that leukoencephalopathy was secondary to the GLUT1 deficiency.

Leukoencephalopathhy in association with GLUT1 deficiency was previously reported in one child[7]; as his scan was done following the initiation of the ketogenic diet, the MRI changes were attributed to the diet. The MRS was different to our case and where suggestive of demyelination and axonal loss with markedly lower N-acetylaspartate peak, higher choline peak, and slightly higher myo-Inositol and glutamate-glutamine peaks[7]. Milder white matter changes were also reported in 3.5 year old boy which were thought to represent delayed myelination[8]

Lack of glucose supply to the brain tissue could be the causative factor of the white matter changes seen in patients with GLUT-1 deficiency. Indeed multiple subcortical reversible white matter hyperintensities were reported in children with chronic hypoglycaemia such as glycogen storage

disease[9] and 3-hydroxy-3-methylglutaryl coenzyme A deficiency[10].

Taken together, GLUT1 deficiency should be considered in the differential diagnosis of infants with genetic leukoencephalopathies. Importantly as GLUT1 deficiency is treatable, early diagnosis and initiation of the ketogenic diet will result in significantly improved neurocognitive outcome.

Figure 1: Brain MRI (A) age 5-month, Axial T2 demonstrating confluent hyperintense signal abnormalities symmetrically in both anterior frontal lobes which involves the periventricular, deep and juxtacortical white matter with delayed myelinayion (B) Repeat imaging at 11month of age demonstrated resolution of the white matter changes, improvement in the white matter bulk and normal age appropriate myelination.

References:

1. De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. N Engl J Med 1991;325:703-709.
2. Pearson TS, Akman C, Hinton VJ, Engelstad K, De Vivo DC. Phenotypic spectrum of glucose transporter type 1 deficiency syndrome (Glut1 DS). Curr Neurol Neurosci Rep 2013;13:342.
3. Seidner G, Alvarez MG, Yeh JI, et al. GLUT-1 deficiency syndrome caused by haploinsufficiency of the blood-brain barrier hexose carrier. Nat Genet 1998;18:188-191.
4. Gordon N, Newton RW. Glucose transporter type1 (GLUT-1) deficiency. Brain Dev 2003;25:477-480.
5. Pascual JM, Van Heertum RL, Wang D, Engelstad K, De Vivo DC. Imaging the metabolic footprint of Glut1 deficiency on the brain. Ann Neurol 2002;52:458-464.
6. Parikh S, Bernard G, Leventer RJ, et al. A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephelopathies. Mol Genet Metab 2015;114:501-515.
7. Shiohama T, Fujii K, Takahashi S, Nakamura F, Kohno Y. Reversible white matter lesions during ketogenic diet therapy in glucose transporter 1 deficiency syndrome. Pediatr Neurol 2013;49:493-496.
8. Klepper J, Engelbrecht V, Scheffer H, van der Knaap MS, Fiedler A. GLUT1 deficiency with delayed myelination responding to ketogenic diet. Pediatr Neurol 2007;37:130-133.
9. Melis D, Parenti G, Della Casa R, et al. Brain damage in glycogen storage disease type I. J Pediatr 2004;144:637-642.
10. Zafeiriou DI, Vargiami E, Mayapetek E, Augoustidou-Savvopoulou P, Mitchell GA. 3-Hydroxy-3-methylglutaryl coenzyme a lyase deficiency with reversible white matter changes after treatment. Pediatr Neurol 2007;37:47-50.