HK J Paediatr (new series) 2017;**22**:46-49

Glucose Transporter Type 1 Deficiency Syndrome in a 4-year-old Chinese Boy

CK ***Chow***, SN ***Wong***, CK ***Ma*** , HM ***Luk***

Abstract Glucose transporter type 1 deficiency syndrome (GLUT-1 DS) is a rare neurological disease first described in 1991. We describe a four-year-old Chinese boy with GLUT-1 DS who presented with hypoglycorrhachia, developmental delay, clinical seizure and microcephaly. This diagnosis was arrived from array Comparative Genomic Hybridization (aCGH) which identified a heterozygous deletion of *SLC2A1* gene. We alert clinicians this relatively new entity, as well as the use of aCGH in unexplained neurological condition, as early recognition and treatment by ketogenic diet is critical to mitigate the progression of the disease.

Key words Glucose transporter type 1 deficiency syndrome; Hypoglycorrhachia, *SLC2A1*

Introduction

Glucose transporter type 1 deficiency syndrome (GLUT-1 DS) is a rare neurological disease first described in 1991, and increasing number of patients have been reported. As glucose is a vital fuel for the normal function and development of the brain, defective glucose transport causes various clinical manifestations. *SLC2A1* is the genetic defect causing this disease. Here, we describe a Chinese patient with confirmed GLUT-1 DS by genetic study, followed by a brief review of this topic.

Department of Paediatrics and Adolescent Medicine, United Christian Hospital, 130 Hip Wo Street, Kwun Tong, Kowloon, Hong Kong, China

CK **Chow**（周哲光） *MBBS(HK), MRCPCH*
SN **Wong**（王雪娜） *MBBS(HK), FHKAM(Paed)*
CK **Ma**（馬子軍） *MBChB, FHKAM(Paed)*

Clinical Genetic Service, Department of Health, Hong Kong, China

HM **Luk**（陸浩明） *MBBS(HK), FHKAM(Paed)*

Correspondence to: Dr CK **Chow**

Received November 1, 2015

Case Report

The patient was a four-year-old Chinese boy, who first presented to the Department of Paediatrics, United Christian Hospital, HKSAR in January 2011 for myoclonic jerk. He was born full term with a normal body weight, with unremarkable antenatal and postnatal course. Both parents were non-consanguineous and healthy, and he had an elder brother who had normal development all along. There was no family history of epilepsy or other neurological disease.

He was first noticed to have jerky movement, developmental delay and small head at three months of age in July 2010. The semiology was bilateral symmetrical myoclonic jerks occurred in multiple clusters per day, both in awake and sleep state, and was not particularly associated with fasting or exercise. There was no associated loss of consciousness or cyanosis. He did not have other movement disorders. He was just able to raise his head on prone position, but could not roll over; he could reach out and performed palmar grasp, but could not demonstrate transfer at nine months of age.

Physical examination showed that his head circumference was 41.5 cm at nine months of age, which was less than third percentile, while his body length

and weight were at 25th percentile. There were no neurocutanous stigmata, and Wood's lamp examination was negative. His four limbs muscle bulk and power were normal, but mild hypotonia was noted. The deep tendon reflexes were symmetrical and normal, and there was no clonus elicited. Ophthalmological examination did not reveal any evidence of tuberous sclerosis.

Initial blood and urine test did not point to a specific metabolic disorder, which included ammonia, lactate, plasma amino acid, carnitine profile, very long chain fatty acid and urine organic acid. Electroencephalogram (EEG) at nine months of age showed symmetrical background activities compatible with his age with bursts of synchronous sharp activities, no definite hypsarrhythmia was noted, no change was observed after injection of 100 mg pyridoxine intravenously. Magnetic resonance imaging of the brain showed mild delay in myelination pattern. In subsequent follow-up, option of lumbar puncture was offered to parents for neurological investigations, but they initially refused.

He was initially treated as myoclonic epilepsy and was started on sodium valproate. Seizure control was satisfactory after sodium valproate was stepped up to therapeutic dosage. However he was noted to have increased frequency of breakthrough seizure since 15 months of age, and was started on lamotrigine for better control. He was assessed to have delay in development, and was arranged special school, and there was all along no evidence of regression. At the age of four, he still had breakthrough seizure once every one to two months despite using two anticonvulsants. He could only walk a few steps with support, demonstrated inferior pincer grip, spoke a few single words and understood simple one step command.

Owning to non-specific clinical presentation, molecular cytogenetic technique is used for analysis. Array Comparative Genomic Hybridization (aCGH) using CGXTM V1.0 8-plex array platform was performed which showed arr[hg19] 1p34.2p34.1(43,108,058-45,074,819)x1. That means there is a heterozygous deletion of chromosome 1p34.1 to 1p34.2 region with a size of at least 1.97Mb that encompassed the entire *SLC2A1* gene. Parental study showed this deletion was de novo (Figure 1).

Lumbar puncture was done and showed normal cerebrospinal fluid cell (CSF) counts and negative cultures. CSF glucose was 1.5 mmol/L, protein was 115 mg/L and lactate was 1.22 mmol/L. The paired serum glucose level was 4.2 mmol/L, calculated CSF to serum glucose ratio was 0.36.

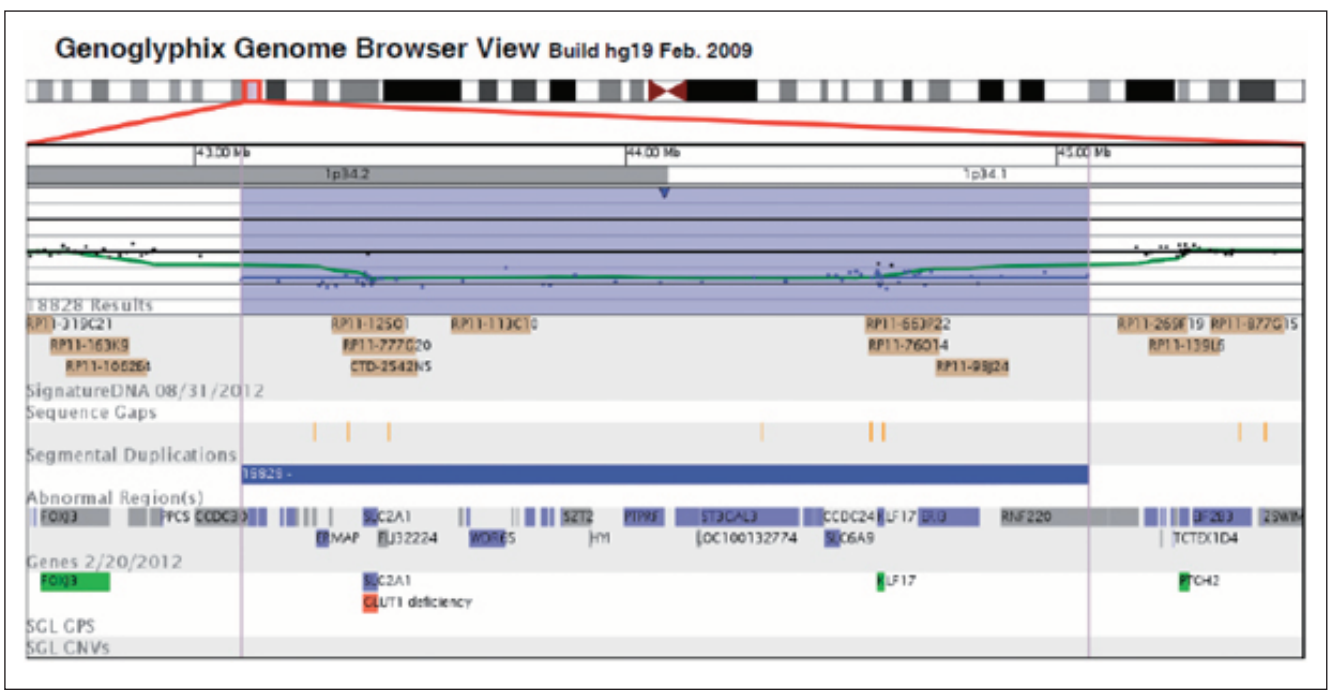

Figure 1 aCGH in this patient showed 1.97Mb heterozygous deletion in 1p34.1 to 1p34.2 region that encompassed the entire *SLC2A1* gene.

He was subsequently started on ketogenic diet after the diagnosis of GLUT-1 DS was made, all anticonvulsants were weaned off in one year's time without any further seizure, and he was making slow progress in his development.

Discussion

We report a Chinese boy with typical biochemical, clinical and genetic features of GLUT-1 DS. He had normal perinatal course to start with, but later developed developmental delay, clinical seizure which was fairly controllable with anticonvulsants, and microcephaly. CSF study showed hypoglycorrhachia in the setting of normoglycaemia, and CSF lactate level was normal. The final diagnosis was reached by using aCGH demonstrating heterozygous deletion of *SLC2A1* gene.

A continuous supply of glucose to the brain is vital to its normal function and development. Various glucose transporters have been identified in the past decades for transport of glucose across the blood brain barrier to neurons and glia. The primary isoforms in the brain include GLUT-1, 3 and 5.[1] GLUT-1 DS is also known as De Vivo disease. In 1991, De Vivo et al described two cases of persistent hypoglycorrhachia, seizure and developmental delay, and he attributed to defective glucose transport across the blood-brain barrier.[2]

Hypoglycorrhachia is the hallmark of the disease, which is persistent on repeated lumbar puncture test and in the setting of normoglycaemia. A systemic review determined the value of CSF analysis in workup of GLUT-1 DS, and concluded that this can be used as a reliable biomarker for this disease.[3] A typical CSF profile for GLUT-1 DS is to take CSF glucose and lactate less than 10th percentile, and CSF to serum glucose ratio less than 25th percentile. For his age, the 10th percentile of CSF glucose and lactate are 2.6 mmol/L and 1.2 mmol/L respectively, and 25th percentile of CSF to serum glucose ratio is 0.56,[3] so the biochemical profile is typical of GLUT-1 DS in our patient.

The classical phenotype of GLUT-1 DS usually involves infant-onset hypotonia and seizure poorly responsive to anticonvulsants. Seizure types reported include generalised tonic and/or clonic, absence, partial, myoclonic, and astatic.[4] A spectrum of movement disorders was also described, with the most frequent gait abnormalities being ataxic-spastic and ataxic. Action limb dystonia, chorea, cerebellar action tremor, myoclonus and dyspraxia were also reported.[5] Therefore there are a wide variation of phenotypes reported in this disease, which are not evident in our patient.

EEG features of GLUT-1 DS are non-specific. A normal interictal EEG is found in most of the children affected.[4] Non-specific changes such as focal slowing and epileptiform discharges were also reported. Neuroimaging is also considered non-specific, a case with delayed myelination in a child with GLUT-1 DS is reported, but it can be a finding seen in children with developmental delay.[6]

To reach the final diagnosis in this case, genetic study plays an important role. The gene encoding GLUT-1 is "solute carrier family 2, facilitated glucose transporter member 1" (*SLC2A1*) located on the first chromosome. Approximately 90% of mutation-positive GLUT-1 DS is due to sequence variant in *SLC2A1* gene, and 10% is due to deletion of duplication in the coding exon just like in our case.[7] The use of aCGH in this case demonstrated heterozygous deletion of chromosome 1p34.1 to 1p34.2 region with a size of at least 1.97Mb. *SLC2A1* is the only one important gene encoded in this region, while the function of other genes in this region are currently unknown, deletion of those are not reported to be associated with specific human phenotype. GLUT-1 DS is an autosomal dominant disease, so demonstration of deletion in this case by aCGH can already confirm the diagnosis. Concerning the genotype-phenotype correlation, it is reported that deletional type mutation has severe phenotype in term of epilepsy and intellectual disability as compared with other mutational type.[7]

The use of chromosomal microarray (CMA) in unexplained developmental delay is gaining popularity, and it can offer a much higher diagnostic yield (15-20%), compared with G-banded karyotype (around 3%). It is now recommended to offer CMA as the first-tier genetic test for patients with unexplained developmental delay.[8] However, CMA still has its limitation, as balanced rearrangements and low-level mosaicism are not uniformly detectable by CMA. Therefore, clinical judgement is important when arranging and interpreting these genetic results.

However, some patients with classical clinical and biochemical picture may have negative genetic findings. De Vivo et al also studied the decreased erythrocyte 3-O-methylglucose (3-OMG) uptake when he described the first cases of GLUT-1 DS.[2] Later studies showed that erythrocyte 3-OMG uptake assay can be considered as a functional test for GLUT-1 DS.[9,10] However, this has still not translate to wide based clinical use, and may be reserved for those with mutation-negative disease.

The mainstay of treatment is ketogenic diet, which involves high-fat, low-carbohydrate diet, aiming to provide

alternative fuel to the brain. Significant improvement has been demonstrated in various studies and case reports.[2,10]

Early recognition of GLUT-1 DS is important for early commencement of treatment, which will halt the progression of the disease. Clinicians should be aware that this disease can have a wide variation in phenotype, patient with intractable epilepsy and/or developmental delay should have an early lumbar puncture done, and those with unexplained persistent hypoglycorrhachia may be indicative of this disease. In addition, the use of CMA becomes the first tier test in unexplained developmental delay, and in some case this can result in significant improvement in the management of patients.

Declaration of Interest

All the authors report no conflicts of interest.

References

1. Vannucci SJ, Maher F, Simpson IA. Glucose transporter proteins in brain: delivery of glucose to neurons and glia. Glia 1997;21: 2-21
2. 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;325:703-9.
3. Leen WG, Wevers RA, Kamsteeg EJ, Scheffer H, Verbeek MM, Willemsen MA. Cerebrospinal fluid analysis in the workup of GLUT1 deficiency syndrome: a systematic review. JAMA Neurol 2013;70:1440-4
4. Leary LD, Wang D, Nordli DR Jr, Engelstad K, De Vivo DC. Seizure characterization and electroencephalographic features in Glut-1 deficiency syndrome. Epilepsia 2003;44:701-7
5. Pons R, Collins A, Rotstein M, Engelstad K, De Vivo DC. The spectrum of movement disorders in Glut-1 deficiency. Mov Disord 2010;25:275-81.
6. Klepper J, Engelbrecht V, Scheffer H, van der Knaap MS, Fiedler A. GLUT1 deficiency with delayed myelination responding to ketogenic diet. Pediatr Neurol 2007;37:130-3.
7. Leen WG, Klepper J, Verbeek MM, Leferink M, Hofste T, van Engelen BG, et. al. Glucose transporter-1 deficiency syndrome: the expanding clinical and genetic spectrum of a treatable disorder. Brain 2010;133(Pt 3):655-70.
8. Miller DT, Adam MP, Aradhya S, Biesecker LG, Brothman AR, Carter NP, et. al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010;86:749-64.
9. Yang H, Wang D, Engelstad K, Bagay L, Wei Y, Rotstein M, et. al. Glut1 deficiency syndrome and erythrocyte glucose uptake assay. Ann Neurol 2011;70:996-1005.
10. De Giorgis V, Veggiotti P. GLUT1 deficiency syndrome 2013: current state of the art. Seizure 2013;22:803-11.