Case Report

Early infantile epileptic encephalopathy: unique characteristics on brain MRI leading towards diagnosis of *SLC13A5* gene mutation. Case report and literature review

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Keywords

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Abstract

Developmental and epileptic encephalopathy (DEE) is a severe epileptic condition characterized by frequent, drug-resistant seizures and developmental delay with onset in infancy. The aetiology is diverse but genetic causes are mostly discovered. Clinically it is a variable condition with different degrees of psychomotor and/or cognitive delay. One type of infantile epilepsy is believed to be caused by a biallelic mutation in the *SLC13A5* gene, which codes for a cytoplasmic sodium-dependent citrate carrier that is primarily expressed in neurons. The gene mutation has been recognised in infants with punctate white matter lesions on brain magnetic resonance imaging (MRI) who do not have a history of hypoxic-ischemic encephalopathy.

We present a case of a full-term baby girl who had repeated seizures and encephalopathy starting on the first day of life. Diagnostic work-up revealed no infectious cause and metabolic testing was normal. Several small punctate white matter lesions were discovered on brain MRI, leading to a genetic mutation that causes DEE. A homozygous mutation in *SLC13A5* was confirmed by genetic testing.

The characteristic MRI pattern in our case offered a clue to the diagnosis of the refractory neonatal seizures. The pathophysiology of the *SLC13A5* gene mutation is not well understood, and therapeutic options have not been thoroughly investigated.

Introduction

Neonatal seizures are a common issue on the neonatal ward (1-5 per 1000 new-borns) with a variety of clinical and etiological causes: hypoxic-ischemic encephalopathy, stroke or haemorrhage, infections, cortical malformations, errors of metabolism and genetic etiologies (table 1) (1-3). Because of the immature brain, several seizures are subclinical or non-specific and so are mostly electrographic-only seizures (3, 4). Amplitude-integrated electroencephalogram (aEEG) plays a crucial role in classification of seizures as the new International League Against Epilepsy (ILAE) seizure classification proposes (electro-clinical or electrographic only), and is crucial for therapy and prognosis (3).

Next generation sequencing (NGS) has been a significant advance in the study of genetic causes of neonatal epilepsy and early-onset epileptic encephalopathies in recent years. While more epileptic encephalopathies are being linked to a genetic cause, therapeutic options remain restricted. This case report shows how a combination of clinical features and unique characteristics on neuro-imaging can lead to targeted genetic testing. An analysis of the literature was conducted on the few existing studies on developmental and epileptic encephalopathy (DEE) caused by a *SLC13A5* gene mutation.

Case report

We report a full-term baby girl born by vacuum extraction and having a good start with Apgar scores of 9 and 10 at 1 and 5 minutes and normal cord blood gases. She developed seizures one hour postpartum, beginning with cyanotic, 30-second tonic focal seizures and progressing to generalized repeated clonic seizures. The seizures were of similar nature. Parents were not consanguineous. Biochemical tests showed normal glucose and electrolytes. She was transferred to the University hospital's neonatal intensive care unit for neurological evaluation. On clinical neurological examination, there was some agitation, axial hypotonia, normal tendon reflexes, no other abnormalities and no facial dysmorphism. Several antiepileptic drugs were given. The seizures stopped only with continuous midazolam. Due to insufficient respiratory drive as a side effect of midazolam, intubation was required. She was diagnosed with epileptic encephalopathy as a result of refractory epilepsy with clinical seizures confirmed with continuous aEEG. A ketogenic diet was started with initial success, but when the antiepileptic drug doses were reduced, the seizures returned. They were unresponsive to high doses of antiepileptic drugs. Figure 1 depicts a summary of the therapy. Blood, urine and liquor samples, as well as imaging, revealed no infectious cause. We conducted an thorough neurometabolic work-up. Normal ammonia, normal lactate (serum and cerebrospinal fluid), normal urinary organic acids and plasma aminoacids, and normal acylcarnitines were found, ruling out nonketotic hyperglycinemia, serine biosynthesis disorder, GLUT1 deficiency, and pyridoxine-dependent epilepsy. Several small punctate white matter lesions were seen on MRI imaging at day 2 (figure 2), which led to the differential diagnosis of *SLC13A5* gene mutation, a genetic cause of the epilepsy. A whole genome sequencing (WES) ID panel confirmed this two weeks later: homozygous *SLC13A5*:c.680C>T, p.(Thr227Met). Both parents are carriers of this autosomal recessive gene mutation. A homozygosity mapping of the parents was not performed.

Due to the poor prognosis with therapy resistant seizures, it was decided by the team in consultation with the parents to discontinue intensive care treatment and start a palliative process. She died 21 days after birth.

Discussion and literature review

Gene mutations may cause early onset epileptic disorders in the neonatal period, which are clinically and aetiologically heterogeneous. Ohtahara syndrome (OMIM #308350), early myoclonic epilepsy, malignant migration par-

Table 1: Causes of neonatal seizures / Differential diagnosis (1, 2)

Cause	Example	Incidence	Term	Preterm
Primary intracranial origin				
Hypoxic-ischemic encephalopathy		37-60%	+++	
Vascular	- Intracranial haemorrhage	5-18%	+	+++
	- Infarction, stroke	6-15%	+++	++
Infectious	Meningitis, encephalitis, congenital infection	5-15%	+++	++
Brain malformations	Cerebral dysgenesis, migration disorders, malformation	5-17%	++	+
Trauma		Unknown		
Systemic / other origin				
Metabolic				
- Inborn errors of metabolism	- Disorder in metabolism of amino acids, urea cycles, purines	1-4%	++	+
	- Vitamin sensitive disorders			
	- Peroxisomal disorders and mitochondrial disorders			
	Hypoglycaemia, hypocalcaemia, hypo- or hypernatremia, hypomagnesaemia, hyperammonaemia by urea cycle disorder			
- Acute: electrolyte imbalance		1-5%	?	?
Genetic				
- Benign epilepsy syndrome		Unknown (1%)	?	?
- Malignant epilepsy syndrome		Unknown (1%)		
			?	?
Toxicity / Withdrawal		Sporadic (4%)	++	+

Table 2: Mutations and MRI features in different families (7, 8)

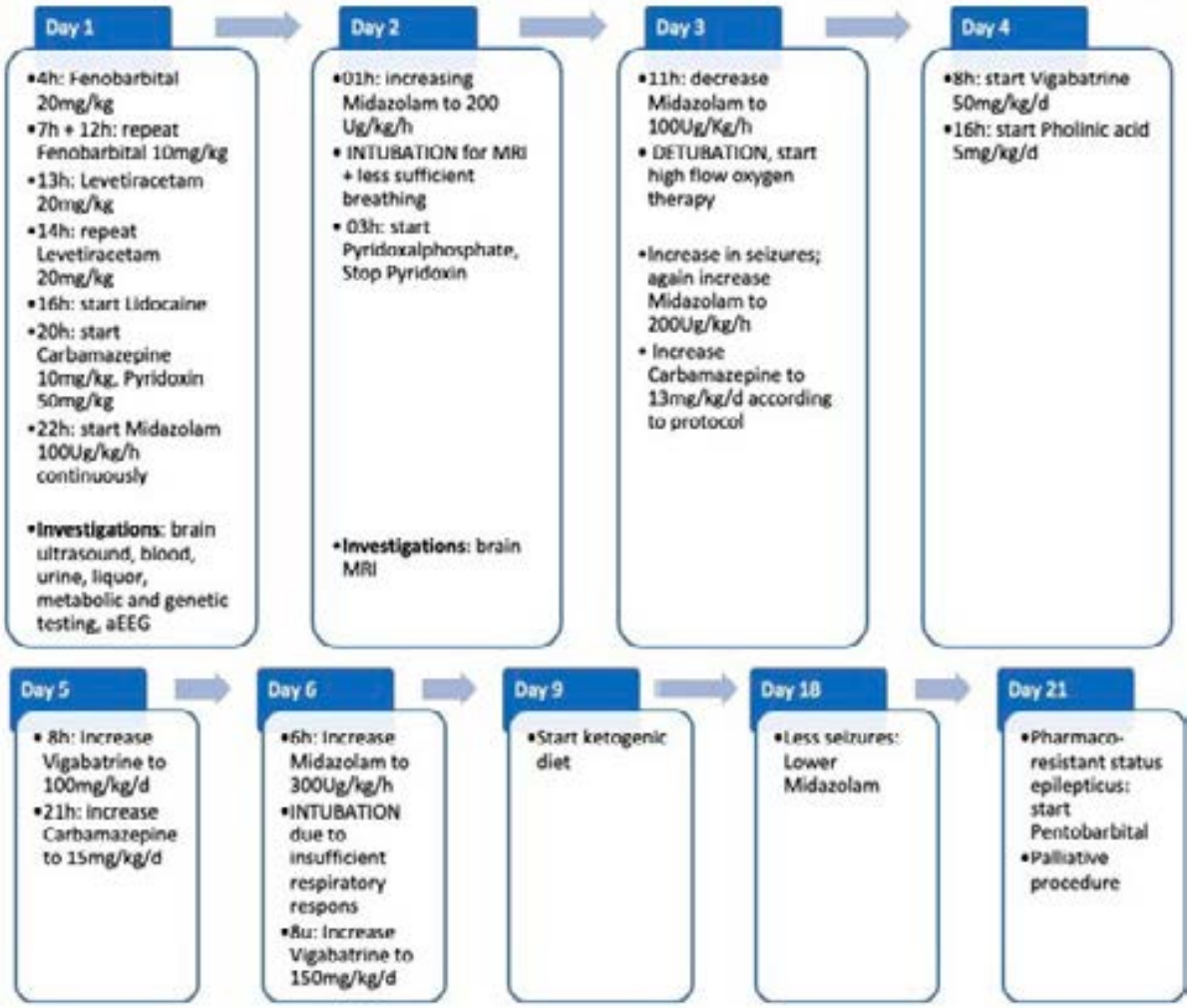
	Family 1	Family 2	Family 3	Family 4	Family 5	Family 6
Number of patients	2	2	2	1	2	1
Mutations	c.1280C>T p.(Ser427Leu) homozygous	c.655G>A p.(Gly219Arg) and c.1280C>T p.(Ser427Leu)	c.1280C>T p.(Ser427Leu) homozygous	c.680C>T p.(Thr227Met) and c.1280C>T p.(Ser427Leu)	c.655G>A p.(Gly219Arg) homozygous	c.680C>T p.(Thr227Met) and c.1570G>C p.(Asp524His)
MRI results	Both patients: PWML	Both patients: Extensive bilateral PWML	-Patient 1. Extensive bilateral PWML, lactate peak -Patient 2. No abnormalities	Multiple bilateral PWML, small lactate peak	-Patient 1. Extensive bilateral PWML -Patient 2. Five small PWML bilateral	Three small PWML bilateral
Follow-up imaging	-	White matter loss, delayed myelination and gliosis	Delayed myelination and gliosis, white matter loss	-	-	No abnormalities
Reference	Hardies et al	Weeke et al	Weeke et al	Weeke et al	Weeke et al	Weeke et al

tial seizures (*KCNQ2*, *KCNT1* gene mutations), West syndrome and Dravet syndrome (*SCN1A* gene mutation, OMIM #607208) are the most well-known developmental and epileptic encephalopathies (5). With the development of new diagnostic tools such as massive parallel sequencing, a new technique in next generation sequencing, the number of pathogenic gene mutations causing monogenic epileptic syndromes is increasing. The most common mutations can now be tested using targeted gene panels.

Early-onset epileptic encephalopathy is linked to *SLC13A5* mutations, which include homozygous or compound heterozygous mutations on chromosome 17 (6). Developmental and epileptic encephalopathy type 25 (OMIM #615905) is another name for this autosomal recessive disorder. The mutation is described in 32 patients from 16 unrelated families (6-8). *SLC13A5* encodes a high affinity homodimeric cytoplasmic sodium-coupled tricarboxylate transporter expressed on hepatocytes, neurons, spermatozoa and teeth (9). Citrate transporter function is either absent or decreased when the gene is mutated (6, 8, 10). Citrate is required for cellular metabolism (energy production) and neurotransmitter synthesis (e.g. glutamate) (6). Since the molecular mechanism of the transporter in neurons is largely unknown, the pathogenesis of neuronal dysfunction and epilepsy in this mutation is still poorly understood (9). In animal models, loss of function in this transporter does not result in the same neurological phenotype as in humans, making research difficult (9, 11). The disease phenotype is complex, but is characterised by drug-resistant neonatal or infantile onset seizures in the first days to months, global developmental delay (communication and motor skills) and teeth hypoplasia or hypodontia (amelogenesis imperfecta) (6, 7, 10, 11).

Multifocal and focal discharges, rhythmic theta/delta focal discharges from

Figure 1 : *Timeline of investigations and therapy in the patient*



both hemispheres or multifocal status epilepticus, and a continuous or discontinuous low voltage background activity are all seen on electroencephalograms (6-8). Medical characteristics and genetic confirmation are used to make the diagnosis (WES or targeted panel sequencing).

Biochemical tests are usually normal, with a slight increase of citrate in the serum and/or cerebrospinal fluid on occasion (11). The results of neuroimaging may be normal or show a distinct MRI pattern on T2-weighted imaging with punctate white matter lesions (PWML) (7, 8). The lesions are not seen on diffusion-weighted images (DWI) or susceptibility-weighted imaging (SWI). Hardies et al. found periventricular leukomalacia-like abnormalities (7). Weeke et al. discovered these lesions at neonatal age in six out of seven full-term infants without a history of hypoxic-ischemic encephalopathy receiving MRI, who progressed in some patients to gliotic scarring by the age of 18 months (table 2) (8). This supports the theory that these patients are more vulnerable to ischemia (7, 8). Since the PWML seen in this study is less severe than cystic periventricular leukomalacia or hypoxic-ischemic encephalopathy, no connection can be drawn between PWML and severe cognitive impairment in patients with *SLC13A5* mutations (8). A few patients had an increase in lactate demonstrated with magnetic resonance (MR) spectroscopy (7). Our patient did not receive MR spectroscopy. A summary of the different MRI results in literature are listed in table 2.

We saw the clinical hallmark of early-onset seizures leading to epileptic encephalopathy and drug therapy resistance in our patient. MR imaging during the diagnostic process revealed white matter lesions similar to those described in this genetic syndrome. In addition to studying 1200 other genes linked to epileptic encephalopathy, *SLC13A5* was given top priority in genetic testing.

SLC13A5 mutations actually do not have a precision treatment (9). The most popular antiepileptic medications are phenobarbital and valproic acid, the last one is not suitable for neonates, which have varying degrees of effectiveness. GABA altering medications (e.g. lorazepam, diazepam), sodium channel inhibitors (e.g. phenytoin, lamotrigine), acetazolamide and stiripentol, according to some anecdotal evidence, may be effective in treating seizures caused by loss-of-function mutation (12). The ketogenic diet has been suggested to be beneficial because it raises citrate levels (7, 10, 13). However a study of Klotz et al. also found an exacerbations of seizures during ketogenic treatment, so it's effect is controversial (12). There is currently no therapeutic option that can put the epileptic symptoms caused by this genetic disorder into remission.

There is still a lot to learn about this disorder, and more research is needed, such as comparing imaging (MRI) to identify potential subtle brain defects characteristic in a type of DEE and tailored therapies for therapeutic purposes.

Conclusion

The initiation of refractory seizures in early infancy as consequence of DEE is associated with impaired cognitive developmental delay and motor growth. Most early onset developmental and epileptic encephalopathy are genetic, combined genetic-metabolic or combined genetic-structural.

The *SLC13A5* mutation associated with DEE is only described in a few stud-

ies. It has a phenotypic heterogeneity, with a delayed neurological outcome ranging from moderate to severe and no targeted treatment choice. The presence of PWML on brain MRI scans may serve as a diagnostic clue. More genetic testing will lead to the discovery of further genetic mutations that cause DEE.

Conflict of interest statement

The authors of this case report declare that they have no conflict of interest. They do not have any affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter or materials discussed in this case report.

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Figure 2 : *MRI images with abnormalities on T2-weighted imaging*
Several millimetric punctiform white matter lesions seen as low signal intensity in the supratentorial white matter, especially in the deep and subcortical white mater, bilateral frontal and parietal seen on T2-weighted sequencing.