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RESEARCH NOTE

SCN2A mutation in an infant with Ohtahara syndrome and neuroimaging findings: expanding the phenotype of neuronal migration disorders

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Abstract. Neuronal migration disorders (NMDs) are a heterogeneous group of conditions caused by the abnormal migration of neuroblasts in the developing brain and nervous system, resulting in severe developmental impairment, intractable epilepsy and intellectual disability (Spalice *et al.* 2009). To date, many genes have been identified as the leading cause of migration defects, i.e. agyria/pachygyria, polymicrogyria, heterotopias, agenesis of the corpus callosum and agenesis of the cranial nerves (Spalice *et al.* 2009). Here, we present a patient with early infantile epileptic encephalopathy (Ohtahara syndrome) with seizure onset on the first day of life, severe developmental delay and an abnormal brain MRI with excessive folding of small, fused gyri and bilateral perisylvian polymicrogyria, suggestive of neuronal migration disorder. To clarify the unknown aetiology, we conducted whole-exome sequencing, which detected a *de novo* missense variant (c.5308A>T; p.(Met1770Leu)) in the *SCN2A* gene. This is a report of *SCN2A* gene variant identified in a patient with neuronal migration disorder which could further expand the phenotypic spectrum of these genetic disorders.

Keywords. ohtahara syndrome; whole exome sequencing; neuronal migration disorders; *SCN2A* gene; developmental delay; children.

Introduction

An 11-month-old boy presented with intractable seizures since the first day of birth. He was one of the four children born to consanguineous parents. He was born prematurely at 33 weeks gestation in breech position, requiring full resuscitation and elective intubation. The maternal antenatal ultrasound scans and baseline blood tests were normal, with only report of back pain around the fifth month of pregnancy.

From the first day of birth, he developed seizures associated with cyanosis followed by generalized body stiffening and eye deviation. The complete neurological examination revealed abnormal dolichocephaly and mild head lag, microcephaly, axial hypotonia, peripheral hypertonia, macrosomia and contractures of all limbs. His deep tendon reflexes were also prominent throughout. He kept his eyes open and was unable to fix or follow, but he had no nystagmus. Hepatosplenomegaly was also noticed. His muscle bulk was good and his plantars equivocal on the right.

During pediatric intensive care unit (PICU) admission, the patient was fed via PEG tube. He developed a refractory seizure disorder and had a variable seizure frequency of 20–40 episodes per day. Several antiepileptic medications were trialled in different combinations, adjusting their doses to achieve therapeutic ranges. Despite continuous optimization of doses, he failed to respond to multiple

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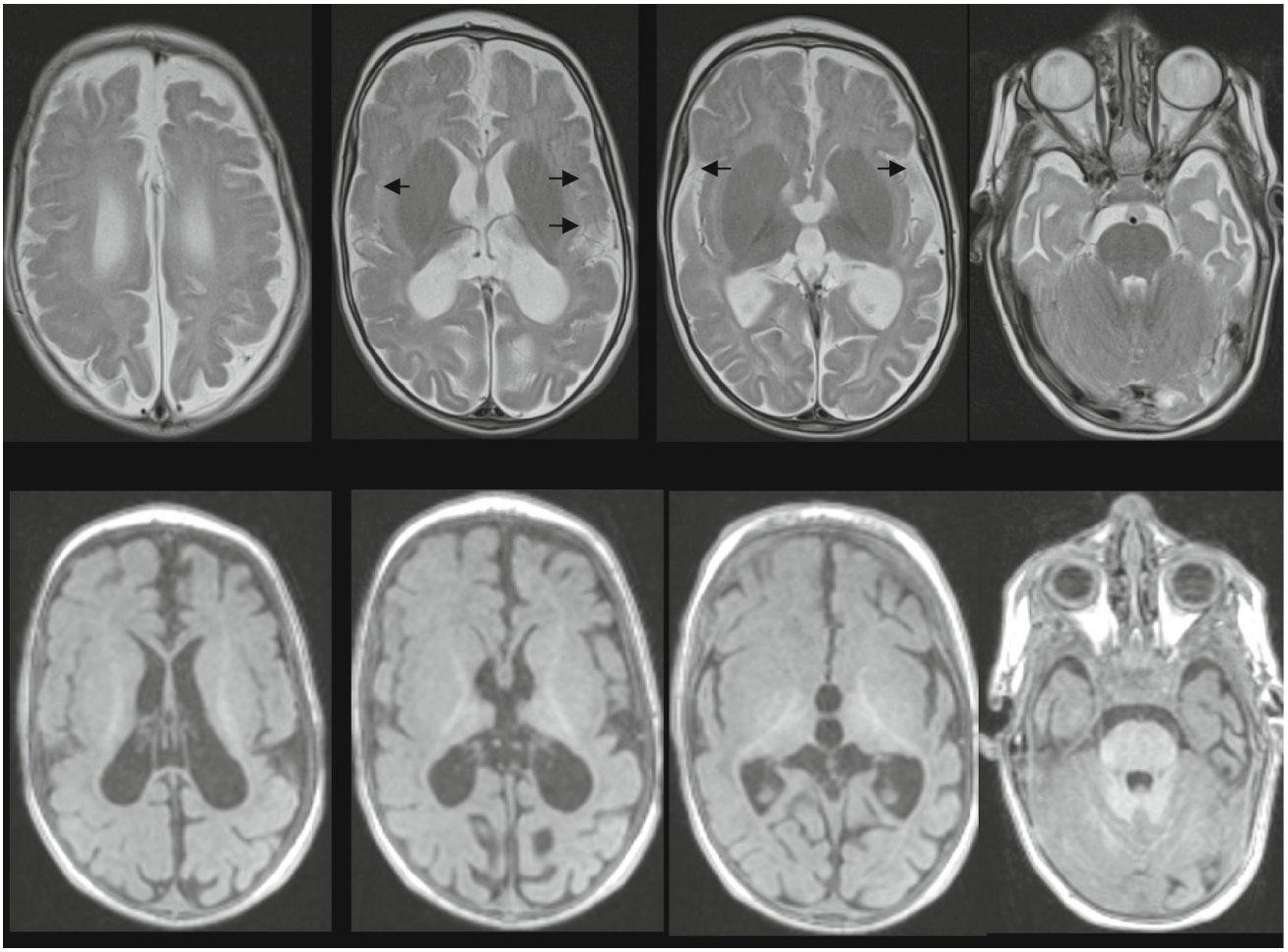

Figure 1. Top panel axial T2 weighted and lower panel axial T1 weighted images at 11 months of age, showing simplification of the gyral pattern with bilateral peri-sylvian polymicrogyria (black arrow). Note is also made of small volume thalami. Normal brain stem and posterior fossa structures.

combinations of antiepileptic medications (phenobarbital, levetiracetam, clozabam, valproate, midazolam and topiramate) and vitamins (pyridoxine, pyridoxal phosphate, biotin and calcium folinate). A trial of ketogenic diet was also unsuccessful to control his seizures.

At 18 months of age remained at PICU on five antiepileptic medications (phenobarbital, clobazam, levetiracetam, phenytoin and carbamazepine) with a moderate seizure control of about 10 seizures per day, which were brief and self-resolving.

Investigations

All initial laboratory investigations were normal, including full blood count, electrolytes, renal function, liver function, thyroid function, creatine kinase, lactate, carnitine and acyl carnitine profile, lipid profile, folate, urine and serum amino acids. CSF studies, including CSF neurotransmitters and CSF pterins were also within normal limits. Of note, CSF pyridoxal phosphate was slightly raised, as the patient was on vitamin B6 supplements at the time of investigation. TORCH screen was also negative.

At the point of referral to our service aged 11 months, a 24-h video EEG telemetry study revealed frequent tonic seizures with diffuse fast wave EEG synchronization and marked presence of electrical suppression, confirming the initial diagnosis of Ohtahara syndrome. Tonic spasms occurred in clusters, while awake or at sleep. There did not appear to be any myoclonic components associated with clinical seizures. There was also consistent left hemispheric onset of seizures such as particular focus of epileptic activity arising from the left centrotemporal region.

A repeat epilepsy protocol brain MRI study under general anaesthesia at 11 months showed microcephaly with reduced cerebral white matter volume. The maturation of myelin was also delayed for the age. Over coagulation of the cortex was noticed in the posterior perisylvian and parietal lobes bilaterally, consistent with polymicrogyria, signifying a malformation of cortical development. Note was also made of some malrotation of the hippocampal formations.

Figure 2. Multiple sequence alignment across different species of the sodium channel protein type 2 subunit alpha. The Methionine at position 1770 is highlighted in green and highly conserved.

Therefore the malformation of cortical development raised the possibility of an underlying neurometabolic or neurogenetic condition (see figure 1).

Our patient also developed nephrocalcinosis deemed to be a side effect of topiramate, detected by a renal ultrasound which was performed at 12 months old.

Results

As no causative diagnosis had been reached, WES was performed. This identified a *de novo* missense variant c.5308A>T in *SCN2A* gene, which resulted in the substitution of leucine for methionine at position 1770 of the protein. The amino acid methionine is highly conserved up to fruitfly and is located in the protein domains (ion transport domain and voltage gated sodium channel, alpha subunit). This variant c.5308A>T is novel, not reported in ExAC, ESP and other publicly available databases. We also sought to investigate the location of the mutation across different species (figure 2). *In silico* analysis using multiple softwares predicted a damaging effect (MutationTaster, disease causing; SIFT, damaging; Provean, damaging; FATHMM, damaging). Based on the *de novo* inheritance, location in the protein domain and *in silico* prediction of damaging effect on the protein function, this SCN2A variant c.5308A>T was concluded as a likely pathogenic variant.

Discussion

Polymicrogyria is a relatively common malformation of the cortical development. Bilateral perisylvial polymicrogyria (BPP) is the most common subcategory characterized by epilepsy, cognitive impairment, pseudobulbar palsy and psychomotor dysfunction and pyramidal signs (Guerrini and Dobyns 2014). With regard to the genetic causes, BPP has mainly been identified in patients with copy number of 1p36.3 variant (Dobyns *et al.* 2008) or 22q11.2 deletion syndromes (Robin *et al.* 2006). Given the genetic heterogeneity and diversity of MCDs, it is often challenging to detect a specific genetic cause in the vast majority of patients (Parrini *et al.* 2016) and though relevant DNA panels exist, it is important to progress with comparative genome hybridization and WES to reach a neurogenetic diagnosis in a timely and cost effective manner. Mutations in the OCLN, COL4A1/COL4A2, ALX4 and MSX2, GPR56, WDR62, EOMES, LAMC3 and the tubulin genes (*TUBA1A*, *TUBB2B*, *TUBB3* and *TUBA8*) are all known to cause polymicrogyria (Jaglin *et al.* 2009). TUBA1A mutations can cause agenesis of the corpus callosum, polymicrogyria, microcephaly, refractory epilepsy and eye abnormalities (Myers *et al.* 2015). Mutations in PIK3R2 and other PI3K-AKT-mTOR pathway genes have also been identified in a number of overgrowth syndromes associated with polymicrogyria (Cushion *et al.* 2013) and may be accountable for up to 15% of patients with BPP with or without megalencephaly (Mirzaa *et al*. 2015).

De novo mutations in *SCN2A* gene have been increasingly linked to a wide spectrum of disorders, varying from autistic disorders (Tavassoli *et al.* 2014) to epileptic encephalopathy and epilepsy syndromes (Howell *et al.* 2015). The penetrance of *SCN2A* gene is highly variable, as suggested by Syrbe *et al.* (2016) based on a family with an identical *de novo* missense SCN2A variant, initially causing a moderate epileptic phenotype, but resulting in benign or even more severe epileptic syndromes in the following generation. Moreover, it is difficult to determine whether additional modifying variants, epigenetic or environmental factors are involved. Recently, Bernardo *et al.* (2017) reported an unusual case of SCN2A epileptic encephalopathy with severe cortical dysplasia, diagnosed prenatally on MRI.

Over the last years, molecular biology and genetic investigations of cortical development have shed light on the mechanisms and physiological pathways of the regulation of neuronal migration. Interestingly, a study on mouse embryonic stem cells has revealed a novel function of voltage-gated sodium channel in oligodendroglial progenitor cells (OPCs) in their functional maturation and myelination, thus suggesting a plausible pathway of voltage-gated sodium channel interfering with the neuronal migration (Jiang *et al.* 2013). In our case, we hypothesize an abnormal migration of OPCs cells due to sodium channel malfunction.

In conclusion, we suggest that the phenotypic spectrum of neuronal migration disorders may be broader than that had been previously described and we aim to emphasize the

importance of diagnosing genetic malformations of cortical development, to identify new genes and mechanisms interfering with the development of the human cerebral cortex. Further research also needs to be conducted to elucidate the dynamics of pluripotent stem cells with derived OPCs for future clinical applications.

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