Infantile epileptic encephalopathy with a hyperkinetic movement disorder and hand stereotypies associated with a novel *SCN1A* mutation

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ABSTRACT – We report a female patient who presented with intractable epileptic seizures, profound developmental delay since early infancy, and hyperkinetic movements with hand stereotypies. The patient initially developed focal seizures with multiple foci at 3 months of age. Thereafter, the seizures evolved to frequent episodes of hyperthermia-induced status epilepticus. A novel *de novo SCN1A* mutation was identified by whole-exome sequence analysis. This case demonstrates that *SCN1A* mutations may cause movement disorders as an atypical phenotype and the case history of this patient may expand our understanding of the clinical spectrum of *SCN1A*-associated epileptic encephalopathy. [*Published with video sequences*]

Key words: epileptic encephalopathy, *SCN1A*, chorea, ballismus, hyperkinetic movement, hand stereotypies

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SCN1A encodes the α1 subunit (Na$_V$1.1) of neuronal voltage-gated sodium channels. Mutations in this gene play an important role in the aetiology of Dravet syndrome. Dravet syndrome, otherwise known as severe myoclonic epilepsy in infancy (SMEI), is a severe childhood epilepsy characterised by multiple seizure types, prolonged febrile convulsive seizures, and frequent episodes of status epilepticus. Development is usually normal in the first year of life, followed by developmental slowing and regression (Harkin *et al.*, 2007). Through extensive genetic studies, more than 700 mutations in the *SCN1A* gene

have been described to date, and the phenotypic spectrum of patients with *SCN1A* mutations has been extended beyond Dravet syndrome. Mutations in *SCN1A* are sometimes found in genetic epilepsy with febrile seizures plus (GEFS+), malignant migrating partial seizures in infancy (MSPI), other infantile epileptic encephalopathies, and rarely in infantile spasms (Carranza Rojo *et al.*, 2011; Hirose *et al.*, 2013). We report, herein, on a female patient with intractable epileptic seizures, frequent status epilepticus, profound developmental delay since early infancy, and hyperkinetic movements with hand stereotypies. She was finally found to carry a *de novo SCN1A* mutation. We believe this case history contributes to an expanding clinical spectrum of *SCN1A*-associated epileptic encephalopathy.

Case study

A female patient, the second child of healthy unrelated parents, was born at 38 weeks gestational age by means of a repeat Caesarean section after an uncomplicated pregnancy. At birth, body weight was 3,466 g, body length was 49.0 cm, and head circumference was 34.5 cm. She suffered from neonatal transient tachypnoea and received oxygen therapy for two days. At 2 months of age, she started showing tonic movements of both arms and legs with horizontal nystagmus for 10 minutes. At 3 months of age, she developed left-hemiclonic seizures and soon after, right-hemiclonic seizures, and secondary generalised seizures were also observed. Carbamazepine was started at 3 months of age by the referring doctor, prior to her being transferred to our hospital.

When she was first admitted to our hospital at 3.5 months of age, body weight was 5.7 kg (-1.2 SD), height was 62.0 cm (-0.3 SD), and head circumference was 39 cm (-1.1 SD). On physical examination, blepharophimosis, upslanted palpebral fissures, and a broad nasal tip were observed. Neurological examination revealed no muscle weakness or spasticity. Ophthalmologic examinations were normal. Her psychomotor development was delayed; she was not able to control her head or demonstrate eye contact. After admission, right-hemiclonic seizures and attacks of unconsciousness with oral automatism were frequently observed. The attacks lasted a few seconds to a few minutes and occurred more than ten times a day.

Video-EEG recording at four months revealed theta activities with right predominance. The paroxysmal discharges consisted of right central dominant sharp waves. Her ictal EEG demonstrated trains of left-hemisphere-dominant 4-Hz theta activity, predominantly at Fp1, F3 and F7, or trains of right-hemisphere-dominant 4-Hz theta activity.

Her seizures were temporally controlled by the administration of valproate at five months of age. At 6 months of age, when she suffered pneumonia, she developed left-hemiclonic convulsions again. After this episode, hyperthermia-induced seizures and occasional status epilepticus were observed. The fever and infection triggered her seizures, which led to status epileptics and required intensive care. Her seizures were refractory to various antiepileptic drugs including carbamazepine, clobazam, clonazepam, phenobarbital, zonisamide, levetiracetam, and vitamin B6. Lamotrigine, topiramate, and potassium bromide were partially effective against her seizures. After the episode of seizures at 6 months of age, hyperkinetic involuntary movements of upper and lower limbs developed, for which the patient was treated with phenobarbital, valproate, and potassium bromide. These sudden, jerky movements particularly involved the upper limbs and partially resembled chorea and ballismus. They were accompanied by hand stereotypies with hand touching and washing. No hand mouthing or thrusting movements were observed. These movements were observed almost continuously when the patient was awake, and became exaggerated soon after the episodes of status epilepticus; they were gradually alleviated between the respective seizures.

At 6 years of age, profound intellectual and motor impairment was evident. The patient's body weight at this age was 19.5 kg (-0.1 SD), height was 112.0 cm (-0.3 SD), and head circumference was 47.5 cm (-1.9 SD). Spastic quadriplegia with exaggerated tendon reflex was observed. She had acquired head control, however, she was unable to sit alone or to speak. She was almost bed-ridden. No purposeful hand movement was observed. Hyperthermia-induced seizures continued to appear frequently, even though she was treated with phenobarbital, valproate, clobazam, topiramate, levetiracetam, potassium bromide, and stiripentol. Hyperkinetic movements were also continuously observed during awakening and these remained exaggerated after episodes of status epilepticus. During the hyperkinetic movements and hand stereotypies, video-EEG recording revealed no changes in brain electrical activity.

Brain MRI at 3 months of age showed slight atrophy of the brain and subsequent MRI at 1 year, 3 years, and 6 years of age showed progressive atrophy of the cortex and white matter, thin corpus callosum, and impaired myelination, especially in the frontal lobe (*figure 1*).

Laboratory analysis

Routine haematological and chemical examination and extensive metabolic screening tests were nor-
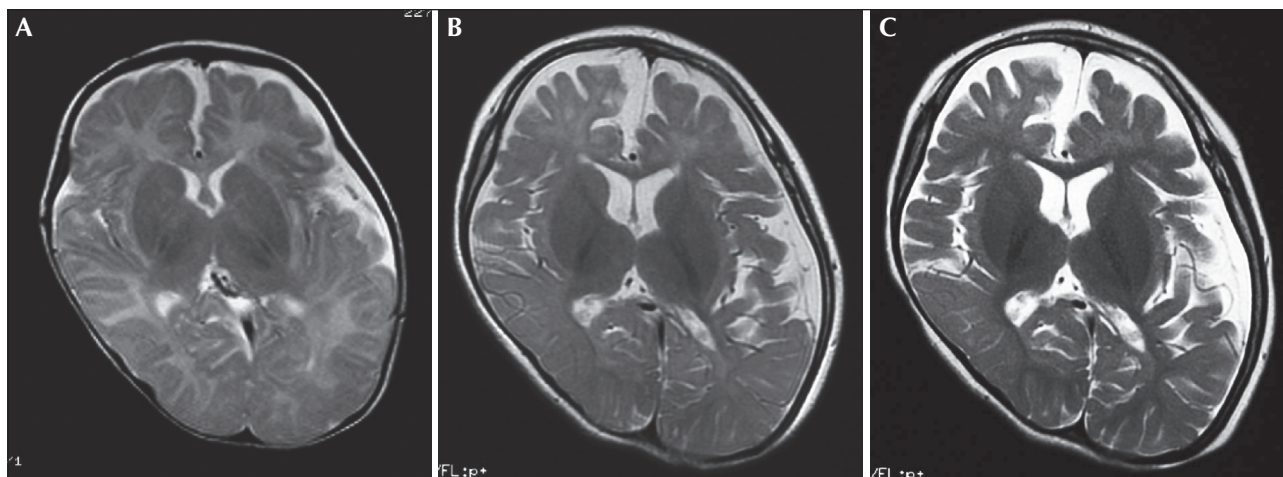
Figure 1. Brain MRI of patient. (A) A transverse T2-weighted image of the cerebrum at the age of 3 months shows slight atrophy in the left hemisphere. (B) A transverse T2-weighted image of the cerebrum at the age of 3 years and 8 months shows diffuse cortical atrophy in addition to white matter, particularly in the frontal lobe, a thin corpus callosum, and impaired myelination, particularly in the frontal lobe. (C) A transverse T2-weighted image of the cerebrum at the age of 6 years and 6 months shows progressive atrophy of the cortex, and a thin corpus callosum. Myelination of the hemispheric white matter is shown to have commenced gradually, especially in the occipital lobe.

mal. Cerebral spinal fluid (CSF) analysis including homovanillic acid, 5-hydroxylindolacetic acid, and methoxy-l-hydroxyphenylglycol showed no abnormalities. Chromosomal analysis of her peripheral blood lymphocytes indicated she was 46,XX, and genomic array analysis revealed no abnormal findings. Owing to the appearance of epileptic encephalopathy and severe developmental delay without any features, suggesting a specific epilepsy syndrome, we decided to perform whole-exome sequence analysis using DNA extracted from blood leukocytes, and found a *de novo* missense mutation, c.1264G>T (p.Val422Leu), in *SCN1A*. This mutation was not found in either parent, and was absent in the 6,500 exomes sequenced by the National Heart, Lung, and Blood Institute exome project, as well as in our 408 in-house control exomes (all Japanese). Mutations in other genes such as *STXBP1*, *GNAO1*, *FOXG1*, and *ARX*, in which mutations have been shown to be associated with both movement disorders and early infantile epileptic encephalopathies, were not found in all the exome data. The extent of these genes was well represented in the exome data except for *ARX*, in which only small parts of the gene were available (*table 1*).

Discussion

The patient's clinical condition partially resembled MSPI (migrating partial seizures in infancy) or Dravet syndrome (hyperthermia-induced status epilepticus

and myoclonus), but did not fit well with any of the known epilepsy syndromes. Although her facial appearance was slightly dysmorphic, no specific dysmorphic syndrome was suspected. Extensive testing, including metabolic screening, karyotyping, MRI, and EEG, did not elucidate the cause of her condition. Finally, whole-exome sequencing identified a *de novo* *SCN1A* mutation. Hirose *et al.* (2013) stated that *SCN1A* testing is unlikely to be helpful for a child with epileptic encephalopathy with features such as neonatal onset, or developmental delay prior to seizure onset. However, the extent of the phenotypic spectrum of *SCN1A* epilepsies includes MPSI features (Carranza Rojo *et al.*, 2011). The presence of an *SCN1A* mutation in our patient suggests that genetic testing of *SCN1A* could be useful for severe infantile multifocal epilepsy with profound developmental delay.

Involuntary movements are a rare complication of *SCN1A* mutation or early-onset epileptic encephalopathy. Our patient presented with hyperkinetic movements of her extremities with hand stereotypies since 6 months of age. Because *SCN1A*-related movement disorders have rarely been reported, we did not consider *SCN1A* mutations to be an underlying cause of her condition. Most abnormal involuntary movements result from a dysfunction of, or lesion in, the basal ganglia. Recently, choreoballistic movement was reported in a patient with *STXBP1* mutation (Kanazawa *et al.*, 2010). Generalised tremor has also been noticed in patients with *STXBP1* mutations (Deprez *et al.*, 2010; Mignot *et al.*, 2011). Kanazawa *et al.* stated that

Table 1. Sequence performance for known genes associated with movement disorders and early infantile epileptic encephalopathies.

Gene	Cytoband	No. of coding exons	Mean read depth	% bases above 5 × depth (%)	% bases above 10 × depth (%)
SCN1A	2q24.3	26	116.54	100	99.5
STXBP1	9q34.11	20	141.55	100	100
FOXG1	14q12	1	191.54	100	97.4
GNAO1	16q12.2	10	175.12	100	100
ARX	Xp21.3	5	111.78	94.5	88.2

*Coverage was calculated against coding sequences of RefSeq genes.

STXBP1 mutations might well be a cause of basal ganglia disorders as well as epilepsy and intellectual disability (Kanazawa *et al.*, 2010), while *ARX* and *FOXG1* genes have been associated with movement disorders (Guerrini *et al.*, 2007; Guerrini and Parrini, 2012). In addition, it has recently been reported that *de novo* mutations in *GNAO1*, encoding a Gαo subunit of heterotrimeric G proteins, cause epileptic encephalopathy and involuntary movements such as dystonia, chorea, and athetosis (Nakamura *et al.*, 2013). McTague *et al.* (2013) reported four MPSI patients with no identified mutation, who developed a movement disorder. Because the present patient developed involuntary movements with hand stereotypies, this suggests that *SCN1A* mutation should be considered as a possible cause in patients with epileptic encephalopathy and involuntary movements.

It is important to remember that some antiepileptic drugs may induce abnormal movements through their action on ion channels such as the SCN1A sodium ion channel. Antiepileptic drugs that have often been reported to induce movement disorder include phenytoin, carbamazepine, and zonisamide (Ohtsuka *et al.*, 2003). In the present case, our patient had not used phenytoin, and her prescription of carbamazepine and zonisamide was not continued when they were found to be ineffective at controlling her seizures. It is also notable that the severity of her involuntary movements was correlated with the episodes of status epilepticus. Thus, we speculate that these involuntary movements were not related to the effects of antiepileptic drugs.

The associated phenotypes of *SCN1A* range from benign febrile seizures to extremely serious conditions, including Dravet syndrome. To the best of our knowledge, the c.1264G>T (p.Val422Leu) mutation in the present patient is novel. The altered residue is located in the sixth transmembrane region (S6) of the first of four homologous domains (D1) within the α1 subunit of neuronal voltage-gated sodium channels. Interestingly, other epileptogenic mutations have been identified at this position. A p.Val422Glu and

a p.Val422Met mutation were previously reported in patients with cryptogenic generalised epilepsy and Dravet syndrome, respectively (Harkin *et al.*, 2007; Kwong *et al.*, 2012). This raises the possibility that specific amino acid substitutions at particular residues could differentially affect the function of Na$_V$1.1 and generate involuntary movements in our patient, or alternatively, some modifier effect may possibly give rise to the phenotypes.

In summary, we have described a patient with a novel *SCN1A* mutation who showed infantile epileptic encephalopathy, profound developmental delay, progressive brain atrophy, and hyperkinetic movements with hand stereotypies. The present patient demonstrates that *SCN1A* mutations may be a possible cause of movement disorders, as an atypical phenotype.

Legends for video sequences

These video sequences show continuous hyperkinetic movements with hand stereotypies at 4 years (*video sequence 1*) and 5 years (*video sequence 2*) of age. No ictal epileptic discharges were observed during simultaneous EEG recording.

Key words for video research on www.epilepticdisorders.com

Syndrome: epileptic encephalopathy not otherwise classified
Etiology: genetic disorder
Phenomenology: nonepileptic paroxysmal event
Localization: not applicable

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