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Acute encephalopathy in Dravet syndrome: Case reports and literature review

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Abstract

Dravet syndrome is a rare and catastrophic type of epilepsy in infants. Acute encephalopathy has been sporadically reported in patients with Dravet syndrome; however, the risk factors for this serious complication have not been identified. We report two patients with a clinical diagnosis of Dravet syndrome who experienced acute encephalopathy initiated by refractory status epilepticus. SCN1A mutational analysis revealed a previously reported nonsense mutation in one patient and a novel missense mutation in the other. Analysis of our cases and previously published cases revealed that patients with Dravet syndrome who have a more severe phenotype have an increased likelihood of developing acute encephalopathy compared with patients with less severe phenotypes.

INTRODUCTION

Dravet syndrome (DS) is a rare and severe type of epilepsy in infants. It is characterized by febrile and afebrile generalized and unilateral, clonic or tonic-clonic seizures that begin in the first year of life. Later, patients develop multiple seizure types, ataxia, medical intractability and cognitive decline.[1] Approximately 70-80% of DS cases are caused by mutations in *SCN1A*, the gene encoding the alpha-1 subunit of the sodium channel. More than 1,000 *SCN1A* variants have been identified, making it the most clinically relevant gene in epilepsy.[2]

Acute encephalopathy (AE) was defined by Mizuguchi *et al.,* as a generic term for acute brain dysfunction that is usually preceded by infection.[3] The main symptoms are impaired consciousness and signs of intracranial pressure, which are often accompanied by convulsions or seizures. AE has been reported in the literature to occur under a variety of conditions and has been linked to various causes, the most frequent of which being influenza. However, the role of influenza virus is debatable, and in many cases, the aetiology is unknown.[4] In addition to being widely reported in Japanese populations, cases from other countries have also appeared in the literature. In severe cases, the prognosis is poor, with either a fatal outcome or neurological sequelae.[5]

AE in children with DS has occasionally been reported recently in the literature.[6-10] Okumura *et al*. published a series of 15 Japanese cases in 2012. The authors defined AE as the sudden onset of brain dysfunction that usually follows an infectious disease with fever. It is principally characterized by decreased consciousness, with or without other neurologic findings, such as seizures, involuntary movement, and delirious behaviour, lasting for >24 hours.[6] To date, there have been 23 cases of AE in DS being described in the literature. There was lack of discussion to identifying the risk factors for the development of AE. Here, we report two cases of DS accompanied by AE in our cohort of 22 patients followed up at the Children Hospital 2, HCMC, Vietnam, and review the literature about AE in DS to identify the risk factors

CASE REPORTS

Patient 1

Thiswas the second male child born to non-consanguineous parents in . There was no family history of seizures, and the development during the first year of life was normal. The first seizure occurred at five months and was described as a hemiclonic seizure lasting for about seven minutes, without fever. Subsequently, similar seizures appeared every one or two weeks, with or without fever. Generalized convulsion and complex partial seizures appeared soon thereafter, and eyelid myoclonus appeared at 28 months. From 12-50 months, seizures were very frequent, often precipitated by fever, and were often

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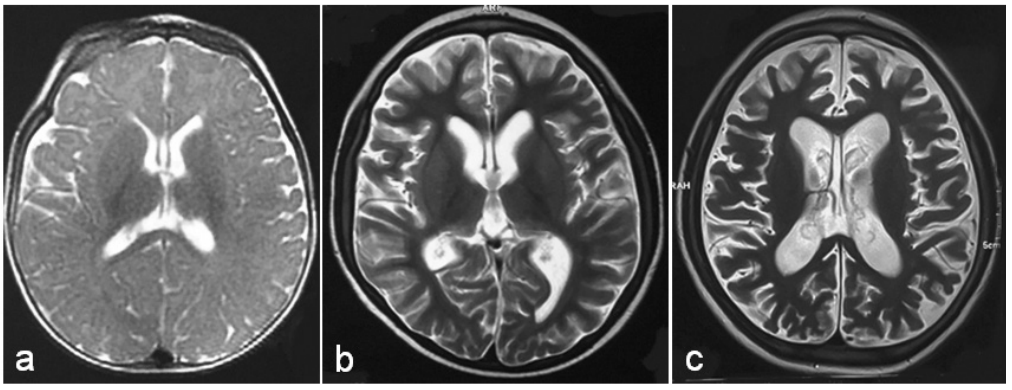

Figure 1. MRI brain T2W images: No abnormality detected before the AE (at seven months) (a). Prominent cortical and white matter atrophy, with marked ventricular dilatation and involvement of the basal ganglia three weeks after the onset of AE (b). More advanced cerebral atrophy was seen seven months after the onset of AE (c).

either prolonged (>15 minutes) or progressed to status epilepticus (SE) (>30 minutes) in spite of anticonvulsant polytherapy with sodium valproate, levetiracetam, topiramate, and clonazepam. A brain MRI at seven months and a repeat study at 31 months were normal. The blood screening tests for metabolic diseases were also normal. At 18 months, the patient began to show signs of developmental delay. He started walking at 23 months. At 40-50 months, he could speak only some simple sentences and had ataxia.

At 50 months he had a lower respiratory infection with fever (39.2°C) and had a generalized convulsive SE that lasted 55 minutes in spite of rectal diazepam, IV midazolam, and IV phenobarbital. IV propofol (2 mg/kg administered within 15 mins) and mechanical ventilation were administered, and the seizure was finally controlled. However, sporadic generalized tonic convulsions intermixed with a comatose state persisted, and he was treated with phenobarbital, followed by continuous IV midazolam infusion for another three weeks. Transient multiorgan failure was observed while haemodynamic parameters, blood pressure and cardiac function remained stable. There was no evidence of central nervous system infection or other systemic disorders. Viral studies were not performed due to the lack of typical clinical features of a particular viral infection and the AE was not in the context of an outbreak. The results of bacterial culture for infectious agents were unremarkable in spite of evidence of bacterial infection in blood tests.

The patient eventually developed spastic quadriplegia, poor eye contact and total loss of speech and required gastrostomy tube feeding. Three weeks and seven months after the event, his brain MRI showed severe atrophy (Figure 1). At the last follow-up one-and-a-half years later, the patient showed very limited improvement. *SCN1A* gene analysis by direct sequencing (for small abnormalities) and MLPA (for large

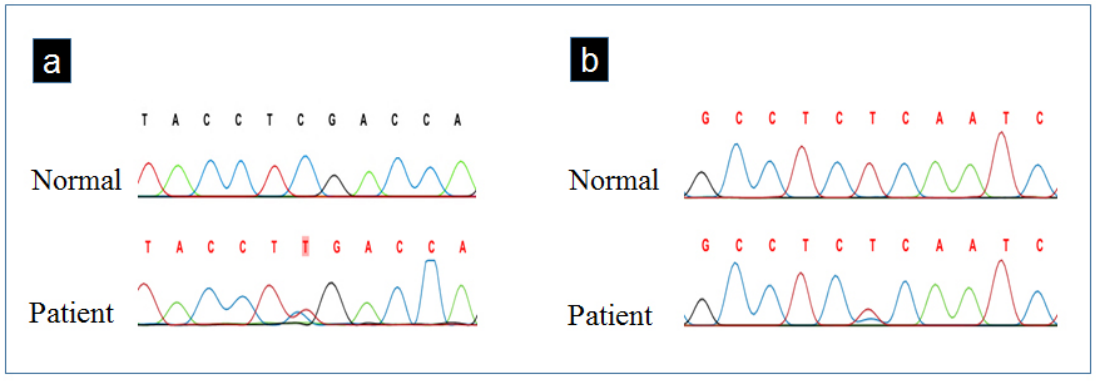

Figure 2. Direct sequencing revealed a truncation mutation (c.4573 C>T) in Patient 1 (a) and a missense mutation (c.5516T>C) in Patient 2(b).

deletion/duplication) was performed when the patient experienced AE. He was found to have a heterozygous truncation mutation, p.R1525X (c.4573 C>T), in exon 24 (Figure 2a). Parental testing confirmed that the mutation was *de novo.* This mutation has been previously reported in patients with the DS phenotype.[2]

Patient 2

This was the first male child born to a non-consanguineous union. The pregnancy was normal, and the boy was born uneventfully. His mother had a history of convulsions during infancy that were not associated with fever. Her seizures disappeared without treatment over time, and she had no developmental problems. At three months of age, the boy had his first febrile seizure, which lasted for 20 minutes. It manifested as clonic jerks in the upper limbs, with secondary generalisation. Head CT and blood tests screening for metabolic disorders were normal. After that, he had repeated febrile and unprovoked seizures every two weeks to monthly in spite of valproic acid and topiramate. By the age of 12 months, he had 18 clusters of seizures, including nine episodes of SE. His brain MRI and EEG at six months were normal. His seizure types included generalized convulsion and focal clonic seizures, and myoclonic seizures. His development was normal during the first year of life. At 11 months of age, he could stand with support and made some simple babbling sounds.

At 13 months, the patient had a febrile generalized convulsion during a respiratory infection. There were clinical signs and laboratory evidence of bacterial infection but the bacterial culture was negative. The seizure was refractory to IV midazolam and IV phenobarbital. Continuous IV midazolam infusion was given and the seizure stopped after 60 minutes. However, the patient remained in coma for another three days. After that, clusters of myoclonic and generalized clonic seizures developed on day three. The patient was treated with midazolam, IV phenobarbital and continuous IV midazolam, and his seizures

Table 1: Summary of clinical features and SCN1A mutations of the present cases (case 1 and 2) and previously reported cases

Case no.	Onset of DS (months)	Onset of AE (months)	Myoclonic seizure	Status epileptius	SCN1A mutation	References
1	4	50	YES	17	Truncation (R1525X)	
2	3	13	YES	9	Missense-C terminus (p.L1839P)	Present report
3	7	13	Not known	2 or more	Truncation (IVS4+1G>A)	Hiraiwa-Sofue *et al*., 2013[4]
4	6	38	NO	10	Truncation (IVS26-2A>C)	
5	3	153	YES	Several	Truncation (fsX934)	
6	3	53	YES	3	Truncation (R568X)	
7	4	45	YES	15	Truncation (K1846fsX1856)	
8	7	13	YES	Several	Truncation (IVS4+1G>A)	
9	3	13	YES	0	Truncation (R701X)	
10	2	16	YES	3	Missen-D3/S4-S5in (A1339V)	
11	4	27	YES	2	Missen-D1/S1 (Y145H)	Okumura *et al*., 1012[3]
12	5	45	YES	1	Missen-D4/S3-S4ex (V1630L)	
13	6	61	YES	4	None	
14	5	15	YES	Frequent	None	
15	4	8	YES	3	None	
16	4	92	YES	2	Not done	
17	5	184	YES	1	Not done	
18	4	43	YES	7	Not done	
19	5	64	Not known	Frequent	Missen-N terminus (p.L108R)	
20	5	31	YES	1	Truncation-(c4339-12C>A)	Tang *et al*., 2011[5]
21	3	108	Not known	Frequent	Missen-D4/S6 (p.I1770N)	
22	2	13	Not known	4	Missen-D4/S6 (C5341T>C)	
23	6	16	Not known	5	Missen-D3/S4 (p.S1328P)	Chipaux *et al*., 2011[6]
24	9	38	Not known	7	Truncation (C4720delT)	
25	4	9	NO	3	Truncation (D43fs)	Takayanagi *et al*., 2010[7]

were controlled after 2.5 hours. Continuous IV midazolam was discontinued on day nine. The patient ultimately developed spastic quadriplegia, dystonia, and severe cognitive impairment, which were unchanged at the last follow-up three months later. A follow-up MRI was not performed due to parent refusal. *SCN1A* gene analysis revealed a novel *de novo* missense mutation p.L1839P (c.5516T>C) in exon 26 (Figure 2b). This alteration is predicted to be deleterious by PolyPhen-2,SIFT, and Mutation Tasterin silico analysis.

DISCUSSION

The clinical presentations of these two patients, which began with repeated febrile convulsions and the subsequent emergence of various seizure types, including myoclonus, are consistent with DS. AE in our cases was characterized by refractory seizures, prolonged coma, and severe neurological sequelae. To our knowledge, there have been a total of 25 cases of AE in patients with DS or suspected DS described in the literature, including our two cases (Table 1). The outcomes in these children were invariably poor, including five deaths and moderate to severe neurological deterioration in all of the remaining cases. Thus, AE is an unusual but serious manifestation in DS. Twenty-one among 25 patients (84%) were 8 to 64 months of age at the onset of AE (Table 1). This is consistent with the observation that AE was triggered by episodes of SE in most patients (24 of 25 cases), and that frequent seizures and SE occurred between one and five years after onset of illness.

When analysing the risk factors for the development of AE in patients with DS, the epilepsy in our two patients with AE was significantly more severe than the others in our cohort of 22 patients. Both had an early age of onset of DS (<six months), frequent prolonged seizures and SE, multiple types of seizures, including myoclonus, and exhibited a strong resistance to antiepileptic drugs. Among the 25 cases of AE in patients with DS described in the literature, 20 (88%) were six months of age or less at the onset of DS; 24 (96%) had previously experienced SE; and 17 (89% of the 19 cases with available information for myoclonic seizures) had myoclonic seizures (Table 1). On the other hand, the proportion of overall DS patients having an earlier age of onset (6 months of age or less), SE, and the presence of myoclonic seizures ranges from 60%-69%, 68%-78%, and 38%-55%, respectively.[11-14] The differences between the 25 DS patients with AE and overall DS patients in these studies are statistically significant ($p<0.05$; statistical analysis available upon request). Therefore, DS patients with AE are more likely to have a more severe phenotype, including an earlier age of onset, the presence of myoclonic seizures and repeated episodes of SE, compared with the overall DS population. It is uncertain if a history of severe epilepsy renders the brain more vulnerable to AE or whether AE is a manifestation of a more severe disease phenotype. Thus, it is possible that optimized treatment may help to reduce the incidence of AE. Unfortunately, some medications for DS, including clobazam and stiripentol, are not presently available in Vietnam.

Although mutations in *SCN1A* are likely to be related to underlying pathophysiologic mechanisms of AE in patients with DA[7], the mutation type does not appear to be an important risk factor. Of the 22 patients who underwent *SCN1A* mutational analysis including our two cases, 19 (86%) had *SCN1A* mutations. Eleven of these mutations (58%) were truncating mutations, and eight (42%) were missense mutations. Hence, the difference between the number of truncating mutations and that of the missense mutations was not statistically significant. The ratio of truncation mutations to missense mutations in this 25 patients was also not higher than in the overall DS population.[12-14]

The precise pathophysiologic mechanisms underlying AE in DS patients remains uncertain. Tang *et al.* suggested that selective vulnerability of the cerebellum to injury in patients with *SCN1A* mutations may have been a contributing factor to the progression of symptoms in their patients.[8] Alternatively, excitotoxicity in relation to an *SCN1A* mutation and anoxic ischaemia induced by barbiturates have been proposed by Hiraiwa-Sofue and Chipaux, irrespectively.[7,9] Our two patients had a pathogenic mutation in *SCN1A*. During SE, they were treated with short courses of phenobarbital. In one patient, MRI was available during the recovery phase and showed cortical and white matter atrophy and involvement of the basal ganglia. Therefore, the pathophysiologic mechanisms proposed by Hiraiwa-Sofue and Chipaux may provide an explanation for the similar changes observed in our cases. Although more studies are required to elucidate the precise pathophysiologic mechanism, barbiturates should be used with caution for the treatment of SE in these patients.

In conclusion, we report two patients with DS

who developed AE. A novel *SCN1A* missense mutation was identified in one patient. Based on our two cases and a review of the literature, we suggest that the severity of the phenotype rather than the *SCN1A* mutation type may be associated with the development of AE in patients with DS.

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DISCLOSURE

Conflicts of interest: None

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