Neurology Asia 2017; 22(4) : 307 – 312

Clues to differentiate Dravet syndrome from febrile seizures plus at the first visit

[1,2,4]Hsiu-Fen Lee *MD*, [3,4]Ching-Shiang Chi *MD*

[1]Division of Nursing, Jen-Teh Junior College of Medicine, Nursing and Management, Miaoli; [2]Department of Pediatrics, Taichung Veterans General Hospital, Taichung; [3]Department of Pediatrics, Tungs' Taichung Metroharbor Hospital, Taichung; [4]School of Medicine, Chung Shan Medical University, Taichung, Taiwan.

Abstract

Objective: To investigate the clinical clues to differentiate between Dravet syndrome (DS) and febrile seizures plus (FS+). *Methods:* From September 2001 to March 2014, 44 consecutive patients who were diagnosed with DS or FS+, were recruited. We retrospectively analyzed the characteristics of the first seizure and findings of patients exhibiting seizures during hot water immersion at the first visit. Comparisons between the two groups were analyzed. *Results:* Thirty-two DS and 12 FS+ patients were enrolled. The most prevalent body temperature classification in the DS group was afebrile (43.8% vs. 25%, p=0.001), followed by 37-37.9°C (31.3% vs. 8.3%, p=0.02), and that in the FS+ group was at 39°C or above (33.3% vs. 9.4%, p=0.001). The most prevalent seizure type in the DS group was focal motor seizures (43.8% vs. 25%, p=0.001), followed by alternating hemiconvulsive seizures (12.5% vs. 0%, p=0.005), and that in the FS+ group was generalized clonic and/or tonic-clonic seizures (83.3% vs. 37.5%, p=0.002). Compared with the FS+ group, there was a greater prevalence of vaccination-related seizure as the first presenting feature among the DS patients (46.9% vs. 8.3%, p<0.001). During hot water immersion, myoclonic seizure was seen significantly in the DS group (46.4% vs. 25.5%, p=0.013).
Conclusions: Afebrile and mild body temperature variation below 38°C, focal motor seizure or alternating hemiconvulsive seizure types, and vaccination-related first seizure were found to be clues for highly suspected DS.

Keywords: Body temperature; Dravet syndrome; febrile seizures plus; hot water bath; water temperature

INTRODUCTION

Epilepsy syndromes with seizures precipitated by fever are commonly seen in infants and children. A group of clinically defined epilepsy syndromes, denominated genetic epilepsy with febrile seizures plus (GEFS+) spectrum, shows a predisposition to seizures with fever. The spectrum ranges from the mildest end of classical febrile seizures (FS), febrile seizures plus (FS+), and GEFS+, to Dravet syndrome (DS) at the most severe end of the GEFS+ spectrum.[1-3] The clinical spectrum of epilepsies may share a common molecular linkage to mutations of the SCN1A gene encoding pore-forming alpha subunit of the voltage-gated sodium channel, Nav1.1, which is located on chromosome 2q24.3.[4,5]

FS+ may resemble FS at seizure onset as brief generalized tonic-clonic seizures (GTCS) associated with fever occurring in early childhood. However, distinguishing features are the persistence of GTCS with fever beyond 6 years of age, or the occurrence in early or middle childhood of afebrile GTCS. FS+ might be associated with other seizures types, including myoclonic seizures, absence seizures, atonic seizures, or partial seizures.[1,6] The clinical outcome is usually favorable.

DS, otherwise known as severe myoclonic epilepsy of infancy (SMEI), was first described by Charlotte Dravet in 1978.[7] Classical DS comprises a complex phenotype incorporating factors such as age of onset of specific seizure types, and a distinctive developmental course. DS usually occurs in the first year of life, typically beginning with prolonged febrile and afebrile hemiclonic or GTCS, which characterize the first silent period when the child appears developmentally normal. The condition evolves with other seizure types

Address correspondence to: Dr. Ching-Shiang, Chi, Department of Pediatrics, Tungs' Taichung Metroharbor Hospital, 699, Taiwan Boulevard Sec. 8, Wuchi, Taichung, 435, Taiwan. Tel: + 886-4-2658-1919; E-mail address: chi-cs@hotmail.com

such as myoclonic, absence, partial, and atonic seizures developing between 1 and 4 years of age, which characterize the second aggressive phase when the child exhibits developmental slowing and regression, and often experiences behavior problems and motor impairments, including spasticity and ataxia. The aggressive period is followed by a more static third period where the seizures become less frequent but persist, and cognitive and neurological impairments are irreversible.[8] Fever and factors that raise body temperature, such as vaccinations or hot water immersion, can precipitate seizures.[9,10] This high convulsive susceptibility is a factor of pharmacoresistance.

In order to diagnose DS earlier, which may allow for the provision of an optimal therapy as soon as possible[11,12], clinicians have made efforts to predict DS before the age of one year. However, it remains a challenge for pediatric neurologists to distinguish DS from FS+ at disease onset because of clinically similar ages at seizure onset, pleomorphic seizure patterns, and fever as a common precipitating factor for seizures.

With the aim of better understanding the clinical clues for differentiation of the two syndromes, we retrospectively analyzed the characteristics of the first seizure, including body temperature, seizure types, and vaccination-related first seizure events. Hot water immersion is a strong precipitating factor of DS, but infants and children are typically bathed on daily basis in Taiwan. Therefore, we performed hot water immersion at the first visit to observe the differences between patients with DS or FS+ in terms of variations in body and water temperatures, and the ictal seizure types.

METHODS

Patient recruitment

We recruited subjects with a diagnosis of DS or FS+. DS was diagnosed according to the criteria described by Dravet *et al*. 2002[9] plus a positive SCN1A gene mutation. The diagnostic criteria of FS+ was based on evidence of brief GTCS associated with fever in infancy or early childhood in an otherwise normal child, afebrile GTCS in early or middle childhood, and/or appearance of other seizure types of myoclonic seizures, atypical absence seizures, and/or partial seizures.[6]

Clinical assessment

Clinical data of the recruited patients, including gender, age at seizure onset, epileptic phenotypes, and trigger factors for seizures from all patients' parents were collected via questionnaire. Epileptic seizures were categorized based on the Classification of the International League Against Epilepsy of 1981. An ear body temperature was taken when the first seizure occurred. Afebrile body temperature, mild body temperature variation, and febrile body temperature were defined as below 37ºC, 37-37.9ºC, and 38 ºC or above, respectively. Vaccination-related seizure events were restricted within an interval of 7 days between vaccination and the occurrence of seizures. Detailed physical examinations and neurologic evaluations were performed.

EEG recording

EEG recording was performed within one week of the first visit. Routine 21-channel video *EEG was* performed using a Nihon Kohden EEG (EEG-2110, Japan), a Nicolet vEEG (Viasys, USA), or a Comet AS-40 EEG (Grass, USA). Silver-silver chloride electrodes were positioned according to the International 10-20 System. All EEGs were recorded in stages of wakefulness. After a 20-minute routine EEG recording, video EEG recording during hot water immersion[13] was performed after obtaining informed consent from the patients' parents. Ictal electroencephalographic seizure pattern was recorded.

Molecular analysis

Genomic DNA was extracted from peripheral blood samples. All the exons of the SCN1A gene were amplified by polymerase chain reaction (PCR) with their corresponding primers. PCR products were subjected to bidirectional sequencing using a Big-Dye Terminator v3.1 Cycle Sequencing Kit and an ABI Prism 3100 genetic analyzer (Applied Biosystems, Foster City, CA). The protein sequence was based on ENSEMBL ENST00000423058. Written informed consent was obtained from all participants' parents prior to collection of blood samples for molecular studies.

Statistical analysis

From September 2001 to March 2014, a total of 44 consecutive patients who were diagnosed with DS or FS+, were recruited. We retrospectively analyzed the characteristics of the first seizure, including body temperature, seizure types, and immunization-related first seizure event. In patients exhibiting seizures during hot water immersion, the body and water temperatures

and the first recognized ictal seizure patterns were described. This study was approved by the Institutional Review Board.

Comparisons between the two groups were analyzed using the Student's t-test on SPSS for categorical variables. The cutoff significance was a *p* value of 0.05.

RESULTS

Characteristics of the first seizure

As shown in Table 1, 32 DS and 12 FS+ patients, comprising 29 males and 15 females (p<0.001), were enrolled. The median age at seizure onset was 6 months in DS patients, and 9 months in the FS+ group (p=0.001). Fourteen DS and 3 FS+ patients did not exhibit fever at the first seizure (43.8% vs. 25%, p=0.001). Ten DS patients and one FS+ case showed mild body temperature variation at 37-37.9°C (31.3% vs. 8.3%, p=0.02). Three DS and 4 FS+ patients exhibited body temperature 39°C or above (9.4% vs. 33.3%, p=0.001). Regarding the first seizure types, 12 DS and 10 FS+ patients manifested generalized clonic seizures (GCS) and/or GTCS (37.5% vs. 83.3%, p=0.002). Twelve DS patients and one FS+ case had focal motor seizure (37.5% vs. 8.3%, p<0.001). Four DS patients and none of the FS+ patients exhibited alternating hemiconvulsive seizures (12.5% vs. 0%, p=0.005). Only one DS patient showed myoclonic seizure at disease onset. Myoclonic seizures and febrile status epilepticus were not statistically significant between the two groups. Fifteen DS patients and one FS+ patient experienced vaccination-related seizure as their first presenting feature (46.9% vs. 8.3%, p<0.001). Vaccinations preceded seizure events, including Diphtheria, Tetanus, and Pertussis (DTP) vaccine

Table 1 Characters of the first seizure in patients with Dravet syndrome and febrile seizures plus.

	Dravet syndrome N = 32	**Febrile seizures plus N = 12**	***p***
Gender, Male:Female	19:13	10:2	<0.001*
Age at seizure onset, median (range)	6mo (2mo - 10mo)	9mo (3mo -1yr 10mo)	0.001*
Age at first visit, median (range)	1yr 1mo (2mo - 7yr 3mo)	1yr (6mo - 3yr 10mo)	0.322
The characters of the first seizure			
Body temperature			
< 37°C, n (%)	14 (43.8)	3 (25.0)	0.01*
37°C -37.4°C, n (%)	3 (9.4)	0 (0.0)	0.02*
37.5°C -37.9°C, n (%)	7 (21.9)	1 (8.3)	0.023*
38°C -38.4°C, n (%)	4 (12.3)	3 (25.0)	0.067
38.5°C -38.9°C, n (%)	1 (3.1)	1 (8.3)	0.155
≥ 39°C, n (%)	3 (9.4)	4 (33.3)	0.001*
Seizure types			
GCS/GTCS, n (%)	12 (37.5)	10 (83.3)	0.002*
Focal motor seizure, n (%)	12 (37.5)	1 (8.3)	<0.001*
Alternating hemiconvulsion, n (%)	4 (12.5)	0 (0.0)	0.005*
Complex partial seizure, n (%)	2 (6.3)	0 (0.0)	0.068
Myoclonic seizure, n (%)	1 (3.1)	1 (8.3)	0.155
Febrile status epilepticus, n (%)	1 (3.1)	0 (0.0)	0.216
Vaccination			
Vaccination related	15 (46.9)	1 (8.3)	<0.001*
Fever following vaccination	6 (18.8)	1 (8.3)	0.221

GCS: generalized clonic seizures, GTCS: generalized tonic-clonic seizures, mo: months, yr: year.

(13/15), Hepatitis B vaccine (1/15), and rotavirus vaccine (1/15) in DS patients, and DTP vaccine (1/1) in the FS+ group. Among them, 6 DS patients exhibited fever following vaccination and the body temperature was below 38°C in 4 (1 focal motor seizure, 1 alternating hemiconvulsive seizure, 2 GCS/GTCS), 38 °C in one (focal motor seizure), and above 39 °C in one (focal motor seizure). The only FS+ patient had a body temperature of 38 °C following vaccination with clinical seizure type of GCS. The prevalence rates of first seizure with fever following vaccination were not statistically significant between the two groups.

Body and water temperatures during hot water immersion

As shown in Table 2, hot water immersion was performed at a median age of 2 years and 3 months in DS patients, and 2 years and 2 months in FS+ patients. Twenty-eight (87.5%) DS patients and 4 (33.3%) FS+ patients manifested a seizure during hot water immersion. Among them, 9 patients, including 7 DS and 2 FS+ cases, were aged younger than one year. The median interval between starting hot water immersion and initiation of seizure was 15 min 17 seconds in DS patients, and 24 min 34 seconds in FS+ patients (p=0.014). In DS patients, a median body temperature of 37.8°C and simultaneous median water temperature of 39 °C could precipitate clinical seizures. However, in FS+ patients, seizures were provoked at a median body temperature of 38.5°C with a median water temperature of 40°C. Both body and water temperatures during hot water immersion were not significantly different between the two groups.

Ictal seizure types during hot water immersion

Thirteen DS patients and one FS+ case manifested myoclonic seizures (46.4% vs. 25.5%, p=0.013) as the first recognized seizure type during hot water immersion. Eight DS patients and 2 FS+ patients showed atypical absence seizures with or without myoclonic seizure (28.6% vs. 50.0%, p=0.366). One DS patient and 1 FS+ patient had complex partial seizure (3.6% vs. 25.5%, p=0.004). No FS+ cases manifested GCS/GTCS or focal motor seizure as their first ictal seizure pattern. The median numbers of evolutionary ictal seizure types during hot water immersion in DS and FS+ patients were 3 and 2, respectively (p=0.391). The median duration of seizures was 2 min 18 seconds in DS patients, and 4 min 16 seconds in FS+ (p=0.685). Seven patients, including 6 DS and 1 FS+, displayed seizures longer than 15 minutes.

Table 2 Characters of the seizures precipitated by hot water immersion in patients with Dravet syndrome and febrile seizures plus

	Dravet syndrome N = 32	**Febrile seizures plus N = 12**	***p***
Seizures provoked by hot water immersion, N	28	4	
Age at hot water immersion, median (range)	2yr 3mo (7mo - 7yr 4mo)	2yr 2mo (7mo – 5yr 1mo)	
Interval between starting an immersion and a seizure, median (range)	15min 17secs (6min 42secs to 29min 54secs)	24min 34secs (16min 59secs to 29min 58secs)	0.014*
Body temperature, median (range)	37.8°C (36.8°C ~38.7°C)	38.5°C (38.0°C ~ 38.7°C)	0.305
Water temperature, median (range)	39.0°C (37.9°C ~40.0°C)	40.0°C (39.8°C ~ 40.5°C)	0.164
First recognized seizure type			
Myoclonic seizure, n (%)	13 (46.4)	1 (25.0)	0.013*
Atypical absence seizure, n (%)	8 (28.6)	2 (50.0)	0.366
GCS/GTCS, n (%)	4 (14.3)	0 (0.0)	0.067
Focal motor seizure, n (%)	2 (7.1)	0 (0.0)	0.254
Complex partial seizure, n (%)	1 (3.6)	1 (25.0)	0.004*
Evolutionary seizure types, median (range)	3 (1 – 5)	2 (2 – 4)	0.391
Seizure duration, median (range)	2min 18secs (51secs to 50min)	4min 16secs (1min to 19min 30secs)	0.685

GCS: generalized clonic seizures, GTCS: generalized tonic-clonic seizures, mo: months, yr: years.

DISCUSSION

In this study, we observed that about 75% of DS patients exhibited afebrile and mild body temperature variation below 38°C at the first seizure, and one-third of FS+ patients experienced a higher body temperature of 39°C or above. This finding suggests that fever sensitivity (temperature variation) was a characteristic in DS patients since the infant stage, which was consistent with the literature.[14] Focal motor seizures, alternating hemiconvulsive seizures and/or febrile status epilepticus have been reported to be characteristic seizure types before the age of one year in DS patients.[8-10] Our case series found a significantly greater prevalence of focal motor seizures and alternating hemiconvulsive seizures in the DS group, whereas greater prevalence of GCS/GTCS was seen in the FS+ group. Only one DS patient showed febrile status epilepticus as the first seizure feature, which showed no significant difference between DS and FS+ groups. This might be due to the fact that we analyzed the first clinical seizure type, rather than conducting a longitudinal follow-up, which was a limitation of this study. We recommend that DS should be highly suspected in patients who manifest afebrile or temperature variation below 38°C, as well as seizure types of focal motor seizure or alternating hemiconvulsive seizures. In addition, DS is an epileptic encephalopathy whose diagnosis is usually reached after a complete maturation of its signs/symptoms. Although these clues can be used to differentiate between the two groups, it is important to recognize that long-term follow-up remains the mainstay for accurate diagnosis of DS or FS+.[15]

A population-based 10-year cohort study showed that the prevalence of SCN1A-related DS among children with seizures following vaccination in the first year of life was 2.5%.[16] About 25% to 50% of DS patients reported a vaccination-related seizure as the presenting feature of the disease.[17,18] Our case series found that this feature was noted in 46.9% of DS patients and 66.7% of them had a body temperature below 38°C, which was consistent with the literature.[19] According to the results of our case series and studies reported in the literature,[20,21] some DS patients do not have a fever suggesting that fever per se is not the mechanism responsible for triggering seizures. Other mechanisms may be involved in seizure onset, such as vaccination, which might trigger earlier onset of DS in children, whose condition can masquerade as so-called "vaccine encephalopathy".[21] We suggest that close follow-up of patients with vaccination-associated seizures around the age of 6 months, and further seizures or additional symptoms such as developmental slowing could help to identify cases of DS early in its clinical course. Importantly, elucidating the genetic basis in these cases will establish the diagnosis, allow for timely medical intervention to prevent further seizures, and provide the basis for genetic counseling for the family. In addition, our case series observed one SCN1A-negative FS+ patient exhibiting seizure following vaccination. This implies that vaccination could trigger seizure in other subtypes of epilepsy syndromes besides DS. Further studies should be conducted to explore the roles of these subtypes.

Infants and young children in Taiwan tend to be bathed while sitting. Typically, water is collected in a bucket, and then poured over the child's body with a ladle. Our study revealed that hot water immersion could provoke clinical seizures not only in DS but also in patients with FS+, which was consistent with the literature.[22] However, seizures are frequently precipitated by hot water immersion in DS patients with a shorter interval between starting a bath and onset of seizure. Since hot water immersion is a daily practice in many Asian countries such as Taiwan and Japan, this observation has important implications as patients' parents or caregivers must be instructed to pay particular attention to body and water temperatures during a hot water immersion in order to avoid triggering seizures.

Ictal seizure types during hot water immersion showed pleomorphic seizure types both in DS and in FS+ patients. Compared to FS+, evolutionary seizure patterns with greater numbers of seizure patterns were observed in DS patients. We observed that there was a significantly greater prevalence of myoclonic seizure as the first ictal recognized seizure type in DS patients during hot water immersion compared to that of other patterns. Our study showed there was a discrepancy between hot water immersion-provoked ictal seizure type and the first described seizure type in DS. Possible reasons for this phenomenon include: (1) myoclonic seizures could be subtle and easily overlooked by parents at disease onset, and (2) video EEG during hot water immersion was recorded at a median age of 2 years 3 months when patients' seizure pattern evolved and myoclonic seizure emerged after the first year of life.[17] A similar observation was also found in FS+ patients for whom GCS/GTCS was

the most common seizure type at disease onset, but there was a significantly greater prevalence of complex partial seizure as the first ictal seizure type. The case number in our case series was limited, and thus, further studies with larger patient populations are needed.

In conclusion, both epilepsy syndromes, DS and FS+, showed signs which can be used to recognize disease onset. Afebrile and mild body temperature variation below 38°C, seizure types of focal motor seizures or alternating hemiconvulsive seizures, and vaccination-related first seizure in healthy infants aged around 6 months were clues for highly suspected DS. Body temperature 39°C or above and GCS/GTCS were significant factors in FS+. Hot water immersion-provoked seizure event was more frequently and readily observed in DS patients who exhibited myoclonic seizure as the first recognizable ictal seizure type. Although these clues can be used to differentiate between the two groups, long-term follow-up of patients' clinical manifestations as well as developmental milestones remain the mainstay for accurate diagnosis of DS and FS+.

ACKNOWLEDGEMENTS

The authors would like to thank Chi-Ren Tsai MS for genetic analysis of SCN1A gene, and Chin-Hsuan Chen MT for great assistance of EEG recording.

DISCLOSURE

Financial support: None

Conflict of interest: None

REFERENCES

1. Scheffer IE, Berkovic SF. Generalized epilepsy with febrile seizures plus: a genetic disorder with heterogeneous clinical phenotypes. *Brain* 1997; 120:479-90.
2. Scheffer IE, Berkovic SF. Generalized (genetic) epilepsy with febrile seizures plus. In: Engel JJ, Pedley T, editors. *Epilepsy: a comprehensive textbook* Philadelphia: Lippincott, Williams & Wilkins; 2008. P.2553-8.
3. Singh R, Andermann E, Whitehouse WPA, et al. Severe myoclonic epilepsy of infancy: extended spectrum of GEFS+? *Epilepsia* 2001; 42:837-44.
4. Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy in infancy. *Am J Hum Genet* 2001; 68:1327-32.
5. Volkers L, Kahlig KM, Verbeek NE, et al. $Na_v1.1$ dysfunction in genetic epilepsy with febrile seizure-plus or Dravet syndrome. *Eur J Neurosci* 2011; 34:1268-75.
6. Picard F, Scheffer IE. Recently defined genetic epilepsy syndromes. In Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence 3rd ed.* United Kingdom: John Libbey & Co Ltd; 2002:481-93.
7. Dravet C. Les epilepsies graves de lénfant. *Vie Med* 1978; 8:543-8.
8. Covanis A. Update on Dravet syndrome. *Dev Med Child Neurol* 2011; 53 (Suppl 2):v-vi
9. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy (Dravet syndrome). In Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence 3rd ed.* United Kingdom: John Libbey & Co Ltd; 2002:81-103.
10. Dravet C. The core Dravet syndrome phenotype. *Epilepsia* 2011;52(Suppl. 2):3-9.
11. Kassaï B, Chiron C, Augier S, et al. Severe myoclonic epilepsy in infancy: a systematic review and a meta-analysis of individual patient data. *Epilepsia* 2008; 49:343-8.
12. Chiron C, Dulac O. The pharmacologic treatment of Dravet syndrome. *Epilepsia* 2011; 52(Suppl. 2):72-5.
13. Lee HF, Chi CS, Tsai CR, Chen CH, Wong CC. Electroencephalographic features of patients with SCN1A-positive Dravet syndrome. *Brain Dev* 2015; 37:599-611.
14. Genton P, Velizarova R, Dravet C. Dravet syndrome: The long-term outcome. *Epilepsia* 2011; 52(Suppl. 2):44-9.
15. Scheffer IE, Zhang YH, Jansen FE, Dibbens L. Dravet syndrome or genetic (generalized) epilepsy with febrile seizures plus? *Brain Dev* 2009; 31:394-400.
16. Verbeek NE, van der Maas NAT, Jansen FE, van Kempen MJA, Lindhout D, Brilstra EH. Prevalence of SCN1A-related Dravet syndrome among children reported with seizures following vaccination: a population-based ten-year cohort study. *PLoS One* 2013; 8: e65758.
17. Caraballo RH, Fejerman N. Dravet syndrome: a study of 53 patients. *Epilepsy Res* 2006; 70S:231-8.
18. Zamponi N, Passamonti C, Petrelli C, et al. Vaccination and occurrence of seizures in SCN1A mutation-positive patients: a multicenter Italian study. *Pediatr Neurol* 2014; 50:228-32.
19. Berkovic SF, Harkin L, McMahon JM, et al. De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurol* 2006; 5:488-92.
20. Cendes F, Sankar R. Vaccinations and febrile seizures. *Epilepsia* 2011; 52(Suppl. 3):23-5.
21. Mclntosh AM, McMahon JM, Dibbens LM, et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *Lancet Neurol* 2010; 9:592-8.
22. Fukuda M, Morimoto T, Nagao H, Kida K. Clinical study of epilepsy with severe febrile seizures and seizures induced by hot water bath. *Brain Dev* 1997; 19:212-6.