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Stichpunkte und Hinweise zur Gliederung des Referates:
Diagnostik: Diagnostisches Vorgehen (Goldstandard), EEG, Genetik (PCR), prädiktive klinische Faktoren.
Studienansatz: Motivation für die Studie, Studientyp, Ein- und Ausschlusskriterien bei der Patientenrekrutierung (Tabelle 1).
Statistische Verfahren: Welche statistischen Methoden wurden zu welchen Fragen angewandt? Schwerpunkt exakter Fisher Test, ROC und Gütekriterien!
   b) Gegenüberstellung der Faktoren (Tabelle 2).
   c) Diagnostische Bewertung (Tabelle 4).
Diskussion: Die Modelle 1 – 4 (Abbildung 2); Kritische Bewertung der Studie hinsichtlich der verwendeten Methoden und statistischen Verfahren. Anwendbarkeit und Limitierung der Ergebnisse.

A screening test for the prediction of Dravet syndrome before one year of age

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SUMMARY

Purpose: Our aim was to develop a screening test to predict Dravet syndrome before the first birthday based on the clinical characteristics of infants and the SCN1A mutation analysis.

Methods: Ninety-six patients who experienced febrile seizures before the age of one were enrolled. The patients were divided into two groups—the Dravet syndrome group (n = 46) and the non-Dravet syndrome group (n = 50). We compared the clinical characteristics before one year of age of the two groups. We analyzed all coding exons of the SCN1A gene by the direct sequencing method. Scores from 0 to 3 were assigned to each risk factor based on the odds ratio and p-value.

Results: An age of onset of febrile seizure ≤ 7 months, a total number of seizures ≥ 5, and prolonged seizures lasting more than 10 min. were regarded as significant risk factors for Dravet syndrome. Other factors highly predictive of this syndrome were hemiconvulsions, partial seizures, myoclonic seizures, and hot water–induced seizures. A total clinical score of six or above was the cutoff value indicating a high risk of Dravet syndrome. SCN1A missense and truncated mutations were detected significantly more often in the Dravet syndrome group than in the non-Dravet syndrome group.

Discussion: This simple screening test was designed to be used by general pediatricians. It could help to predict Dravet syndrome before one year of age. If the sum of the clinical risk score is ≥ 6, then the performance of an SCN1A mutation analysis is recommended.

KEY WORDS: SCN1A, Dravet syndrome, SMEI, Screening test.

Febrile seizures (FS) are the most common type of seizure in childhood between five months to six years of age. Their incidence rate ranges from 2% to 14% of all children (Stanhope et al., 1972; Van den Berg, 1974; Hauser & Kurland, 1975; Nelson & Ellenberg, 1978; Tsuboi, 1984). FS spontaneously stop before six years of age; therefore, it is generally accepted that treatment with an antiepileptic drug regimen is not required. Dravet syndrome (previously termed SMEI) is an intractable form of epilepsy characterized by the occurrence of FS before one year of age (Dravet, 1978). Dravet syndrome is diagnosed at two to four years of age after the appearance of all of its clinical features. Due to the recurring presence of prolonged febrile and afebrile seizures in early childhood, it is desirable that certified pediatric neurologists or epileptologists manage the patients with Dravet syndrome as early as possible. However, it is difficult for general pediatricians to distinguish Dravet syndrome from benign FS or epilepsy before one year of age because of their similar clinical features at onset.

In recent years, SCN1A mutations have been identified in 30–80% of patients with Dravet syndrome (Claes et al., 2001; Ohmori et al., 2002; Sugawara et al., 2002; Nabbout et al., 2003; Wallace et al., 2003; Fukuma et al., 2004). The SCN1A mutations were also observed in 3.1...
to 5.7% of patients with generalized epilepsy with FS plus (GEFS+) (Escayg et al., 2001; Wallace et al., 2001). GEFS+ is a familial epilepsy syndrome characterized by heterogeneous phenotypes including FS, febrile seizures plus (FS+), mild generalized epilepsies, and severe epileptic encephalopathies (Scheffer & Berkovic, 1997). One SCN1A missense mutation has been reported in a type of familial febrile seizure (Mantegazza et al., 2005). It is not clear whether a genetic test of the SCN1A gene is useful for predicting Dravet syndrome at an early age.

We retrospectively investigated the risk factors in patients who experienced a febrile seizure before one year of age. Clinical features and SCN1A mutations were analyzed to predict Dravet syndrome. The development of a risk score screening test may enable general pediatricians to identify patients with Dravet syndrome at an early stage.

**Subjects and Methods**

**Participants**

Individuals who experienced FS before one year of age were recruited from outpatient pediatric clinic of seven participating medical centers (Okayama university hospital, Tottori university hospital, Kagawa prefectural central hospital, Kurashiki medical center, Hiroshima city hospital, NKK Fukuyama hospital, and Matsuyama Red Cross hospital) during 2003 and 2004 for whom clinical details and DNA were obtainable. A case was determined to have a febrile seizure when a temperature equivalent to ≥38.5°C was measured within 1 h of the event. This definition excludes seizures that accompany neurologic illnesses, such as meningitis, encephalitis, or toxic encephalopathy. The criteria for inclusion in the study were the onset of FS before the first year of life, normal development before the onset of seizures, and a follow-up period longer than three years. The exclusion criteria included underlying neurological disorders. One hundred and twelve participants were assessed for eligibility by at least two child neurologists, and sixteen participants were thus excluded.

The study protocol and informed consent documents were approved by the Ethics Committee of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences. Participants or parents provided written informed consent before enrollment.

The participants were recruited retrospectively. One of the inclusion criteria was a follow-up period longer than three years to know the outcome. At study enrollment, all participants had already been followed at various medical centers for several years. The participants had additional seizures after the first seizure or somewhat concerning factors. In addition, the collaborative hospitals were medical center hospitals with advanced medical technology to treat refractory cases. Therefore, refractory cases tended to be more frequently collected at such centers while benign cases with isolated FS tended to be excluded in this study.

**Methods**

The epileptic syndromes of the 96 patients at study enrollment were divided into two groups—the Dravet syndrome group and the non-Dravet syndrome group. The Dravet syndrome group includes typical Dravet syndrome and borderline Dravet syndrome patients. The patients with Dravet syndrome fulfilled the following criteria: normal development before seizure onset, the occurrence of either generalized, unilateral, or partial seizures during the first year of life, seizures that were frequently provoked by fever, the presence of myoclonic seizures with spike-and-wave complex or segmental myoclonus, diffuse spike-waves or focal spikes on EEG during the clinical course, intractable epilepsy, and gradual evidence of psychomotor delay after two years of age. Epileptic conditions of the non-Dravet syndrome group were subclassified according to the diagnostic criteria of the International League Against Epilepsy classification (ILAE, 2001). If the patients had recurrent seizures or neurological signs, CT or MRI brain scans were performed to exclude a focal organic lesion. The mental developmental levels at study enrollment (the mean age was 11.6 years in non-Dravet syndrome and 17.1 years in Dravet syndrome) were classified into three groups—normal development, mild retardation, and moderate to severe retardation. We carried out either the WISC-R, WISC-III, or Kaufman assessment battery for children for an assessment of psychomotor development for participants who had an imperfect ability in school performance. Participants who had a normal school performance or participants whose IQ were more than 70 were classified into the normal group. Participants whose IQ ranged 50 ≤ IQ < 70 were classified into the mild retardation group. Participants whose IQ less than 50 were classified into the moderate-to-severe retardation group.

To determine the clinical predictive factors for Dravet syndrome, we retrospectively studied the clinical data of participants before one year of age. The cases were systematically evaluated based on an exhaustive review of medical records from certified child neurologists. We compared the following clinical characteristics of the two groups: age at onset, sex, family history of a febrile seizure or epilepsy in first- or second-degree relatives, the total number of any type of seizures before one year of age, the absence or presence of a prolonged seizure longer than 10 min, seizure types, precipitating factors, EEG findings, and SCN1A mutations.

An EEG was recorded with a 10–20 system during the sleeping and waking state, and the infants received intermittent photic stimulation at time periods ranging from two months to one year and four months. All patients had EEG data available before one year of age except one patient.
SCN1A mutations were analyzed by the previously reported methods (Ohmori et al., 2002). In brief, genomic DNA was extracted from peripheral blood cells. Twenty-six exons of the SCN1A gene were amplified with the intronic primers. All PCR products were purified with a PCR products presequencing kit (Amersham Biosciences, Little Chalfont, Buckinghamshire, United Kingdom), reacted with the Big Dye Terminator FS ready-reaction kit (Applied Biosystems, Foster City, CA, U.S.A.), and analyzed on an ABI PRISM3100 sequencer (Applied Biosystems). We performed a multiplex ligation-dependent probe amplification (MLPA) using SALSA MLPA P137 SCN1A reagent for all SCN1A-mutation-negative patients to detect microdeletion (MRCL, Holland, Amsterdam, The Netherlands). Twenty-nine of the 46 patients with Dravet syndrome had been previously enrolled in a SCN1A mutation analysis in our study (Ohmori et al., 2002).

Statistical analysis

The cutoff values of age at onset and the total number of seizures were evaluated by the receiver operating characteristic (ROC) curve. The sensitivity, specificity, positive predictive value, and negative predictive value were calculated by the differentiation of the participants who developed Dravet syndrome and those who did not. The ROC curves were plotted and the area under the curves (AUC) was calculated.

Chi-square or Fisher’s exact tests were used to test differences for each potential predictive factor for Dravet syndrome. Statistical modeling using logistic regression analysis was used to calculate the odds ratio (OR) of individuals with Dravet syndrome to those without Dravet syndrome. ORs were expressed with the 95% confidence interval (95% CI). We subsequently assigned a risk score for each predictive factor based on OR or p-value. If the odds ratio ≤ 1 or p > 0.01, the risk score = 0; if 1 < OR < 20 or 0.01 ≥ p > 1 × 10⁻⁵, the risk score = 1; if 20 ≤ OR < 40 or 1.0 × 10⁻⁵ ≥ p > 1.0 × 10⁻¹⁰, the risk score = 2; and if 40 ≤ OR or 1 × 10⁻¹⁰ ≥ p, the risk score = 3. We applied the risk score to each patient and calculated the final sum of the risk scores. The ability of the risk score screening test to discriminate Dravet syndrome from non-Dravet syndrome was evaluated using the ROC curve analysis. ROC curves were also used to compare the diagnostic performance of different sets of risk factors.

All statistical analysis in this study was performed using the SPSS software package version 12.0 (SPSS Inc., Tokyo, Japan).

RESULTS

The clinical characteristics of the participants are summarized in Table 1. In the Dravet syndrome group, 20 of the 46 patients had myoclonic seizures with spike-and-wave complex on EEG while the remaining 26 patients had only segmental myoclonus. Twenty-two of the 50 patients in the non-Dravet syndrome group experienced only FS. The remaining 28 patients had also experienced afebrile seizures.

We investigated the cutoff values of the age at onset of a febrile seizure and the total number of seizures. Based on the distribution of the age at onset of a febrile seizure (Fig. 1A) and the ROC curve (Fig. 1B), seven months and younger was selected as the cutoff point. This cutoff value had a sensitivity of 0.94, a specificity of 0.66, a positive predictive value of 0.72, and a negative predictive value of 0.92. Considering the distribution of the total number of seizures (Fig. 1C) and the ROC curve (Fig. 1D), a total number of 5 and above was selected as the cutoff point. This cutoff value had a sensitivity of 0.89, a specificity of 0.84, a positive predictive value of 0.84, and a negative predictive value of 0.89.

The patients’ characteristics before one year of age are summarized in Table 2. The Dravet syndrome group had a significantly higher frequency of an age at onset ≤ 7 months, a total number of seizures ≥ 5, hot water–induced seizures, and the presence of hemiconvulsions, focal seizures, myoclonic seizures, and prolonged seizures lasting more than 10 min. Sex and family history were not significantly associated with Dravet syndrome.

Among the patients who experienced prolonged seizures for more than 10 min, 2 patients in the non-Dravet syndrome group and 27 patients in Dravet syndrome group (59%) had status epilepticus lasting more than 30 min. The sensitivity of prolonged seizures for more than 10 min...
is higher than that of status epilepticus lasting more than 30 min. Our aim of this study is to develop a screening test in order to predict Dravet syndrome, therefore, we selected the prolonged seizures of more than 10 min as a risk factor.

The photoparoxysmal response (PPR) on EEG was observed in 16 of the 46 patients (32%) in the Dravet syndrome group during the clinical course. These 16 patients belonged to the typical Dravet syndrome group (20 patients). PPR appeared before one year of age in one patient, between one and two years of age in four patients, between two and three years of age in four patients, and after three years of age in seven patients. PPR on EEG before one year of age was not useful for predicting Dravet syndrome in our patients.

The SCN1A mutations in the participants were summarized in the supplementary Table 1. Six of the 50 patients (12.0%) in the non-Dravet syndrome group had SCN1A mutations. All of these were missense mutations. However, 38 of the 46 patients (82.6%) in the Dravet syndrome group had various types of mutations. Approximately half of these mutations were missense and half were truncated mutations containing nonsense mutations and frameshift mutations. A deletion of exon 10 was detected in one patient using MPLA. SCN1A missense and truncated mutations were detected significantly more often in the Dravet syndrome group than in the non-Dravet syndrome group. Clinical characteristics of SCN1A-mutation-positive patients in non-Dravet syndrome group were shown in the supplementary Table 2.

Risk scores for each factor were assigned to predict Dravet syndrome based on their ORs and p-values as described in subjects and methods (Table 3). We applied the risk score to each patient’s clinical risk factors at one year of age and calculated the sum. The ROC curves were used to establish the cutoff points for each screening test (Table 4). The cutoff point of the total clinical score to identify Dravet syndrome was established as 6 or above (Model 3). If hot water–induced seizures were not observed because the patient did not bathe in hot water, this factor...
Table 2. Patients’ characteristics before one year of age

<table>
<thead>
<tr>
<th>Patients’ characteristics at onset</th>
<th>Non-Dravet, n = 50</th>
<th>Dravet, n = 46</th>
<th>p-value</th>
<th>Odds ratio</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at onset (months)</td>
<td>8.2</td>
<td>5.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Onset ≤ 7 months</td>
<td>17 (34%)</td>
<td>43 (93%)</td>
<td>$6.62 \times 10^{-10}*$</td>
<td>27.82</td>
<td>7.52–102.97</td>
</tr>
<tr>
<td>Sex, male</td>
<td>25 (50%)</td>
<td>20 (43%)</td>
<td>0.522</td>
<td>1.3</td>
<td>0.58–2.91</td>
</tr>
<tr>
<td>Family history in first-degree relatives</td>
<td>25 (50%)</td>
<td>13 (28%)</td>
<td>0.03</td>
<td>0.39</td>
<td>0.17–0.92</td>
</tr>
<tr>
<td>Family history in second-degree relatives</td>
<td>31 (62%)</td>
<td>19 (41%)</td>
<td>0.043</td>
<td>0.43</td>
<td>0.19–0.98</td>
</tr>
<tr>
<td>Number of seizures before one year of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number ≥ 5</td>
<td>8 (16%)</td>
<td>41 (89%)</td>
<td>$1.23 \times 10^{-13}*$</td>
<td>43.05</td>
<td>13.00–142.55</td>
</tr>
<tr>
<td>Seizure types before one year of age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GTC, GC</td>
<td>50 (100%)</td>
<td>44 (96%)</td>
<td>0.227*</td>
<td>1.30</td>
<td>0.58–2.91</td>
</tr>
<tr>
<td>Hemiconvulsion</td>
<td>1 (2%)</td>
<td>33 (72%)</td>
<td>$9.42 \times 10^{-14}*$</td>
<td>124.39</td>
<td>15.52–996.92</td>
</tr>
<tr>
<td>Focal seizure</td>
<td>2 (4%)</td>
<td>17 (37%)</td>
<td>$5.61 \times 10^{-5}$</td>
<td>14.07</td>
<td>3.03–65.36</td>
</tr>
<tr>
<td>Myoclonic seizure</td>
<td>0 (0%)</td>
<td>6 (13%)</td>
<td>0.01*</td>
<td>∞</td>
<td>–</td>
</tr>
<tr>
<td>Prolonged seizure</td>
<td>3 (6%)</td>
<td>37 (80%)</td>
<td>$1.38 \times 10^{-14}$</td>
<td>64.41</td>
<td>16.27–254.94</td>
</tr>
<tr>
<td>Precipitating stimuli</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot water</td>
<td>3 (6%)</td>
<td>27 (59%)</td>
<td>$1.28 \times 10^{-8}$</td>
<td>22.26</td>
<td>6.03–82.22</td>
</tr>
<tr>
<td>Laboratory characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epileptic discharges on EEG</td>
<td>13 (26%)</td>
<td>4 (9%)</td>
<td>0.033*</td>
<td>0.27</td>
<td>0.08–0.90</td>
</tr>
<tr>
<td>Genetic test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCN1A missense mutation</td>
<td>6 (12%)</td>
<td>19 (41%)</td>
<td>0.001</td>
<td>5.16</td>
<td>1.83–4.53</td>
</tr>
<tr>
<td>SCN1A truncated mutation</td>
<td>0 (0%)</td>
<td>20 (43%)</td>
<td>$2.59 \times 10^{-8}$</td>
<td>∞</td>
<td>–</td>
</tr>
</tbody>
</table>

*p-value by Fisher’s exact test.

should be deleted. In this case, the cutoff point was 5 and above (Model 4). The cutoff points for the sum of clinical and genetic score were also calculated in the same way (Models 1 and 2). Seven and above for the cutoff point of the model 1 exhibited high sensitivity and specificity. Figure 2 illustrates the distribution of the sum of the risk scores when each model is applied to an individual. Table 4 summarizes the predictive value of each model for sensitivity, specificity, PPV, and NPV.

**DISCUSSION**

Dravet syndrome is a refractory epileptic syndrome displaying various types of seizures. Due to the fact that the appearance of the clinical features of the syndrome is age dependent, a definitive diagnosis based on the presence of all the symptoms is delayed until early childhood. It is difficult to differentiate Dravet syndrome from benign febrile convulsions before an infant’s first birthday. Both of these disorders manifest as febrile convulsions with no neurological delay at the age of onset. Furthermore, general pediatricians who treat FS in infants have difficulty in discriminating between Dravet syndrome and benign FS. Dravet syndrome is characterized by recurrent seizures and status epilepticus during infancy, so it is necessary for a child neurologist or epileptologist to treat patients with this syndrome as early as possible. We therefore sought to develop a risk score screening test to predict Dravet syndrome before one year of age.

Regarding the characteristics of infants at the onset of Dravet syndrome, there were no data on how often Dravet syndrome patients have seizures before one year of age. Our data suggested that a total number of five or more seizures was the cutoff value in distinguishing between Dravet syndrome and non-Dravet syndrome. Regarding the characteristic seizure types, the incidence rates of hemiconvulsions, focal seizures, myoclonic seizures, and prolonged seizures lasting more than 10 min were significantly higher in Dravet syndrome. FS in Dravet syndrome often eventually evolve into status epilepticus. Oguni et al. (2005) reported that the incidence of status epilepticus was 67–77%. In our series, status epilepticus was observed in 27 patients (59%) before the first year of life. The rate of status epilepticus was thus lower in our study than in the previous study. A family history of convulsive disorders (including FS and epilepsy) was reported

Table 3. A proposed risk score for a screening test

<table>
<thead>
<tr>
<th>Predictive risk factors</th>
<th>Risk score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical score</td>
<td></td>
</tr>
<tr>
<td>Onset ≤ 7 months</td>
<td>2</td>
</tr>
<tr>
<td>Total number of seizures ≥ 5</td>
<td>3</td>
</tr>
<tr>
<td>Hemiconvulsion</td>
<td>3</td>
</tr>
<tr>
<td>Focal seizure</td>
<td>1</td>
</tr>
<tr>
<td>Myoclonic seizure</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged seizure</td>
<td>3</td>
</tr>
<tr>
<td>Hot water–induced seizure</td>
<td>2</td>
</tr>
<tr>
<td>Genetic score</td>
<td></td>
</tr>
<tr>
<td>SCN1A missense mutation</td>
<td>1</td>
</tr>
<tr>
<td>SCN1A truncated mutation</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 4. Diagnostic value of combination of risk factors

<table>
<thead>
<tr>
<th>Screening test (No. of risk factors)</th>
<th>Non-Dravet, n = 50</th>
<th>Dravet, n = 46</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1 (9 factors) Clinical score + genetic score (\geq 7)</td>
<td>1</td>
<td>45</td>
<td>0.978</td>
<td>0.980</td>
<td>0.978</td>
<td>0.980</td>
</tr>
<tr>
<td>Model 2 (8 factors) Clinical score (\geq 6) + hot water</td>
<td>5</td>
<td>44</td>
<td>0.957</td>
<td>0.900</td>
<td>0.989</td>
<td>0.957</td>
</tr>
<tr>
<td>Model 3 (7 factors) Clinical score (\geq 6) - hot water</td>
<td>3</td>
<td>45</td>
<td>0.978</td>
<td>0.940</td>
<td>0.938</td>
<td>0.979</td>
</tr>
<tr>
<td>Model 4 (6 factors) Clinical score (\geq 5) - hot water</td>
<td>6</td>
<td>44</td>
<td>0.957</td>
<td>0.880</td>
<td>0.880</td>
<td>0.957</td>
</tr>
<tr>
<td>Model 5 (2 factors) Genetic score (\geq 1)</td>
<td>6</td>
<td>38</td>
<td>0.826</td>
<td>0.880</td>
<td>0.864</td>
<td>0.846</td>
</tr>
</tbody>
</table>

PPV, positive predictive value; NPV, negative predictive value.

in 25–64% of patients with Dravet syndrome (Dravet et al., 2005). In this study, both the Dravet syndrome group and the non-Dravet syndrome group had a high frequency of a family history of seizures, so there was no significant difference between the groups.

Risk factors for epilepsy after FS have been investigated for a number of years. An onset of seizures before one year of age, convulsions with focal features, prolonged seizures, repeated seizures within 24 h, and a family history of seizures in first-degree relatives have been reported as risk factors (Nelson & Ellenberg, 1976; Annegers et al., 1979; Annegers et al., 1987). It is interesting that the risk factors for Dravet syndrome were similar to those for epilepsy after FS in some respects.

Hot water–induced seizures are often observed in Japanese patients with Dravet syndrome (Oguni et al., 2001; Ohmori et al., 2003). The Japanese have a custom of bathing with hot water at 40–42°C. Most of the patients had experienced a generalized or unilateral convulsion after elevation of the body temperature by a hot bath for several minutes. A significantly higher ratio of this phenomenon in patients with Dravet syndrome may suggest that Dravet syndrome displays a greater degree of thermosensitivity than common FS.

The incidence of epileptic discharge on EEG in the non-Dravet syndrome group was high (26%). Twenty-eight of the 50 patients (56%) in the non-Dravet syndrome group had subsequent afebrile seizures. The non-Dravet syndrome group included not only benign cases with simple

Figure 2.
Distribution of the sum of the risk scores when the Model 1 is applied to each patient.

Epilepsia © ILAE
FS but also the complicated cases. As a result, the complicated cases in the non-Dravet syndrome group may thus contribute to high rates of epileptic discharges and subsequent epilepsy.

Early photosensitivity is known to be one of the EEG characteristics of Dravet syndrome. Our subjects included both typical Dravet syndrome and borderline Dravet syndrome. The incidence of photosensitivity in borderline Dravet syndrome cases is usually low (Oguni et al., 2001; Ohmori et al., 2003). This may therefore be the cause of the lower incidence of PPR on EEG in our cases in comparison to previous studies (Dravet et al., 2005).

SCN1A mutations were initially found in large families with GEFPS+ in 2000 (Escayg, 2000). A missense SCN1A mutation was reported in a family with children who experienced simple febrile convulsions (Mantegazza et al., 2005), but this mutation was considered to be a rare case (Malacarne et al., 2002). There was no comparison of the detection of SCN1A mutations in children under one year of age with FS who did and did not develop Dravet syndrome. In this study, 6 of the 50 (12%) patients who experienced FS before their first birthday had SCN1A missense mutations. The rate of SCN1A mutations in the non-Dravet syndrome group was higher than that reported in previous studies (Escayg et al., 2001; Wallace et al., 2001). In previous studies, the subjects included idiopathic generalized epilepsy such as juvenile myoclonic epilepsy, childhood absence epilepsy, juvenile absence epilepsy, and generalized tonic–clonic seizures on awakening. A single-stranded conformation analysis was undertaken for mutation screening. The difference in the detection rate might be due to differences in either the subjects or in the methodology of the genetic test.

Our data exhibited that both missense mutations and truncated mutations were significantly more common in the Dravet syndrome group. The SCN1A mutation analysis was a potential test for the prediction of Dravet syndrome.

Dravet syndrome has been diagnosed by a comprehensive evaluation of seizure types, clinical course, and EEG findings. An accurate diagnosis of Dravet syndrome at an early age requires an experienced child neurologist. Our risk score screening test in this study may enable general pediatricians to identify patients with Dravet syndrome at an early stage. A clinical risk score sum ≥ 6 was a successful cutoff value with a high sensitivity and specificity (Table 4, Model 3). Although adding a genetic score improved the diagnostic value of specificity, PPV, and NPV (Model 1), clinical score seemed to have sufficient sensitivity and specificity (Model 3). Since the SCN1A mutations were detected in other childhood epileptic syndromes, the SCN1A-associated epilepsies are considered to have a wide spectrum (Harkin et al., 2007). Moreover, considering that a genetic test is expensive to perform and it is not always available at all clinics, the screening test of clinical risk factors is therefore considered to be of growing in importance. Since the parental mosaicism of SCN1A mutations can lead to sibling cases of Dravet syndrome, an SCN1A mutation analysis will thus become more beneficial for genetic counseling rather than a diagnostic test of Dravet syndrome (Gennaro et al., 2006; Marin et al., 2006; Morimoto et al., 2006).

FS commonly begin between five months to six years of age. The occurrence of afebrile seizures after a febrile seizure is 2–7% (Nelson & Ellenberg, 1976, Annegers et al., 1979, Annegers et al., 1987). In this study, 28 of the 50 patients (56%) with a febrile seizure before one year of age later experienced afebrile seizures. The patients in the non-Dravet syndrome group also needed careful observation; however, they had a much more favorable outcome compared with those in the Dravet syndrome group.

As a result of our findings, we would like to propose the practical use of the screening test. If the sum of clinical risk scores ≥ 6, the patient has a high risk of Dravet syndrome (Model 3). If the patient does not habitually bathe in hot water, a sum of the clinical risk scores ≥ 5 is recommended as the predictive value for Dravet syndrome (Model 4). The SCN1A mutation analysis may be not available for all patients due to the high expense of the test. If the sum of the clinical risk scores before a genetic test is conducted is ≥ 6, the SCN1A mutation analysis is recommended. We focused on the utilization of the risk score screening test by general pediatricians. The proposed risk score could help to identify Dravet syndrome among infants who experience a febrile seizure. This proposal is a novel approach to predict Dravet syndrome before one year of age. Since it is a case control study, our proposal should be prospectively validated and further improved to increase its predictive value.

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REFERENCES


