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BRIEF COMMUNICATION

A retrospective study of the relation between vaccination and occurrence of seizures in Dravet syndrome

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Summary

Dravet syndrome is a severe epileptic encephalopathy starting in the first year of life. Mutations in *SCN1A* can be identified in the majority of patients, and epileptic seizures in the setting of fever are a clinical hallmark. Fever is also commonly seen after vaccinations and provocation of epileptic seizures by vaccinations in patients with Dravet syndrome has been reported, but not systematically assessed. In a retrospective evaluation of 70 patients with Dravet syndrome and *SCN1A* mutations, seizures following vaccinations were reported in 27%. In 58% of these patients vaccination-related seizures represented the first clinical manifestation. The majority of seizures occurred after DPT vaccinations and within 72 h after vaccination. Two-thirds of events occurred in the context of fever. Our findings highlight seizures after vaccinations as a common feature in Dravet syndrome and emphasize the need for preventive measures for seizures triggered by vaccination or fever in these children.

KEY WORDS: Vaccination, Seizure, Dravet, Severe myoclonic epilepsy of infancy, Fever, *SCN1A*.

Dravet syndrome, formerly severe myoclonic epilepsy of infancy (SMEI), is characterized by prolonged febrile seizures starting at about the age of 6 months. Other seizure types might be present at onset or develop later, including myoclonic seizures, complex partial seizures, and generalized tonic–clonic seizures, sometimes presenting as alternating hemiclonic seizures,. Although development is initially normal, plateauing occurs in the second year of life with subsequent intellectual disability (Dravet et al., 2005; Depienne et al., 2009). Mutations in *SCN1A,* coding for the alpha-1 subunit of the voltage-gated sodium channel, can be detected in up to 80% of children (Claes et al., 2001; Nabbout et al., 2003; Mulley et al., 2006).

The age of manifestation of Dravet syndrome overlaps with time points of routine vaccinations in children.

So-called ''vaccine encephalopathies'' are a poorly characterized group of heterogeneous conditions for which vaccinations are considered to be causal for a child's subsequent neurologic condition. Several authors commented on this being a misunderstanding, especially with respect to Dravet syndrome (Stephenson, 1991). A previous study has revealed 11 of 14 patients with alleged vaccine-related epileptic encephalopathies to be patients with Dravet syndrome carrying *SCN1A* mutations (Berkovic et al., 2006).

Because missing knowledge on the frequency of seizures following vaccination in patients with Dravet syndrome still causes delayed diagnoses as well as misperception of vaccination side effects and reduced vaccination coverage, we aimed to further delineate the relation of vaccination and the occurrence of seizures in 70 patients with Dravet syndrome.

Methods

Patient databases of eight German and Austrian pediatric epilepsy and neuropediatric centers were screened for patients with a diagnosis of Dravet syndrome (Dravet et al., 2005) and previously identified mutations in *SCN1A*. Genetic analysis including sequence analysis and screening for intragenic deletions and duplications was performed by commercial providers. All mutations identified were considered to be pathogenic.

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All seizures with reported relation to vaccination were recorded by review of clinical records and parental interviews. Because events occurring outside previously reported time intervals (0–3 days for inactivated vaccines and 6–11 days for attenuated vaccines, Farrington et al., 1995) might cause overestimation of the total number of events, further analysis was performed including only events within reported intervals.

Information on the type of vaccination and temporal relationship between vaccination and seizure was obtained. Parent's attitudes toward subsequent vaccinations and preventive measures were recorded if a vaccination-related seizure had been reported.

Results

Seventy patients (age at inclusion: median 10 years, range 2–22 years) with diagnosis of Dravet syndrome and *SCN1A* mutations were included. Information on vaccination-related events was obtained through medical records (21 cases) or parental interview (49 cases). All patients received at least one routine vaccination as recommended by the German federal institution for disease control and prevention (Robert-Koch Institute).

In total, 34 seizures following vaccination were reported in 19 (27%) of 70 patients at a median age of 6 months (range 3 months to 4.5 years). In 11 (16%) of 70 patients, that is, 58% of all patients with seizures following vaccination, the vaccination-related seizure was the first manifestation of Dravet syndrome, with a median interval between vaccination and seizure of 24 h.

Twenty-three (68%) of 34 seizures were accompanied by fever, occurring in 10 of 19 patients. Median intervals between vaccination and seizure were 24 h and 12 h for febrile and afebrile seizures, respectively. For patients who presented with their first seizure following vaccination, 6 (55%) of 11 events occurred with fever.

Prolonged seizures or status epilepticus resulting in hospitalization were present in eight patients (inactivated vaccines: 7 of 8, attenuated vaccines: 1 of 8); all patients had further prolonged seizures or status epilepticus independent of vaccination during the course of the disease.

Vaccinations preceding seizures included DTP (diphtheria, tetanus, pertussis; 6 of 34), MMR (measles, mumps, rubella; 5 of 34), influenza (1 of 34), and pneumococcal vaccine (1 of 34). DTP vaccinations were also administered as part of a pentavalent vaccine (plus polio and haemophilus influenzae type B) in 6 of 34 cases, a hexavalent vaccine (plus hepatitis B) in 8 of 34 cases, and in other combinations in 7 of 34 cases (Table S1 and Fig. S1).

Because parental interviews might be fraught with recollection bias, we separately analyzed the group of cases ascertained by retrospective analysis of medical records with 7 (33%) of 21 patients presenting with 12 seizures following vaccination (all of them within reported time intervals).

There were no significant differences when analyzing the whole group including all seizures reported ($p > 0.6$ for pairwise testing, chi square test, and Fisher's exact test where appropriate). Details on subgroup analyses are presented in Table 1.

In 7 (37%) of 19 patients, no further vaccinations were given as a consequence of previous vaccination-related seizures. In 2 of 19 patients, antipyretics were administered before or directly after the vaccination. Three of 19 patients received compensation as vaccine injuries according to German regulations.

Discussion

We retrospectively investigated the occurrence of vaccination-related seizures in 70 patients with Dravet syndrome. To create a homogenous group regarding clinical character-

Table 1. Subgroup analysis

	Retrospective analysis of medical records only (n = 21 patients)	Events within previously reported intervals (n = 70 patients)	Whole group (n = 70 patients)
Total no. of seizures	12	34	45
Total no. of patients with seizures after vaccination	7/21 pat. (0.33, 95% CI 0.15–0.57[a])	19/70 pat. (0.27, 95% CI 0.18–0.39[a])	24/70 pat. (0.34, 95% CI 0.24–0.47[a])
No. of patients with first seizure	5/7 pat. (0.71, 95% CI 0.30–0.95[a])	11/19 pat. (0.58, 95% CI 0.34–0.79[a])	13/24 pat. (0.54, 95% CI 0.33–0.74[a])
No. of febrile seizures	8/12 sz. (0.67, 95% CI 0.35–0.89[a])	23/34 sz. (0.68, 95% CI 0.49–0.82[a])	28/45 sz. (0.62, 95% CI 0.47–0.76[a,c])

This table demonstrates the relevant findings divided by the different subgroups analyzed, that is, the whole group including all patients, the group for which medical records were analyzed retrospectively, and the group of events that occurred within previously reported intervals (Farrington et al., 1995).
[a], $p > 0.6$ for pairwise testing (percentage and 95% confidence interval, chi square test and Fisher's exact test where appropriate).
sz., seizure.

istics and diagnostic certainty, only children with known *SCN1A* mutations were included.

Vaccination-related seizures are reported in about one-third of patients. In general, increased relative incidence for convulsions is found 0–3 days after DTP and 6–11 days after MMR vaccination, respectively (Farrington et al., 1995). We, therefore, restricted the analysis to cases with seizures that occurred within these intervals. However, it seems important to include all events for which parents and caregivers attribute the seizure or even the beginning of the epilepsy to the vaccination, as these will influence the parent's attitude toward further immunizations. As demonstrated in Table 1, results were similar when analyzing the whole group including all seizures reported.

Because of the retrospective nature of our study, the time-lag between the events occurring in childhood and the inclusion in this study might add bias in denominating correct intervals between the vaccination and the event. However, similar results of seizure frequencies were found for the subgroup of patients for which analyses of medical records were performed.

Thirty-two percent of seizures associated with vaccinations occurred in the absence of fever, implicating physiologic stress responses or immunologic reactions as precipitating factors in these patients. In contrast, two-thirds of seizures following vaccination within the whole group as well as within the group presenting with their first seizure were febrile seizures. Although fever and febrile seizures in the setting of vaccination might not differ with respect to clinical and pathophysiologic aspects from febrile seizures occurring in the course of infection, perception of the event might be different, as most parents had taken an active decision pro vaccination, whereas febrile illness might be perceived as an inevitable event in childhood. In response, this might cause feelings of guilt in cases where a severe illness starts following immunization of a child (Berkovic et al., 2006).

In 58% of patients the vaccination-related event was the first reported seizure. This estimate might be fraught with a certain inaccuracy due to the retrospective nature of our study. However, similar numbers were reported previously (Nieto-Barrera et al., 2000; Caraballo & Fejermann, 2006). This suggests that vaccination-related seizures are common in Dravet syndrome, and represent a possible presenting feature of this condition.

In the general population only a minority of children present with seizures after vaccinations, with febrile seizures occurring in 6–9 and 25–34 cases per 100,000 following immunization with DTwP (diphtheria, tetanus, whole cell pertussis) and MMR vaccines, respectively (Barlow et al. 2001). Afebrile seizures occur at even lower frequencies (Barlow et al. 2001). Hence, screening for *SCNA1* mutations in children with epilepsy starting in the first year of life that is clinically suggestive of Dravet syndrome and vaccination-related seizures might help to identify a significant subset of patients, enabling early therapeutic intervention and preventive measures for subsequent vaccinations.

In 37% of patients, parents and health care providers refrained from further vaccinations as a consequence of previous vaccination-related seizures. Although being only a relatively small case series, this may indicate that up to one-third of children with Dravet syndrome might not be adequately immunized. Therefore, misinterpretation of assumed causal relationships should be prevented and complete immunization status of these children has to be attempted to anticipate potentially preventable diseases. Supporting this notion, a recent study did not find any differences in cognitive outcome, neither between patients having their first seizure following a vaccination and patients with seizure-onset independent of a vaccination nor between patients who received vaccinations after seizure onset and those who did not (McIntosh et al., 2010). In one patient, antipyretics were systematically administered before and after all follow-up vaccinations without further vaccination-related seizures. Despite being a single case report, this suggests that vaccination-related seizures might be preventable at least in patients with febrile episodes. Due to the small numbers in this case series, conclusions regarding afebrile seizures following vaccination are limited, although preventive measures such as giving oral benzodiazepines for some days following the vaccination might be discussed. However, larger studies in children with isolated febrile seizures and no history of epilepsy did not demonstrate an effect of prophylactic antipyretic or anticonvulsive treatment (Strengell et al., 2009; Lux, 2010). A study from Japan showed only moderate effects of benzodiazepine, barbiturates, and chloral hydrate in preventing febrile status epilepticus in patients with Dravet syndrome (Tanabe et al., 2008). Further studies are needed to evaluate preventive measures for seizures in the setting of vaccination or febrile illness, especially for patients with Dravet syndrome.

Parents and health care providers should be educated about the natural history of this condition, with vaccination-related seizures being an additional feature in a genetically determined epilepsy syndrome.

Finally, coincidence of the first seizure and vaccination might also occur in other epileptic encephalopathies starting in early infancy, for example, West syndrome. Additional studies are needed to further investigate these correlations and to determine more general guidelines to prevent vaccination-related seizures.

In summary, we find that vaccination-related seizures are a common feature in Dravet syndrome, reported in up to one-third of all patients and might be the first presenting seizure in a significant subset of patients. We, therefore, suggest further studies to develop specific guidelines for the prevention of vaccination-related seizures in these children.

Acknowledgments

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. Sarah von Spiczak receives institutional support from the Christian-Albrechts-University Kiel, Germany and received a scholarship from the German Epilepsy Society for research activities (Otfrid-Foerster-Stipendium).

Disclosure

None of the authors has any conflict of interest to disclose.

References

Barlow WE, Davis RL, Glasser JW, Rhodes PH, Thompson RS, Mullooly JP, Black SB, Shinefield HR, Ward JI, Marcy SM, DeStefano F, Chen RT, Immanuel V, Pearson JA, Vadheim CM, Rebolledo V, Christakis D, Benson PJ, Lewis N; Centers for Disease Control and Prevention Vaccine Safety Datalink Working Group. (2001) The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *N Engl J Med* 345:656–661.

Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, Gill DS, Iona X, Mulley JC, Scheffer IE. (2006) De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. *Lancet Neurol* 5:488–492.

Caraballo RH, Fejermann N. (2006) Dravet syndrome: a study of 53 patients. *Epilepsy Res* 70:S231–S238.

Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. (2001) De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. *Am J Hum Genet* 68:1327–1332.

Depienne C, Trouillard O, Saint-Martin C, Gourfinkel-An I, Bouteiller D, Carpentier W, Keren B, Abert B, Gautier A, Baulac S, Arzimanoglou A, Cazeneuve C, Nabbout R, LeGuern E. (2009) Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. *J Med Genet* 46:183–191.

Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. (2005) 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*. John Libbey Eurotext Ltd, Montrogue, pp. 77–88.

Farrington P, Pugh S, Colville A, Flower A, Nash J, Morgan-Capner P, Rush M, Miller E. (1995) A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines. *Lancet* 345:567–569.

Lux AL. (2010) Treatment of febrile seizures: historical perspective, current opinions, and potential future directions. *Brain Dev* 32:42–50.

McIntosh AM, McMahon J, Dibbens LM, Iona X, Mulley JC, Scheffer IE, Berkovic SF. (2010) Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *Lancet Neurol* 9:592–598.

Mulley JC, Nelson P, Guerrero S, Dibbens L, Iona X, McMahon JM, Harkin L, Schouten J, Yu S, Berkovic SF, Scheffer IE. (2006) A new molecular mechanism for severe myoclonic epilepsy of infancy: exonic deletions in SCN1A. *Neurology* 67:1094–1095.

Nabbout R, Gennaro E, Dalla Bernardina B, Dulac O, Madia F, Bertini E, Capovilla G, Chiron C, Cristofori G, Elia M, Fontana E, Gaggero R, Granata T, Guerrini R, Loi M, La Selva L, Lispi ML, Matricardi A, Romeo A, Tzolas V, Valseriati D, Veggiotti P, Vigevano F, Vallee L, Dagna Bricarelli F, Bianchi A, Zara F. (2003) Spectrum of SCN1A mutations in severe myoclonic epilepsy of infancy. *Neurology* 60:1961–1967.

Nieto-Barrera M, Lillo MM, Rodríguez-Collado C, Candau R, Correra A. (2000) [Severe myoclonic epilepsy in childhood. Epidemiologoc analytical study]. *Rev Neurol* 30:620–624.

Stephenson JBP. (1991) Epilepsy *Curr Opin Neurol Neurosurg* 4:406–409.

Strengell T, Uhari M, Tarkka R, Uusimaa J, Alen R, Lautala P, Rantala H. (2009) Antipyretic agents for preventing recurrences of febrile seizures: randomized controlled trial. *Arch Pediatr Adolesc Med* 163:799–804.

Tanabe T, Awaya Y, Matsuishi T, Iyoda K, Nagai T, Kurihara M, Yamamoto K, Minagawa K, Maekawa K. (2008) Management of and prophylaxis against status epilepticus in children with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome)–a nationwide questionnaire survey in Japan. *Brain Dev* 30:629–635.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Temporal interval between vaccination and seizures.

Table S1. Vaccines and seizures in patients with Dravet syndrome.

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