Etiologies for Seizures Around the Time of Vaccination

WHAT'S KNOWN ON THIS SUBJECT: Childhood vaccinations mildly increase the risk of febrile seizures in the general pediatric population, during specific risk periods. However, vaccinations are common precipitants for (first) seizures in the genetically determined, fever-sensitive Dravet syndrome (formerly severe myoclonic epilepsy of infancy).

WHAT THIS STUDY ADDS: This study shows that in most children with epilepsy onset after vaccination, genetic or structural causes of epilepsy can be identified. This claim includes children with Dravet syndrome (~35%) but also children with benign epilepsy or preexistent encephalopathy.

abstract

OBJECTIVES: This study was an assessment of the incidence, course, and etiology of epilepsy with vaccination-related seizure onset in a population-based cohort of children.

METHODS: The medical data of 990 children with seizures after vaccination in the first 2 years of life, reported to the National Institute for Public Health and Environment in the Netherlands in 1997 through 2006, were reviewed. Follow-up data were obtained of children who were subsequently diagnosed with epilepsy and had had seizure onset within 24 hours after administration of an inactivated vaccine or 5 to 12 days after a live attenuated vaccine.

RESULTS: Follow-up was available for 23 of 26 children (median age: 10.6 years) with epilepsy onset after vaccination. Twelve children developed epileptic encephalopathy, 8 had benign epilepsy, and 3 had encephalopathy before seizure onset. Underlying causes were identified in 15 children (65%) and included *SCN1A*–related Dravet syndrome (formerly severe myoclonic epilepsy of infancy) or genetic epilepsy with febrile seizures plus syndrome (n = 8 and n = 1, respectively), a protocadherin 19 mutation, a 1qter microdeletion, neuronal migration disorders (n = 2), and other monogenic familial epilepsy (n = 2).

CONCLUSIONS: Our results suggest that in most cases, genetic or structural defects are the underlying cause of epilepsy with onset after vaccination, including both cases with preexistent encephalopathy or benign epilepsy with good outcome. These results have significant added value in counseling of parents of children with vaccination-related first seizures, and they might help to support public faith in vaccination programs. *Pediatrics* 2014;134:658–666

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KEY WORDS

Dravet syndrome, epilepsy, etiology, *PCDH19*, *SCN1A*, seizure, vaccination

ABBREVIATIONS

AEFI—adverse events following immunizations
EEG—electroencephalography
GEFS+—genetic epilepsy with febrile seizures plus
MMR—measles-mumps-rubella
PCDH19—protocadherin 19
RIVM—National Institute for Public Health and Environment in the Netherlands
SCN1A—neuronal sodium channel 1 subunit gene

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Parental fear of vaccination-induced neurologic deterioration has led to decreasing vaccination coverage and subsequent outbreaks of preventable infectious diseases in various countries.[1] However, development of neurologic deficits or epileptogenesis could not be related to vaccinations, in several independent epidemiologic studies.[2–6] In the general pediatric population, the risk of febrile seizures is twofold to fivefold increased on the day of administration of an inactivated vaccine and from day 5 up to 2 weeks after administration of a live attenuated vaccine.[2,5–9] A seizure within this risk period might be the first of an epilepsy syndrome, and parents might misinterpret the vaccination as the primary cause of the epilepsy.

In a retrospective study of 14 children with epileptic encephalopathy assumed to be caused by vaccination, 11 had Dravet syndrome due to de novo neuronal sodium channel 1 subunit (*SCN1A*) gene mutations.[10] Dravet syndrome (formerly severe myoclonic epilepsy of infancy) is a rare epilepsy syndrome with seizure onset in the first year of life often triggered by fever, infectious diseases, or vaccinations in a previously healthy child. In the second year, multiple intractable seizure types evolve and neurodevelopment slows.[11] In ∼80% of children with Dravet syndrome, a mutation in the *SCN1A* gene is detected.[12] These mutations occur de novo in ∼95%.[13,14]

The detection of a pathogenic *SCN1A* mutation in children with alleged vaccination encephalopathy proved that, although the vaccination might have triggered the first seizure, the epilepsy and subsequent intellectual disability were caused by a genetic defect.[10] Most published case series and retrospective cohort studies confirming *SCN1A*-related Dravet syndrome as a cause of alleged vaccination encephalopathy[15–18] have focused on epileptic encephalopathy. Only a few case reports have shown that occasionally other genetic causes of epilepsy also present with seizures after vaccination.[19,20]

To assess underlying causes in children with any epilepsy syndrome with onset after vaccination, we studied a nationwide 10-year cohort of children reporting possible epileptic seizures after vaccination.

METHODS

Selection of the Study Cohort (Stage 1)

We selected a cohort of children (N = 1269) with possible epileptic seizures after vaccination in the first 2 years of life, reported to the safety surveillance system of the Dutch National Immunization Program between January 1, 1997, and December 31, 2006.[17,21] This cohort was previously described in detail in a prevalence study of Dravet syndrome that was part of a project on vaccinations and Dravet syndrome approved by the medical ethical committee of the University Medical Centre Utrecht, Utrecht, Netherlands (no. 07/295).[17] Seizures with a temporal relation to vaccination, defined by occurrence within the risk interval of 24 hours after administration of an inactivated vaccine[2] or 5 to 12 days after a live attenuated vaccine (ie, measles-mumps-rubella [MMR] vaccine),[7,22,23] were considered to be vaccination related. Children without vaccination-related seizures were excluded from the present study.

Within the study period, the vaccination schedule in this age group included 4 doses of diphtheria, tetanus, pertussis, inactivated polio vaccine, *Haemophilus influenzae* type b vaccines in the first year of life and 1 dose of MMR vaccine at age 14 months. Additional vaccines were introduced between 2001 and 2006 (Supplemental Tables 4 and 5).[24,25]

Database of Adverse Events After Immunizations

During the study period, safety surveillance of the national immunization program was performed by the National Institute for Public Health and Environment (RIVM) by using an enhanced passive reporting system for adverse events following immunizations (AEFI).[21] AEFIs were reported by either child health clinic staff (∼80%), who routinely inquire about adverse events at the next clinic visit after vaccination (according to national guidelines for notification of AEFIs), or by other physicians or parents. The reporting rate of seizures as AEFIs was stable over the years and similar to the incidence rate within an active study.[26] Reported adverse events were registered in a database after extensive supplementation by obtaining detailed eyewitness accounts, medical history from clinic charts, and information from general practitioners.[25] From this database, we extracted the following data: administered vaccine, ages at vaccination, time of reporting of the AEFI and last follow-up, ages at first and last seizure, classification of seizure (s), body temperature at time of seizure (categorized as $<$37.5, 37.5–38.4, or $\geq$38.5°C), family history of seizures, and results of genetic, metabolic, and imaging studies.

Selection of Children With Epilepsy and Vaccination-Related Onset (Stage 2)

From the cohort of vaccination-related seizures, children in whom this reported seizure had been the first seizure, and who had been diagnosed with epilepsy, were selected. The parents of these children were contacted for written consent to retrieve additional data from medical files.

The following additional data were collected: age at last seizure and at last follow-up, types of seizures, response to treatment, results of electroencephalography (EEG), psychomotor development before and after seizure onset, comorbidity, family history, and results of physical examination and genetic, metabolic, and imaging studies.

Classification of Epilepsy Syndromes

Seizure types, epilepsy syndromes, and etiology were classified by a pediatric neurologist (F.E.J.) and a clinical geneticist (N.E.V.) according to the proposed International League Against Epilepsy classification of 2010 based on data from medical files and EEG reports.[27] Children were further categorized as follows: group I, children with a preexistent encephalopathy, defined as developmental delay preceding the seizure onset; group II, children with epileptic encephalopathy, defined as (temporarily) refractory seizures and developmental decline related to recurrent seizures; and group III, children with relatively benign epilepsy, defined as normal development and good seizure control.

Statistical Analysis

We compared the characteristics of reported seizures between children with and without epilepsy with vaccination-related onset in our cohort, and between the different subgroups of children with epilepsy. The Mann-Whitney U test or Kruskal-Wallis test was used to analyze continuous variables (ie, ages at first vaccination-related seizure, report of event, last follow-up). Binary variables (ie, proportions of types of vaccination [inactivated or live attenuated] and body temperature at the time of seizure [$<$38.5°C or $\geq$38.5°C]) were calculated with either Pearson's χ^2 test or the Fisher exact test. A threshold of α = 0.05 was considered significant.

RESULTS

Baseline Characteristics of Study Cohort

Within the studied 10-year period, 990 children were reported with 1022 possible epileptic seizures occurring in a temporal relation to either an inactivated vaccine (n = 695 [68.0%]) or live attenuated vaccine (n = 327 [32.0%]) administered in the first 2 years of life. The median age at the end of stage 1 follow-up was 15 months (Table 1). In these 10 years, 1.9 million infants received $>$7.5 million diphtheria, tetanus, pertussis, inactivated polio vaccine, *Haemophilus influenzae* type b combination vaccines, and 1.8 million toddlers received their first MMR vaccine.

Of the 990 reported children (Fig 1), 45 (4.5%) had been diagnosed with epilepsy during stage 1 follow-up; 26 (2.6%) had vaccination-related seizure onset and 19 (1.9%) had seizure onset before the reported vaccination-related seizure. A total of 945 children had febrile, afebrile, or atypical seizures but were not diagnosed with epilepsy during stage 1 follow-up. In 14 (1.4%) of the 990 children, an underlying etiology related to the seizures or seizure susceptibility had been reported to the RIVM during stage 1 follow-up. Those reports did not include any of the 26 children with epilepsy with vaccination-related onset (Fig 1, Table 2).

The 26 children with epilepsy with vaccination-related onset (median age at epilepsy diagnosis: 11.5 months; age range: 4–41 months) were older at follow-up than the other children (median: 19 vs 15 months; P = .009). They more often had subsequent vaccination-related seizures (23.1% vs 2.4% in all other children; $P <$ .001) and more often had body temperatures $<$38.5°C during the reported seizures (54.8% vs 20.8%; χ^2 test, $P <$ .001) (Table 1).

Follow-up of Children With Epilepsy and Vaccination-Related Onset

Parents of 23 (88%) of the 26 children with epilepsy with vaccination-related onset provided informed consent for retrieval of extended follow-up (stage 2) information from medical files. There were no significant differences in baseline characteristics between children with and without extended follow-up (data not shown). The median age at this extended follow-up was 10.6 years (range: 5.6–23.6 years). Genetic testing was performed in 14 (61%) of 23 children. Clinical characteristics and results of ancillary investigations are summarized in Table 3.

Group I: Presumed Preexistent Encephalopathy

Three (13%) of the 23 children with vaccination-related epilepsy onset already had developmental delay before seizure onset and developed mild to severe intellectual disability. They were therefore presumed to have preexistent encephalopathy. They developed fever-sensitive epilepsy with focal seizures and had abnormal results on brain MRI scans. One child (case 1) had a terminal microdeletion of chromosome 1q and the second child (case 2) had bilateral periventricular nodular heterotopias without a *FLNA*-mutation detected by using DNA sequencing. Both children had additional multiple congenital malformations and dysmorphic features. In the third child, a distinct developmental delay preceded the seizure onset, but genetic analyses had not been performed.

Group II: Epileptic Encephalopathy

Twelve (52%) of the 23 children with vaccination-related epilepsy onset were considered to have epileptic encephalopathy. All but 2 had intractable seizures. In 10 of the 12 children, an underlying cause was determined. Eight children (cases 4–11) were diagnosed with Dravet syndrome (previously described[17]) and had a pathogenic *SCN1A* mutation. One girl (case 12) had epilepsy and mental retardation restricted to female subjects and a de novo protocadherin 19 (*PCDH19*) mutation (described as case 7 in van Harssel et al[28]). One child (case 13) died unexpectedly at age 19 months. Postmortal microscopic examination of brain tissue showed a bilateral perisylvian neuronal migration disorder. Genetic analyses, performed with DNA

TABLE 1 Baseline Characteristics of Children With Vaccination-Related Seizures, With or Without Vaccination-Related Epilepsy Onset

Characteristics of Reports	All Children (n = 990)		P	Total No.	Children With Vaccination-Related Epilepsy Onset and Stage 2 Follow-up (n = 23)			P	Total No.
	Vaccination-Related Epilepsy Onset (n = 26)	Other Children (n = 964)			Group I: Presumed Preexistent Encephalopathy (n = 3)	Group II: Epileptic Encephalopathy (n = 12)	Group III: Benign Epilepsy (n = 8)		
Median age, mo (range), at									
First reported vaccination	5.6 (2.2–16.2)	11.6 (0.2–22.2)	.154	990	6.4 (5.6–15.1)	4.7 (2.3–12.1)	13.6 (4.7–16.2)	.005	23
Report of seizure to safety surveillance system	10.8 (4.3–166)	14.2 (0.3–73.4)	.860	990	11.9 (5.7–19.9)	6.9 (4.3–166)	16.4 (6.5–25.3)	.171	23
End of stage 1 follow-up	19 (7–166)	15 (0–105)	.009	990	18 (13–21)	19 (9–166)	23.5 (7–45)	.847	23
Number of children with									
Male gender, (%)	11 (42.3)	509 (52.8)	.290	990	1 (33.3)	5 (41.7)	4 (50.0)	.685[a]	23
Multiple reports of seizures after vaccinations, (%)	6 (23.1)	23 (2.4%)	<.001	990	1 (33.3)	4 (33.3)	1 (12.5)	.369[a]	23
Number of reported seizures	33	989		1022	4	17	9		30
Inactivated vaccine (versus attenuated vaccine, %)	27 (81.8)	668 (67.5)	.090	1022	3 (75)	17 (100)	5 (55.6)	.019[a]	30
Temperature <38.5°C, (%)	17 (54.8)	193 (20.8)	<.001*	961	3 (75)	10 (66.7)	3 (33.3)	.114[a]	28

* P = .001 for inactivated vaccines and P = .018 for live attenuated vaccines; P = .025 for inactivated vaccines, when known Dravet syndrome was excluded.

[a] Fisher exact test, group III versus groups I and II.

extracted from postmortal tissue, failed.

One child (case 14) had fever-sensitive epilepsy, which was drug resistant in infancy but relatively well controlled later on. Results of extensive metabolic and molecular testing, including analysis of the *SCN1A* and the *PCDH19* gene and testing for Angelman syndrome, did not reveal an underlying cause. The last child (case 15) was diagnosed with West syndrome, which later developed into Lennox-Gastaut syndrome. Extensive metabolic and genetic analyses, including analysis of the *SCN1A* gene, did not reveal an underlying cause.

Group III: Benign Epilepsy

Eight (35%) of the 23 children with vaccination-related epilepsy onset were considered to have relatively benign epilepsy. Seven of the 8 children were seizure-free without use of antiepileptic drugs at follow-up. The median age at last seizure was 4 years (range: 1.3–8.5 years). An underlying genetic etiology was identified or was plausible on the basis of the family history in 3 of the 8 children.

Five of the 8 children had fever-sensitive epilepsy classified as febrile seizures plus (cases 16 and 19–22). In 3 children, a (grand)parent had had febrile seizures as well, consistent with a diagnosis of genetic epilepsy with febrile seizure plus (GEFS+) syndrome. In only 1 of those 5 children had genetic testing been performed (case 16). In this child, DNA-analysis of the *SCN1A* gene showed a pathogenic mutation, inherited from her affected father (previously described[29]).

The 3 other children had epilepsy without fever sensitivity (cases 17, 18, and 23). Two of these 3 children (cases 17 and 18) had multiple, similarly affected family members and were either diagnosed with benign familial infantile epilepsy or unclassified familial epilepsy (Fig 2). Both

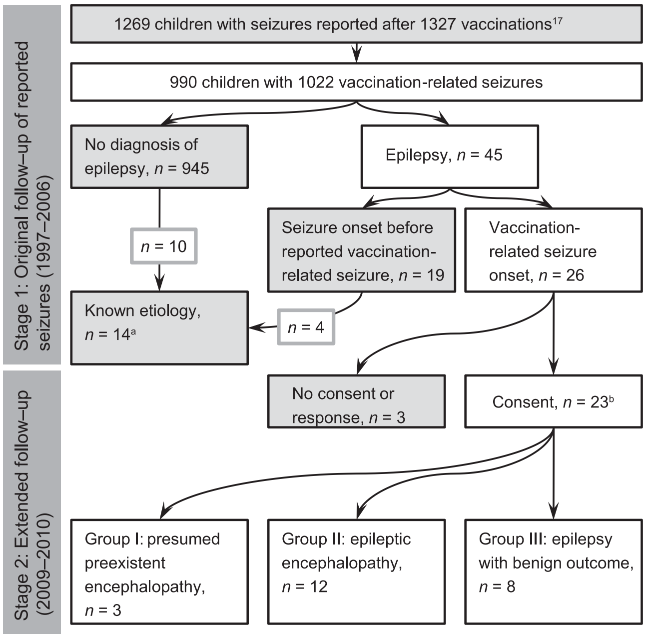

FIGURE 1
Design of study and overview of results. [a]See Table 2. [b]See Table 3.

pedigrees were compatible with autosomal dominant inherited epilepsies, but neither family opted for genetic testing. Case 17 had mild learning problems, as did several other family members with and without epilepsy. The clinical history and EEG results were not compatible with a diagnosis of epileptic encephalopathy. Case 23 had unclassified epilepsy with a negative family history for seizures.

Differences in Characteristics Between Subgroups of Children With Epilepsy Who Had Vaccination-Related Onset

In children with presumed preexistent (group I) or epileptic (group II) encephalopathy, seizures occurred more often after administration of inactivated vaccines (75% and 100%, respectively) and started at younger ages (median: 6.4 and 4.7 months) than in children with benign epilepsy (group III: 55.6% [*P* = .019, Fisher exact test for group I/II versus group III], and 13.6 months [*P* = .005, Kruskal-Wallis test]). There were no statistically significant differences between the 3 subgroups in body temperature at the time of seizure, delay between seizure and time of report, or age at original follow-up by the RIVM (Table 1).

DISCUSSION

In this Dutch, nationwide, 10-year cohort of children reported with possible epileptic seizures in a time frame related to a vaccination, 26 children (2.6%) were identified in whom the reported seizure was the first of an epilepsy syndrome. Extended follow-up of 23 of these children found that 12 had developed epileptic encephalopathy, 3 had preexisting encephalopathy, and 8 had well-controlled epilepsy with normal cognitive outcome.

Underlying causes of the epilepsy syndromes were detected in two-thirds of children, were genetic in the majority of these children, and were likely genetic in 2 additional cases because of the presence of cortical malformations, dysmorphic features, and other congenital anomalies.

TABLE 2 Underlying Causes of Seizures Related to Vaccination, Reported at Stage 1 Follow-up (14 of 990 Children)

Type of Etiology According to ILAE 2010	Etiology	Type of Seizures	Gender	Vaccination	Age at Vaccination (mon)
Children with vaccination-related seizure onset					
Genetic	Sotos syndrome	Multiple simple FS	Male	MMR	15.5
Genetic	Down syndrome	Atypical seizure	Male	dh1	3.0
Genetic	Down syndrome	Atypical seizure	Male	dh3	6.9
Genetic	Wolf-Hirschhorn syndrome	Simple FS	Male	MMR	14.8
Structural	Dandy-Walker cyst and congenital hydrocephalus	Simple FS	Male	dh4	21.5
Acute symptomatic	Acute arterial media infarct due to thrombus in cardiomyopathy	Afebrile, focal seizure	Female	dh2	3.7
Acute symptomatic	Human herpesvirus 6 infection	Complex FS	Female	MC	14.6
Acute symptomatic	Invagination	Atypical seizure, not epileptic	Female	MC	15.5
Children with seizure onset before vaccination-related seizure					
Genetic	GEFS+ syndrome due to *SCN1A* mutation	Multiple complex FS	Female	MC	15.4
Structural	Perinatal intracerebral hemorrhage	Epilepsy	Male	dh3	5.3
Structural	Congenital toxoplasmosis infection	Epilepsy	Female	dh3	6.5
Structural	Perinatal intracerebral hemorrhage	Epilepsy	Male	dh3	6.8
Structural	Pyridoxine-dependent epilepsy	Epilepsy	Female	dh4	11.1
Structural	Previous stroke	Multiple simple FS	Male	d4	16.3

dh, dtp-ipv(-)hib vaccine; FS, febrile seizure; ILAE, International League Against Epilepsy; MC, MMR and meningitis C vaccine.

In children with identified genetic causes, these fully explained the electroclinical syndromes and other clinical features. Although no underlying cause was detected in one-third of children with epilepsy with vaccination-related onset, a genetic basis of epilepsy in these children is still possible: genetic analyses were incomplete, some children had positive family histories for seizures, and molecular defects underlying many genetically determined epilepsies have yet to be discovered. In the past, the absence of a detectable underlying cause in children with vaccination-related seizure onset led to the assumption that the vaccination itself was the cause of the subsequent neurologic deterioration in some. However, the large variability in electroclinical syndromes and corresponding cognitive outcomes in our study further support the hypothesis that predisposing factors within the child, and not the vaccination, cause the observed neurologic deterioration.[10]

The administered vaccines could have acted as a trigger for the first seizure, thereby unmasking the genetic seizure predisposition in the children in our cohort. Seizure precipitation by vaccination or fever is a hallmark of *SCN1A*-related Dravet syndrome.[15,30–32] Although fever is a known seizure precipitant in children with a *PCDH19* mutation, a 1q-terminal deletion, and *SCN1A*-related GEFS+ syndrome,[33–36] our study is the first to acknowledge vaccination-related onset in the latter 3 syndromes. A chance association is unlikely because vaccination-related seizures recurred after a second vaccination in both the GEFS+ and 1qter case, occurred in an additional case of *SCN1A*-related GEFS+ syndrome with only febrile seizures (Table 1), and have previously been reported in another girl with a *PCDH19* mutation[19] and 2 GEFS+ cases.[37]

The majority of children with vaccination-related onset of epilepsy in our study were reported to have fever-sensitive epilepsy at follow-up. Interestingly, these children more often had vaccination-related seizures with body temperature <38.5°C, which was significantly lower than in all other children, confirming previous observations in patients with Dravet syndrome.[17] In this study, we found that significance is sustained after exclusion of children diagnosed with Dravet syndrome (data not shown), suggesting that many children with vaccination-related epilepsy onset have an increased sensitivity to even mild body temperature elevations.

One-quarter of our cases with vaccination-related epilepsy onset had seizures reported after subsequent vaccinations as well. This finding raises the question as to whether these children should receive further vaccinations. The present study was not designed to test the influence of further vaccinations on disease course. However, a study on Dravet syndrome found no differences in outcome between children who did or did not receive further vaccinations.[15] In the groups of children with presumed preexistent and epileptic encephalopathies, all except one reported seizure occurred after inactivated instead of live attenuated vaccines. Because the estimated increased risks of seizures after both vaccine types are roughly the same,[2] this difference is probably largely explained by the higher number of administered inactivated vaccines (ratio: 4 to 1 live attenuated vaccine) in the first 2 years of life. However, currently, developed countries mainly use less reactogenic acellular pertussis vaccines.[26] Moreover, cancellation of vaccination increases the risk of a vaccine-preventable disease (eg, pertussis, measles). These diseases may also induce seizures or cause other, more severe complications. All these aspects must be taken into account when reviewing current vaccination guidelines for children with epilepsy.

In our study, approximately one-third of all children with epilepsy with vaccination-related onset had benign epilepsy. This information is important for clinicians and parents because previous studies focused mainly on epileptic encephalopathy with onset after vaccination. This method may have given the false impression that vaccination-related seizure onset in general has a bad prognosis. The proportion of children with benign epilepsy in our study may even be underestimated because we selected a cohort from an enhanced passive reporting system for AEFI. The parents of children with more severe epilepsies may be more likely to consider vaccinations causative of the epilepsy and more willing to report seizures as an AEFI.[38,39] Because the time interval between the first seizure and the diagnosis of epilepsy is probably longer, and our initial follow-up period was limited, a diagnosis may not have been made within the follow-up period and thus have led to an underestimation of the proportion of benign epilepsy in our study. However, the Dutch vaccine adverse event surveillance system has a very high reporting rate, with limited underreporting of severe adverse events such as seizures.[25,26] Further bias toward a specific subgroup is probably limited because of the high response rate, long prospective follow-up, similar length of initial follow-up, and similar delay in reporting the vaccination-related seizure in the 3 subgroups of epilepsy with vaccination-related onset.

We confirm the high proportion of children with *SCN1A*-related Dravet syndrome (8 of 12 cases within the subgroup of patients with epileptic encephalopathy) that was previously described.[10] In our study,

TABLE 3 Characteristics of Epilepsy and Development and Underlying Causes in Children With Vaccination-Related Epilepsy Onset, At Stage 2 Follow-up

No.	Gender	Age at Vaccination (mon)	Reported Vaccinations	Seizure Classification	Fever sensitivity	Electroclinical Syndromes	Outcome	Etiology
Group I: Presumed preexistent encephalopathy								
1	Female	6.4	dh3, 4	GTCS SE At F	+	Epilepsy due to chromosomal disorder	I	Genetic; 1qter deletion
2	Male	5.6	dh3	F GTCS	+	Epilepsy due to neuronal migration disorder	C	Structural; BPNH
3	Female	15.2	MMR	F	+	Unclassified epilepsy	I	Unknown
Group II: epileptic encephalopathy								
4	Female	3.9	dh2, 4	GTCS F SE M A H At	+	Dravet syndrome	I	Genetic; *SCN1A*
5	Female	3.4	dh1, 2, 3	GTCS H F A M	+	Dravet syndrome	I	Genetic; *SCN1A*
6	Male	4.4	d2	GTCS H A M	+	Dravet syndrome	I	Genetic; *SCN1A*
7	Male	5.2	dh3	GTCS H SE F A M	+	Dravet syndrome	I	Genetic; *SCN1A*
8	Male	4.8	dh3	GTCS H T SE M F A	+	Dravet syndrome	I	Genetic; *SCN1A*
9	Male	4.9	dh2	GTCS H SE M F	+	Dravet syndrome	I	Genetic; *SCN1A*
10	Female	4.6	dh3	GTCS At F SE	+	Dravet syndrome	C	Genetic; *SCN1A*
11	Male	4.4	dh3, 4	GTCS M At A SE	+	Dravet syndrome	I	Genetic; *SCN1A*
12	Female	12.1	dh4	GTCS H T M A	+	Epilepsy and mental retardation limited to female subjects	I	Genetic; *PCDH19*
13	Female	2.3	dh1, 2	F GTCS SE	+	Epilepsy due to neuronal migration disorder	Died	Structural; BPSMD (pathology)
14	Female	6.4	dh3	GTCS SE F	+	Unclassified epilepsy	C	Unknown
15	Female	5.3	dh3	IS, F GTCS M A At	–	West syndrome; Lennox-Gastaut	I	Unknown
Group III: epilepsy with good outcome								
16	Female	13.0	dh4, MMR	GTCS F	+	Febrile seizures plus	SF	Genetic; *SCN1A*
17	Female	4.7	dh3	F	–	Unclassified, familial epilepsy	SF	Genetic; ND
18	Male	5.5	dh3	GTCS	–	Benign familial infantile epilepsy	SF	Genetic: ND
19	Female	11.2	dh4	GTCS A SE	+	Febrile seizures plus	C	Unknown
20	Male	14.5	mc[c]	F A	+	Febrile seizures plus	SF	Unknown
21	Female	14.3	MMR	GTCS SE	+	Febrile seizures plus	SF	Unknown
22	Male	16.2	MMR	GTCS F A	+	Febrile seizures plus	SF	Unknown
23	Male	14.6	mc	F	–	Unclassified	SF	Unknown

A, absence; At, atonic; BPNH, bilateral periventricular nodular heterotopias; BPSMD, bilateral perisylvian migration disorder; C, controlled with antiepileptic drugs; CT, computed tomography; d = diphtheria, tetanus, whole-cell pertussis, inactivated polio vaccine; DD, developmental delay; DN, de novo; F, focal seizure; GTCS, generalized tonic-clonic seizure; h, *Haemophilus influenzae* type b; H, hemiconvulsion; I, intractable; IS, infantile spasms; ND, not determined; M, myoclonia; mc, MMR and meningococcal serogroup C; NA, not available; P, paternal; SE, status epilepticus; SF, seizure free; T, generalized tonic seizure.

[a] Congenital malformations and dysmorphic features.

[b] First- or second-degree relative with febrile seizures or epilepsy.

[c] Seizure categorized as temporally related to meningitis C vaccination because of 13-hour interval.

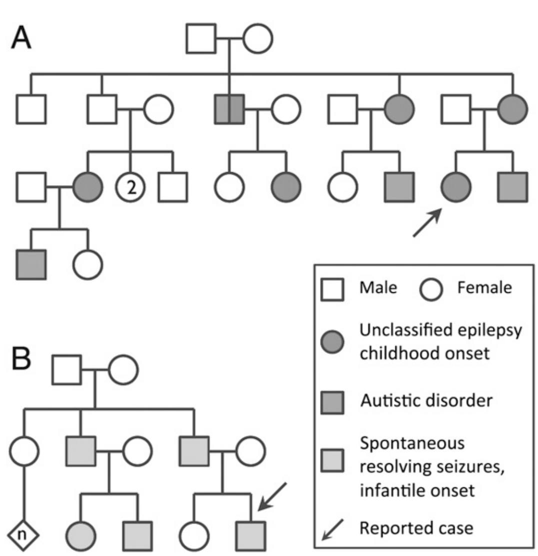

FIGURE 2
Family pedigrees. A, Case 17 with unclassified epilepsy. B, Case 18 with benign familial infantile epilepsy. The inheritance pattern of epilepsy was compatible with autosomal dominant transmission in both families.

West syndrome was a much less frequently identified epilepsy syndrome after vaccination, in contrast to another study,[18] probably because we used strict criteria for a temporal relation between vaccination and seizures.

CONCLUSIONS

In our cohort, underlying genetic or structural causes were identified in 65% of children with epilepsy with vaccination-related onset. These underlying causes were not limited to *SCN1A*-related Dravet syndrome but extended to other genetically determined fever-sensitive epilepsies. In addition, one-third of cases had

Inheritance	CT/MRI scan of brain	Preexistent DD	Developmental Delay	Intellectual Disability	Malformations[a]	Molecular Testing	Family History[b]
DN	Atrophic cortex	+	+	+	+	+	–
	BPNH	?	+	+	+	+	–
	White matter lesions	+	+	+	–	–	–
DN	Normal	–	+	+	–	+	+
DN	Normal	–	+	+	–	+	+
DN	Normal	–	+	+	–	+	–
DN	Aspecific	–	+	+	–	+	+
ND	Aspecific	–	+	+	–	+	+
DN	Normal	–	+	+	–	+	–
DN	Mild atrophia	–	+	+	–	+	–
DN	Normal	–	+	+/–	–	+	–
DN	Normal	–	+	+	–	+	–
	Atrophia, white matter lesions	?	+	NA	+	–	–
	Arachnoid cyst	–	+	+	–	+	–
	Normal	–	+	+	–	+	–
P	NA	–	–	–	–	+	+
	Normal	–	+	–	–	–	+
	NA	–	–	–	–	–	+
	NA	–	–	–	–	–	+
	NA	–	–	–	–	–	–
	Normal (CT)	–	–	–	–	–	–
	Normal	–	–	–	–	–	+
	NA	–	–	–	–	–	–

relatively benign epilepsy with good outcome, showing that vaccination-related epilepsy onset does not necessarily have a poor prognosis. These results imply that early genetic testing should be considered in all children with vaccination-related onset of epilepsy and might help to support public faith in vaccination programs.

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