Alleged Cases of Vaccine Encephalopathy Rediagnosed Years Later as Dravet Syndrome

AUTHORS: Ila S. Reyes, MD,[a] David T. Hsieh, MD,[a,b] Linda C. Laux, MD,[c] and Angus A. Wilfong, MD[d,e]

[a]Department of Pediatrics and [b]Division of Child Neurology, San Antonio Military Medical Center, Fort Sam Houston, Texas; [c]Pediatrics and Neurology, Northwestern University Feinberg School of Medicine, Children's Memorial Epilepsy Center, Children's Memorial Hospital, Chicago, Illinois; [d]Pediatrics and Neurology, Baylor College of Medicine, Houston, Texas; and [e]Comprehensive Epilepsy Program, Texas Children's Hospital, Houston, Texas

KEY WORDS

diphtheria-pertussis-tetanus vaccine, Dravet, seizures, febrile, epilepsies, myoclonic

ABBREVIATION

SCN1A—neuronal sodium channel α1 subunit

The views expressed in this article are those of the authors and do not reflect the official policy or position of the US Air Force, Department of Defense, or the US government.

www.pediatrics.org/cgi/doi/10.1542/peds.2010-0887

doi:10.1542/peds.2010-0887

Accepted for publication Apr 28, 2011

Address correspondence to David T. Hsieh, MD, Division of Child Neurology, Department of Pediatrics, San Antonio Military Medical Center, 3851 Roger Brooke Dr, Fort Sam Houston, TX 78234. E-mail: david.hsieh@us.af.mil

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

abstract

Dravet syndrome is a rare epileptic encephalopathy linked to mutations in *SCN1A* (neuronal sodium channel α1 subunit) and characterized by an onset in infancy with polymorphous seizure types and developmental decline. It was reported recently that a proportion of patients previously diagnosed with alleged vaccine encephalopathy might possess *SCN1A* mutations and clinical histories that enabled a diagnosis of Dravet syndrome, but these results have not been replicated. We present here the cases of 5 children who presented for epilepsy care with presumed parental diagnoses of alleged vaccine encephalopathy caused by pertussis vaccinations in infancy. Their conditions were all rediagnosed years later, with the support of genetic testing, as Dravet syndrome. We hope that these cases will raise awareness of Dravet syndrome among health care providers who care for children and adolescents and aid in earlier recognition and diagnosis. *Pediatrics* 2011;128:e699–e702

Childhood immunization is arguably the most successful modern advance in the promotion of children's health. It is fortunate that serious adverse events after immunizations are rare, but pertussis vaccine in particular has been implicated as an alleged cause of a postvaccination, acquired, chronic encephalopathy despite a lack of supportive epidemiologic evidence.[1] It was recently recognized that a proportion of cases of alleged vaccine encephalopathy might have an alternative explanation: an underlying genetically based channelopathy known as Dravet syndrome.[2]

We describe here 5 cases of alleged vaccine encephalopathy in which the parents of children with developmental delays and medically refractory epilepsy had strong suppositions that their child's chronic encephalopathy was a result of pertussis immunization received in infancy, before the correct diagnosis was made. On the basis of their clinical presentations, these patients had additional genetic testing and were rediagnosed years later with Dravet syndrome.

SAMPLE CASE REPORT: PATIENT 1

A 14-year-old mentally retarded boy with autistic features was continuing to have daily complex partial and myoclonic seizures, which were sensitive to triggering by hot weather and bright lights, despite multiple antiepileptic drugs and a vagal nerve stimulator. The patient was a healthy infant until his scheduled immunizations, which included the diphtheria, tetanus, acellular pertussis (DTaP) vaccine, at 7 months of age. Within hours after immunization, the patient became febrile and had a generalized seizure. Over the next several months, he continued to have frequent and prolonged convulsions with almost any febrile illness, including 3 episodes of febrile status epilepticus. Afebrile seizures and subsequent developmental stagnation was noted by the age of 2 years. It was the parents' impression that the pertussis component of the DTaP vaccination was the underlying etiology.

Previous brain MRI results were normal, and an electroencephalogram revealed both focal and generalized epileptiform discharges. Neuronal sodium channel α1 subunit (*SCN1A*) genetic testing revealed a previously reported[3] de novo G529A mutation, which supported a diagnosis of Dravet syndrome.

SUMMARY OF CASES

These 5 patients (Table 1) all had their initial seizure in the first year of life within 24 hours of their vaccinations; some (patients 1–3) had an associated fever, and some (patients 4 and 5) did not. During the first year of life, recurrent febrile and afebrile generalized and unilateral convulsions were primarily noted. These seizures were often prolonged. After 1 year of age, other seizure types developed, including partial seizures, myoclonic seizures, and atypical absence seizures. These different seizures were intractable to multiple medication trials. After the patients developed intractable epilepsy, subsequent cognitive issues were noted that ranged from mild delay to significant cognitive impairment. Three of the patients also developed behavioral issues with autistic-like features. Results of all etiologic testing were unremarkable, including brain imaging studies. The parents of these 5 patients had felt that pertussis vaccination during infancy was to blame for their child's neurologic symptoms. Subsequent *SCN1A* testing results were positive for all patients and were proved de novo through parental testing in 4 of 5 patients. Parental testing was not available for patient 2 because he had been adopted; his diagnosis of Dravet syndrome was based on both his clinical phenotype and his *SCN1A* deletion, which is predictive of a severe phenotype.

DISCUSSION

Dravet syndrome, recognized by the International League Against Epilepsy as severe myoclonic epilepsy of infancy,[4] is a rare genetic epileptic encephalopathy characterized by treatment-resistant polymorphic seizures and developmental decline.[5] Seizures begin in the first year of life; they are often provoked by fevers and later evolve into afebrile seizures. Photosensitivity and heat sensitivity are classic features. Development is normal initially, but slowing, stagnation, or regression is often evident by 2 to 5 years of age and might include autistic traits or hyperactivity.[6] Initial electroencephalograms are usually normal but might eventually reveal epileptiform discharges. Neuroimaging is also normal initially but might eventually reveal hippocampal sclerosis[7] or mild atrophy. Genetic testing is supportive: mutations in the *SCN1A* gene, which codes for the α subunit of the voltage-gated neuronal sodium channel, can be found in up to 80% of cases and are often de novo mutations.[8,9] Less commonly, some patients might have genetic deletions that are detected by using multiplex ligation-dependent probe amplification.[10] Early diagnosis is essential for optimal treatment, because several antiepileptic drugs are known to exacerbate seizures in patients with Dravet syndrome (eg, carbamazepine[11] and lamotrigine[12]).

It was recently reported from a retrospective study that a proportion of patients previously diagnosed with a postvaccination encephalopathy might actually have Dravet syndrome.[2] In that study it was found that of 14 patients with an onset of an unexplained encephalopathy within 72 hours of pertussis vaccination, 11 had a corre-

TABLE 1 Patient Characteristics

Patient No.	Initial Development	Seizure Onset, mo	Time Between Vaccinations and Seizure, h	Initial Seizure Type	Subsequent Seizures	Development and Behavioral Issues	Brain MRI	EEG at Diagnosis	*SCN1A* Testing	Age at Diagnosis of Dravet Syndrome, y
1	Normal	7	<12	Febrile generalized convulsion	GTCs, myoclonic, partial	Plateau age: 2 y; autistic-like features	Normal	Generalized, focal discharges	De novo missense mutation (G529A, Gly177Arg)	14
2	Normal	2	<12	Febrile generalized convulsion	GTCs, HCs, partial	Delayed; autistic-like features	Normal	Focal discharges, slowing	Deletion of one copy of all 26 exons	20
3	Normal	4	<12	Febrile generalized convulsion	GTCs, partial	Mild expressive speech delay	Initial abnormality resolved	Normal	De novo missense mutation (A1171C, Thr391Pro)	2
4	Normal	6	<24	Afebrile unilateral clonic seizure	GTCs, HCs, myoclonic	Slowing	Normal	Generalized discharges, slowing	De novo nonsense mutation (C5734T, Arg1912Stop)	4
5	Normal	4	<24	Afebrile unilateral clonic seizure	GTCs, HCs, myoclonic, absence	Regression age 1 y; autistic-like features	Normal	Generalized, focal discharges	De novo missense mutation (T4837C, Phe1463Leu)	3

EEG indicates electroencephalogram; GTC, generalized tonic-clonic seizure; HCs, hemiconvulsions; de novo mutations, the parents' test results were negative.

sponding Dravet syndrome phenotype, 10 of whom had *SCN1A* mutations. The results of this study, however, have not been replicated.

Because the natural history of Dravet syndrome includes both onset in infancy and sensitivity to elevated temperatures, these features might coincide temporally with the childhood immunization schedule for infants. In the 5 patients presented in our series, pertussis vaccination during infancy had been viewed by the parents as the primary cause of their child's chronic encephalopathy and refractory epilepsy because of this temporal relationship (all <24 hours after vaccination). Although the presence of a postvaccination fever might further enhance parental misconceptions, in our series, only 3 of the 5 patients had their first seizure after vaccination concomitantly with a fever. An alternative explanation, now with the support of genetic testing, is that vaccination acted as a trigger for seizures in these patients who already had a genetic susceptibility to epileptic seizures. It is also important to note that although vaccination might trigger an earlier onset of the presenting symptoms of Dravet syndrome, there is no evidence that the outcomes, in terms of subsequent seizure types or intellect, are any different between those patients with Dravet syndrome whose symptoms started within 2 days of vaccination and those whose symptom onset was not related temporally to vaccination.[13]

The actual existence of a pertussis vaccine–related encephalopathy, itself, is debatable. Although a slight increased risk of a postvaccination encephalopathy was described by the National Childhood Encephalopathy Study in the United Kingdom,[14] subsequent analyses did not reveal any cases that could be attributed to vacci-

nation.[1] Furthermore, subsequent studies have not found an association between pertussis vaccination and a postvaccination encephalopathy.[15,16] In a prospective active surveillance program in the United States, there was no statistically significant increased risk of a serious acute neurologic illness within 7 days of diphtheria, tetanus, pertussis vaccination.[15]

In our patients, the reasons that the parents held the perception that their child had vaccine encephalopathy were not fully delineated because these perceptions spanned long periods of up to 20 years before proper diagnosis. It is known that parental knowledge of vaccines is obtained from a variety of sources outside of the health care team, including newspapers and magazines, friends and family, and the Internet.[17] However, because physicians are viewed as the most important source of vaccine information,[17] pediatricians play a vital role in avoiding vaccine misconceptions by parents. This role, in part, involves the recognition of the debatable existence of pertussis vaccine encephalopathy and also the recognition of Dravet syndrome as a possible alternative diagnosis.

Although not prospectively validated, a scoring system for identifying patients as possibly having Dravet syndrome after presenting with febrile seizures before 1 year of age has been described.[3] The most significant risk factors identified were an onset before 7 months of age, hemiconvulsions, 5 or more total febrile seizures, and febrile seizures lasting more than 10 minutes.[3] However, any patient with a clinical course suggestive of Dravet syndrome, especially in the context of an onset of symptoms after vaccination, with or without fever, should be considered for further evaluation.

CONCLUSIONS

The clinical presentation of Dravet syndrome can resemble that of cases of alleged vaccine encephalopathy. Because *SCN1A* genetic testing has become more available only recently, patients of any age with an unexplained chronic encephalopathy and a suggestive clinical history should be considered for genetic testing for Dravet syndrome.

Although Dravet syndrome is rare, its recognition is important for pediatricians in the campaign for childhood immunizations, because it offers an alternative genetic explanation to refute alleged cases of vaccine encephalopathy. Of further importance to patients with Dravet syndrome and their families are the genetic, prognostic, and treatment implications that are gained from correct diagnosis and epilepsy syndrome assignment.

We have presented the cases of 5 additional children with perceived diagnoses of vaccine encephalopathy who were all rediagnosed later with Dravet syndrome. We hope that these cases will raise awareness of Dravet syndrome among health care providers who take care of children and adolescents and will aid in earlier recognition and diagnosis.

REFERENCES

1. Shorvon S, Berg A. Pertussis vaccination and epilepsy: an erratic history, new research and the mismatch between science and social policy. *Epilepsia*. 2008;49(2):219–225
2. 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(6):488–492
3. Hattori J, Ouchida M, Ono J, et al. A screening test for the prediction of Dravet syndrome before one year of age. *Epilepsia*. 2008;49(4):626–633
4. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*. 1989;30(4):389–399
5. Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. Severe myoclonic epilepsy in infancy: Dravet syndrome. *Adv Neurol*. 2005;95:71–102
6. Wolff M, Casse-Perrot C, Dravet C. Severe myoclonic epilepsy of infants (Dravet syndrome): natural history and neuropsychological findings. *Epilepsia*. 2006;47(suppl 2):45–48
7. Siegler Z, Barsi P, Neuwirth M, et al. Hippocampal sclerosis in severe myoclonic epilepsy in infancy: a retrospective MRI study. *Epilepsia*. 2005;46(5):704–708
8. Depienne C, Trouillard O, Saint-Martin C, et al. Spectrum of *SCN1A* gene mutations associated with Dravet syndrome: analysis of 333 patients. *J Med Genet*. 2009;46(3):183–191
9. Korff C, Laux L, Kelley K, Goldstein J, Koh S, Nordli D Jr. Dravet syndrome (severe myoclonic epilepsy in infancy): a retrospective study of 16 patients. *J Child Neurol*. 2007;22(2):185–194
10. Mulley JC, Nelson P, Guerrero S, et al. A new molecular mechanism for severe myoclonic epilepsy of infancy: exonic deletions in *SCN1A*. Neurology. 2006;67(6):1094–1095
11. Wakai S, Ito N, Sueoka H, Kawamoto Y, Hayasaka H, Chiba S. Severe myoclonic epilepsy in infancy and carbamazepine. *Eur J Pediatr*. 1996;155(8):724
12. Guerrini R, Dravet C, Genton P, Belmonte A, Kaminska A, Dulac O. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. *Epilepsia*. 1998;39(5):508–512
13. McIntosh AM, McMahon J, Dibbens LM, et al. Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study. *Lancet Neurol*. 2010;9(6):592–598
14. Miller DL, Ross EM, Alderslade R, Bellman MH, Rawson NS. Pertussis immunisation and serious acute neurological illness in children. *BMJ*. 1981;282(6276):1595–1599
15. Gale JL, Thapa PB, Wassilak SG, Bobo JK, Mendelman PM, Foy HM. Risk of serious acute neurological illness after immunization with diphtheria-tetanus-pertussis vaccine: a population-based case-control study. *JAMA*. 1994;271(1):37–41
16. Ray P, Hayward J, Michelson D, et al; Vaccine Safety Datalink Group. Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study. *Pediatr Infect Dis J*. 2006;25(9):768–773
17. Gellin BG, Maibach EW, Marcuse EK. Do parents understand immunizations? A national telephone survey. *Pediatrics*. 2000;106(5):1097–1102

Alleged Cases of Vaccine Encephalopathy Rediagnosed Years Later as Dravet Syndrome

Ila S. Reyes, David T. Hsieh, Linda C. Laux and Angus A. Wilfong

Pediatrics 2011;128;e699; originally published online August 15, 2011;
DOI: 10.1542/peds.2010-0887

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Alleged Cases of Vaccine Encephalopathy Rediagnosed Years Later as Dravet Syndrome

Ila S. Reyes, David T. Hsieh, Linda C. Laux and Angus A. Wilfong

Pediatrics 2011;128;e699; originally published online August 15, 2011;
DOI: 10.1542/peds.2010-0887