

VACCINES, ENCEPHALOPATHIES, AND MUTATIONS

De-Novo Mutations of the Sodium Channel Gene *SCN1A* in Alleged Vaccine Encephalopathy: A Retrospective Study. Berkovic SF, Harkin L, McMahon JM, Pelekanos JT, Zuberi SM, Wirrell EC, Gill DS, Iona X, Mulley JC, Scheffer IE. *Lancet Neurol* 2006;5:488–492. **BACKGROUND:** Vaccination, particularly for pertussis, has been implicated as a direct cause of an encephalopathy with refractory seizures and intellectual impairment. We postulated that cases of so-called vaccine encephalopathy could have mutations in the neuronal sodium channel $\alpha 1$ subunit gene (*SCN1A*) because of a clinical resemblance to severe myoclonic epilepsy of infancy (SMEI) for which such mutations have been identified. **METHODS:** We retrospectively studied 14 patients with alleged vaccine encephalopathy in whom the first seizure occurred within 72 h of vaccination. We reviewed the relation to vaccination from source records and assessed the specific epilepsy phenotype. Mutations in *SCN1A* were identified by PCR amplification and denaturing high performance liquid chromatography analysis, with subsequent sequencing. Parental DNA was examined to ascertain the origin of the mutation. **RESULTS:** *SCN1A* mutations were identified in 11 of 14 patients with alleged vaccine encephalopathy; a diagnosis of a specific epilepsy syndrome was made in all 14 cases. Five mutations predicted truncation of the protein and six were missense in conserved regions of the molecule. In all nine cases where parental DNA was available the mutations arose de novo. Clinical-molecular correlation showed mutations in eight of eight cases with phenotypes of SMEI, in three of four cases with borderline SMEI, but not in two cases with Lennox–Gastaut syndrome. **CONCLUSION:** Cases of alleged vaccine encephalopathy could in fact be a genetically determined epileptic encephalopathy that arose de novo. These findings have important clinical implications for diagnosis and management of encephalopathy and, if confirmed in other cohorts, major societal implications for the general acceptance of vaccination.

COMMENTARY

The report by Berkovic and colleagues forms a nexus between two areas of great controversy in medical research.

The first area of controversy involves the value epilepsy syndromes for use in research and clinical practice. Detractors of the concept of identifying epilepsy syndromes argue that distinguishing specific forms of epilepsy is of little value because (i) only highly trained specialists have the skills and knowledge to identify these syndromes and (ii) most people with epilepsy do not fit into the already recognized syndromic categories. This posture is increasingly untenable in the face of all the advances in genetics that, coupled with precise phenotyping (i.e., recognition and specification of clinical syndromes), are providing an understanding of the genetic basis and associated molecular mechanisms underlying specific and recognizable forms of epilepsy syndromes. Severe myoclonic epilepsy of infancy (SMEI)—also called Dravet syndrome after Dr. Charlotte Dravet, who described the phenomenon—is an example of the value of a syndromic approach in epilepsy. Prior to Dr. Dravet's work, infants with this disorder simply had "bad epilepsy." She described the specific patterns that identify this syndrome (1). Mutations in the *SCN1A* gene coding for part of the voltage-gated sodium channel were first implicated as causal in a range of epilepsy syndromes often referred to as the generalized epilepsy with febrile seizure plus (GEFS+) spectrum (2). Investigators then linked Dravet syndrome to mutations in the *SCN1A* gene (3), thus extending the potential phenotypes of the GEFS+ cluster. Recent analyses indicate that specific manifestation of the epilepsy, including its severity, depends in part on the type of mutation (4). At least one other gene has been implicated in Dravet syndrome, *GABRG2* (5). The association with *SCN1A*, however, is so powerful and so specific that it is now the basis of a genetic diagnostic test.

The second area of controversy concerns severe encephalopathic conditions of infancy and childhood and the possibility that they might be caused by routine childhood vaccinations. In the United States, infants and children receive a large number of vaccinations during the first 18 months of life, including four hepatitis B, four diphtheria–tetanus–pertussis, three polio, one measles–mumps–rubella, one varicella, and four pneumococcal administrations. Encephalopathic conditions, such as that caused by Dravet syndrome (as well as several other specific and nonspecific forms of infant–childhood conditions), often have their initial onset during this 18-month window. Despite numerous studies that have failed to find any positive association between vaccination and encephalopathy, no study can absolutely prove the negative. At best, the Ad Hoc Committee for the Child Neurology Society was willing to conclude in their consensus statement that: "At the present time (1991), there is no means by which a diagnosis of pertussis vaccine-encephalopathy can be established in an individual case." (6) Despite the enormous positive public health impact of childhood vaccinations, on rare occasion, a child develops an encephalopathic condition in close temporal proximity to the receipt of a vac-

cine. These rare occurrences provide an emotionally compelling basis for inferring causality that is hard to dispel, even with the overwhelming quantity of negative data and consensus reports. This phenomenon has led to fear of vaccinations, a flood of lawsuits, and ultimately passage in the United States of the 1986 National Childhood Vaccine Injury Act to provide compensation to alleged victims of vaccine injury. Governments elsewhere have taken other measures (7).

Berkovic and colleagues now shed some light on this vexing problem. In their report, they identify 14 children from a larger series of children with unexplained encephalopathies. These 14 patients met the criteria for vaccine-related injury because of the temporal association between receipt of pertussis vaccine and onset of symptoms (within 72 h) as well as the lack of any other explanation. All 14 children could be assigned a specific syndromic diagnosis. All 11 of the children with SMEI or SMEI-B had mutations in the *SCN1A* gene that, alone, likely explain their neurological conditions. Not all children with encephalopathies following vaccination will have *SCN1A* mutations, as other genes have been implicated in SMEI/Dravet syndrome. There are many efforts under way to understand the genetic basis of other forms of otherwise unexplained childhood encephalopathies, such as West and Lennox–Gastaut syndromes.

The findings of Berkovic et al. are important for at least three reasons. First, they provide a substantial, alternative explanation of cause in cases of alleged vaccine-induced encephalopathy—something the mountains of negative epidemiological data alone could not do. These findings serve as important reassurance concerning the safety of the pertussis vaccine, at least with respect to childhood encephalopathy. Second, this study is a superb demonstration of the power of the syndromic approach to studying and understanding epilepsy and of the persuasive explanatory capabilities of genetic analysis. Without this well-defined phenotype, the role of the *SCN1A* gene likely never would have been recognized, and there would still be the same uncertainty regarding the potential adverse consequences of vaccination. Replication of the findings, of course, is essential. Yet, as it stands, this first report is extremely compelling. Third, the concern over the potential association between vaccines—particularly those with thimerosal, a preservative used in some vaccines—and other disorders of childhood, most notably autism, has gained in momentum during the past several years. The report by Berkovic et al. does not address this association; however, it provides proof of principle that these disorders of early childhood, which many are convinced are caused by vaccinations, may have an entirely different and unrelated cause.

Why is correctly attributing the cause of vaccine-related disorders important? Some parents refuse to have their children vaccinated. This trend has resulted in outbreaks of diseases that

were supposedly eradicated in the developed world. Epidemic outbreaks, such as the recent measles outbreak in Indiana (8) and the huge spike in pertussis cases seen in Sweden after whole cell vaccination stopped in the 1970s, highlight the repercussions of not vaccinating children (7). Measles can have severe and fatal complications, including subacute sclerosing panencephalitis. Pertussis is not a benign disease and has a 0.6% fatality rate. Encephalopathy also may occur in 0.9% of cases (9). These are well-documented and defined risks. The reactions to the perceived dangers of vaccination lead to these risks being realized. Solid, high-quality evidence, such as that presented by Berkovic and colleagues, in addition to the fundamental scientific contribution they represent, may have an important, positive public health impact by allaying fears, at the very least, about the role of pertussis vaccine in causing encephalopathy.

by Anne T. Berg, PhD

References

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