Seizures, Encephalopathy, and Vaccines: Experience in the National Vaccine Injury Compensation Program

Tarannum M. Lateef, MD, MPH[1], Rosemary Johann-Liang, MD[2], Himanshu Kaulas, MD[1], Rakibul Hasan, MD[1], Karen Williams, MS[2], Vito Caserta, MD[2], and Karin B. Nelson, MD[1,3]

Objectives To describe the demographic and clinical characteristics of children for whom claims were filed with the National Vaccine Injury Compensation Program (VICP) alleging seizure disorder and/or encephalopathy as a vaccine injury.

Study design The National VICP within the Department of Health and Human Services compensates individuals who develop medical problems associated with a covered immunization. We retrospectively reviewed medical records of children younger than 2 years of age with seizures and/or encephalopathy allegedly caused by an immunization, where a claim was filed in the VICP between 1995 through 2005.

Results The VICP retrieved 165 claims that had sufficient clinical information for review. Approximately 80% of these alleged an injury associated with whole-cell diphtheria, pertussis (whooping cough), and tetanus or tetanus, diphtheria toxoids, and acellular pertussis vaccine. Pre-existing seizures were found in 13% and abnormal findings on a neurologic examination before the alleged vaccine injury in 10%. A final diagnostic impression of seizure disorder was established in 69%, of whom 17% (28 patients) had myoclonic epilepsy, including possible severe myoclonic epilepsy of infancy. Specific conditions not caused by immunization, such as tuberous sclerosis and cerebral dysgenesis, were identified in 16% of subjects.

Conclusion A significant number of children with alleged vaccine injury had pre-existing neurologic or neurodevelopmental abnormalities. Among those developing chronic epilepsy, many had clinical features suggesting genetically determined epilepsy. Future studies that include genotyping may allow more specific therapy and prognostication, and enhance public confidence in vaccination. *(J Pediatr 2015;166:576-81)*.

See editorial, p 513

Childhood vaccinations have reduced substantially the morbidity and mortality attributable to many infectious diseases worldwide. However, public concern continues regarding their safety because of their alleged ability to cause rare but serious permanent neurologic injury. An example of this concern, with continuing implications, is the possible relationship of immunization against pertussis to acute neurologic morbidity, specifically epilepsy and encephalopathy. Disagreement within the medical community has contributed to the debate as to whether the whole-cell pertussis immunization can cause neurologic injury. A committee of the Child Neurology Society concluded that the vaccine does not cause brain injury,[1] and an Institute of Medicine committee concluded that the evidence supporting a causal link was "weak but not inconsistent."[2] The most recent Institute of Medicine report concluded that the evidence is inadequate to accept or reject a causal relationship between diphtheria toxoid-, tetanus toxoid-, or acellular pertussis-containing vaccine and encephalopathy.[3] Vigorous debate persists, but none of the epidemiologic studies to date has supported a causal relationship between acellular pertussis vaccination and permanent neurologic injury.[4-10] Yet vaccinations rates among certain groups and in certain locations are decreasing.[11,12] Because of both vaccine refusal and due to the lesser duration of immunity with the acellular vaccine, there has been a dramatic resurgence of pertussis in the US.[6,7,13]

Children in the US receive the majority of their vaccinations during the first 18 months of life.[14] During this same age span, young children are vulnerable to a number of serious neurologic disorders, such as epileptic encephalopathies,[15] that may or may not be temporally related to vaccinations. Is it possible, then, that the occurrence of these 2 events, immunization and onset of epilepsy, is coincidental? Or, can the process of immunization unmask an underlying predisposition to neurologic disease?

An Australian study found that 11 of 14 patients with alleged vaccine encephalopathy had severe myoclonic epilepsy of infancy (SMEI), or Dravet syndrome, and that 8 of these children had de novo mutations of the sodium channel gene

DPT	Diphtheria, pertussis (whooping cough), and tetanus
SMEI	Severe myoclonic epilepsy of infancy
VICP	Vaccine Injury Compensation Program

From the [1]Department of Neurology, Children's National Medical Center and George Washington University School of Medicine, Washington, DC; [2]Division of Vaccine Injury Compensation, Department of Health and Human Services, Rockville, MD; and [3]National Institute of Neurologic Disorders and Stroke, National Institutes of Health, Bethesda, MD

The authors declare no conflicts of interest.

0022-3476/$ - see front matter.
http://dx.doi.org/10.1016/j.jpeds.2014.10.054

SCN1A.[16] A case series in the US found 5 patients with alleged vaccine encephalopathy rediagnosed years later as Dravet syndrome.[17] SMEI, first described by Dravet in 1978, is characterized by febrile and afebrile, generalized and focal, clonic or tonic-clonic seizures occurring in the first year of life in an otherwise apparently healthy infant.[15] Many subsequent studies confirmed the association of Dravet syndrome with identifiable de novo mutations in the neuronal sodium channel α1 subunit gene SCN1A.[18-25] Hypothetically, vaccination might trigger an earlier onset of Dravet syndrome in children who carry an SCN1A mutation and are destined to develop the disease; however, a subsequent study by the same Australian group found no evidence that vaccination before or after disease onset affected the clinical outcome.[26]

We reviewed the medical records of children diagnosed with epilepsy and/or encephalopathy after immunization on whose behalf there had been a petition to the National Vaccine Injury Compensation Program (VICP) asking for compensation between 1995 through 2005. We examined the clinical characteristics, work-up, and diagnostic classifications of these children and further attempted to identify children who had clinical features suggestive of SMEI or other identifiable neurologic disorders and their clinical characteristics before and soon after the onset of their disorders.

Methods

The VICP, established by the National Childhood Vaccine Injury Act of 1986, requires physicians and other health care providers who administer vaccines to maintain certain vaccination records and to report occurrences of certain adverse events to the US Department of Health and Human Services.[27] The VICP compensates children and adults who develop a variety of illnesses, including neurologic diseases, if the claim fulfills the vaccine injury table criteria for a vaccine-related injury or if the claim is adjudicated by the US Court of Federal Claims to be caused by specific vaccine(s)[27,28] or fit the Vaccine Injury Table. The VICP receives claims and medical records of young children with epileptic disorders whose presentation, vaccine experience, clinical course, and diagnostic work-up were documented, including the medical history of the child and family, physical findings, and laboratory, imaging, and electrophysiologic data. The procedures involved in processing such claims have been described elsewhere.[29,30]

For this study, we abstracted medical records submitted to the VICP in the Health Resources and Services Administration, from claims seeking compensation for adverse events they believed to be caused by a vaccine. Two hundred twenty-two claims were submitted to the VICP from 1995 through 2005 with "seizures" and/or "encephalopathy" as the alleged injury and for children whose age was younger than 2 years at the time of alleged injury. All data were deidentified before abstraction and analysis, maintaining confidentiality throughout. An exemption was applied for and received through the Children's National Medical Center Institutional Review Board. Data were recorded on vaccine(s) implicated, age of the child at onset of seizures/encephalopathy, previous history, including prenatal factors and development until time of presentation, history and evolution of neurologic disease, diagnostic workup, and medications used. Special attention was paid to the epilepsy phenotype, with occurrence and age at onset of first seizure, seizure frequency, whether provoked by fever or not, duration, and response to anticonvulsants being noted. Seizure types included hemiclonic seizures, generalized tonic-clonic seizures, status epilepticus, myoclonic seizures, and atypical absence seizures. Developmental status was classified as normal, abnormal, or suspect before alleged vaccine injury, at 18-24 months, and at last documented visit. Phenotypes were assessed by a single child neurologist (T.L.), and all equivocal cases were discussed with a collaborating child neurologist (K.N.). Diagnostic criteria for possible Dravet syndrome included seizure onset in infancy; first seizure typically febrile; later occurrence of various other seizure types, including focal seizures, atypical absence seizures, and tonic clonic seizures; and normal early cognitive and developmental profile with subsequent deterioration.

Available imaging and electrodiagnostic and laboratory studies were documented, including complete blood count, routine chemistry, urine toxicology screen, and routine cerebrospinal fluid analysis, including cell count differential, gram stain, and culture. When other metabolic and genetic studies were available, these results were documented in detail. Final diagnostic impression was based on history, evolution of phenotype, and all imaging and laboratory evidence. To be reviewed, charts had to have information on vaccines implicated, onset, previous history, developmental status, and workup.

Results

The VICP retrieved 222 claims from 1995 through 2005 alleging vaccine injury as a cause of seizure disorder or encephalopathy. Of these cases, 165 had charts containing enough information to permit a comprehensive review. In 80% of these claims, the vaccine implicated was whole-cell diphtheria tetanus pertussis (61%) or acellular diphtheria tetanus acellular pertus (19.3%). Nonpertussis-containing vaccines included measles, mumps, rubella vaccine (17.8%), *Haemophilus influenzae* type b (9.1), injectable polio (6%), hepatitis B (4.8%), oral polio (3.0%), pneumococcal conjugate (2.4%), and Td tetanus diphtheria (0.6%). Approximately 16% of children with claims had received more than one vaccine at the time of alleged injury. Slightly more than one-half of children on whose behalf claims were made were girls. In more than one-half of these 165 cases, the initial seizure after vaccine was reported before the child was 6 months of age, and in three-quarters the initial seizure occurred before the first birthday. The majority (59%) of claims listed seizures, and 36% listed seizures and encephalopathy as the alleged injury resulting from vaccination (**Table I**).