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“What Else Could It Be?” When Neurologic Disorders Follow Immunization

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Introduction and Subject

When brain disorders such as seizures or *encephalopathy* occur after an immunization, people (including many doctors) have a strong natural tendency to blame the vaccine. This is especially so when the interval between immunization and symptom onset was short and the child was considered normal beforehand. Without an obvious alternative cause such as trauma or intercurrent infection, immunization may be considered guilty by default: what else could the cause have been? Studies in recent years using increasingly sophisticated diagnostic tools have revealed a substantial number of alternative causes that may not be evident unless looked for. In fact, alternative causes exist for almost all of the severe neurologic disorders that follow infant vaccinations.

Recent Research Results

Post-immunization seizures

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Fever is a recognized link between infant immunizations and seizures. Fever typically occurs in ~15% of infants given acellular pertussis-containing (DTaP) vaccines and in ~45% of those given whole cell pertussis-containing vaccines. Most fevers occur within 1-2 days after vaccination and are well tolerated. High fevers occasionally occur and may trigger seizures although the observed rate of febrile seizures after DTaP-type vaccines did not exceed baseline rates for U.S. infants in a large study.[1] Most instances occur in infants with a familial predisposition to febrile convulsions in early childhood, a trait present in 2-5% of some populations.[2] If vaccination is the first stimulus for fever in a young infant it may reveal this predisposition for seizures. Fortunately, familial seizures usually have a benign outcome, with no influence on later development.[2] If an *electroencephalogram (EEG)* is obtained after the seizure episode, the brain wave pattern is normal.

Fever after vaccination can also trigger seizures with less benign conditions not previously recognized in an infant, such as brain malformations or scarring from injuries in utero caused by vascular events, congenital infection or toxic drugs. Birth-related injuries or those associated with prematurity can predispose to later seizures. Here too, immunization may be the first cause of fever to trigger seizures. The nature of the underlying problem may be revealed by investigations including brain imaging studies, EEG, *cerebrospinal fluid (CSF)* analysis and others, depending upon the individual context.

Post-immunization encephalopathy

“Encephalopathy” broadly encompasses acute neurologic conditions with diminished level of consciousness and/or altered mental functions, with or without seizures. Conditions with prominent inflammation in CSF are called *encephalitis* or meningoencephalitis.

Infants are at higher risk of encephalitis with certain viral infections than are older age groups, so some instances will follow immunization purely by chance. Viruses commonly responsible for encephalitis in infants include herpes simplex, enteroviruses and human herpes virus type 6. Inflammatory changes in CSF (increased leukocytes, protein concentration) are an important clue to the presence of a viral infection of the central nervous system. A newly-recognized cause of encephalitis in infants is *parechovirus*, previously overlooked because it typically causes minimal abnormalities in the CSF of affected infants.[3] Testing CSF with *polymerase chain reaction (PCR)* assays for the common agents of encephalitis is the optimal diagnostic approach as most of these viruses are difficult or impossible to grow from CSF.

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The most alarming situation for parents and health professionals is the occurrence after vaccination of acute encephalopathy that results in persistent seizures and developmental delay or reversal. This rare situation typically follows one of the first vaccinations in early infancy. Since those “baby shots” contain pertussis vaccine, the syndrome was labeled “pertussis vaccine encephalopathy” by some authors[4] although here was no direct evidence implicating pertussis vaccine as the cause. However, after brain malformation, injury, infection etc. were ruled out in individual cases, pertussis vaccine was the alleged cause (“What else could it be?” was the rationale at the time). Fortunately, that question now has answers.

A team of neurologists in Australia, led by Dr. Samuel Berkovic, has provided an alternate explanation for alleged “vaccine encephalopathy.” They investigated 14 patients in Australia and New Zealand who were considered to have chronic encephalopathy from vaccination.[5] Each had a first seizure within 72 hours after vaccination in infancy, with a pertussis-containing vaccine. Each had epileptic encephalopathy with refractory seizures and developmental slowing or regression, after previously normal development. Less than half had fever noted at seizure onset. None of the parents had a history of seizures. Patients had a variety of seizure syndromes and none had evidence at onset of brain inflammation or damage. The noteworthy insight was that 11 of the 14 patients had mutations in the sodium channel (SCN1A) gene on molecular genetic analysis. These appeared to be de novo, or new, mutations as they were absent in the parents. A number of different mutations existed, perhaps explaining the variety of seizure syndromes. This genetic defect was discovered relatively recently as the basis for most instances of severe myoclonic epilepsy of infancy, also known as Dravet syndrome.[6-9] The authors recommend testing for SCN1A mutations in cases of encephalopathy after vaccination that lack other identified causes because “correct diagnosis will reassure the family as to the true cause, remove the blame for having vaccinated the child, direct appropriate treatment and allow realistic planning for prognosis.” [5]

The Australian team subsequently studied 40 patients with mutations in SCN1A regarding the relationship between seizure onset and vaccination.[10] Twelve patients had onset within 2 days after vaccination, at a mean age of 18.4 weeks, and 28 had greater separation between vaccination and seizure onset, which occurred at a mean age of 26.2 weeks. The authors’ interpretation was that vaccination may have precipitated onset of some cases, although all were destined to be affected. Those with onset soon after vaccination had the same subsequent course of illness as the other patients, both groups having similar intellectual outcomes and seizure

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types as well SCN1A mutations. Onset of seizures soon after vaccination followed any one of the three scheduled infant vaccinations, with whole cell or acellular pertussis-containing vaccines and with or without fever. Vaccinations given after the onset of seizures did not affect intellectual outcome. The authors described the situation as a "gene-environment interaction," with vaccination being one of many potential triggers in a child's early life to reveal the underlying disorder. In retrospect, it is easy to understand why infant vaccinations appeared to cause this rare but severe condition as affected children appeared to be normal beforehand but it is gratifying to see "science prevail over speculation."[11]

Conclusion

Vaccine safety perspective

Experience from a Canadian vaccine safety surveillance network of pediatric hospitals illustrates the rarity of encephalopathy after infant vaccinations and the importance of investigating the true cause.[12] The 12 participating surveillance hospitals account for over 90% of the country's specialized pediatric beds and admit children with serious conditions from wide referral areas. During 10 years of active surveillance, Canadian children received approximately 6 million doses of vaccines containing whole cell pertussis and 7 million doses containing acellular pertussis. During this same period, nurse monitors at those hospitals reviewed every acute neurologic admission (>12,000) and found 7 cases of acute encephalopathy with onset within 7 days after pertussis-containing vaccination. Brain imaging and CSF studies revealed an alternate cause in every instance, including a previously unrecognized metabolic disorder and acute viral infections including herpes simplex and influenza. Presently, PCR testing of CSF is being expanded to detect parechovirus, given its newly recognized importance as a cause of encephalitis in infancy.[3] In selected infants with epileptogenic encephalopathy, testing for SCN1A mutations is arranged. Clearly, this is a dynamic situation that requires expanded testing as more causes of encephalopathies of early childhood are identified. For cases that occur soon after vaccination, every reasonable effort should be made to identify the actual cause and avoid incorrectly blaming the vaccine. For the earlier question of "What else could it be?," many answers are possible with appropriate investigations. It is increasingly unlikely that "vaccine encephalopathy" exists at all following the inactivated vaccines such as DTP or DTaP given to infants.

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