Vaccination Triggers, Rather Than Causes, Seizures

Etiologies for Seizures Around the Time of Vaccination.

Verbeek NE, Jansen FE, Vermeer-de Bondt PE, de Kovel CG, van Kempen MJA, Lindhout D, Knoers NVAM, van der Maas NAT, Brilstra EH. *Pediatrics* 2014;134:658–666. doi:10.1542/peds.2014-0690.

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.

Common Variants Associated With General and MMR Vaccine–Related Febrile Seizures.

Feenstra B, Pasternak B, Geller F, Carstensen L, Wang T, Huang F, Eitson JL, Hollegaard MV, Svanström H, Vestergaard M, Hougaard DM, Schoggins JW, Jan LY, Melbye M, Hviid A. *Nat Genet* 2014;46:1274–1282. doi:10.1038/ng.3129.

Febrile seizures represent a serious adverse event following measles, mumps and rubella (MMR) vaccination. We conducted a series of genome-wide association scans comparing children with MMR-related febrile seizures, children with febrile seizures unrelated to vaccination and controls with no history of febrile seizures. Two loci were distinctly associated with MMR-related febrile seizures, harboring the interferon-stimulated gene *IFI44L* (rs273259: $P = 5.9 \times 10^{-12}$ versus controls, $P = 1.2 \times 10^{-9}$ versus MMR-unrelated febrile seizures) and the measles virus receptor *CD46* (rs1318653: $P = 9.6 \times 10^{-11}$ versus controls, $P = 1.6 \times 10^{-9}$ versus MMR-unrelated febrile seizures). Furthermore, four loci were associated with febrile seizures in general, implicating the sodium channel genes *SCN1A* (rs6432860: $P = 2.2 \times 10^{-16}$) and *SCN2A* (rs3769955: $P = 3.1 \times 10^{-10}$), a TMEM16 family gene (*ANO3*; rs114444506: $P = 3.7 \times 10^{-20}$) and a region associated with magnesium levels (12q21.33; rs11105468: $P = 3.4 \times 10^{-11}$). Finally, we show the functional relevance of ANO3 (TMEM16C) with electrophysiological experiments in wild-type and knockout rats.

Commentary

Controversy has long surrounded whether vaccination causes seizures and encephalopathy in infants and children (1). The implications of causative claims have been profound with anti-vaccination lobby groups gaining ground in public debate by sowing seeds of concern in the minds of anxious parents. This fear of vaccination has fueled preventable outbreaks of disease such as measles in developed countries escalating from 40 cases in France in 2006 to >22,000 cases during 2008–2011 (2); such diseases are associated with significant long-term morbidity and even death. To add to this dilemma, claims of vaccine-related injury have resulted in large medicolegal payouts from vaccine manufacturers, further compromising vaccine access and uptake (1). Often, families facing a devastating disease firmly believe the vaccine is causative; nonetheless, large epidemiologic studies have refuted a causal link between vaccination and seizures (3).

So-called "vaccine encephalopathy" was a relatively poorly defined entity in which previously well, developmentally

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normal, infants presented with seizures followed by developmental slowing or regression within days of vaccination. Belief in the vaccine being causative was not surprising given the striking temporal association and lack of family history of epilepsy in affected individuals. In 2006, we showed that many of these patients actually had unrecognized Dravet syndrome due to mutations of the sodium channel α1 subunit gene, *SCN1A* (4). Dravet syndrome is a severe developmental epileptic encephalopathy with infantile onset of seizures and developmental slowing. The absence of a family history of seizures was explained by the *SCN1A* mutation arising de novo in the affected individual, which is the usual finding in >90% of patients with Dravet syndrome. We then examined whether there was any true relationship between vaccination and Dravet syndrome and found that one-third of Dravet patients present with their first seizure within 40 hours of vaccination (5).

Nevertheless, the risk of febrile seizures increases 2 to 5 times on the day of administration of an inactivated vaccine and on days 5 to 14 following a live attenuated vaccine (6). Epidemiologic studies of vaccine-related seizures have the power to drill down on the question of causation. This is elegantly demonstrated in a Dutch study of 990 children, followed for over 10 years, who experienced seizures following vaccination under the age of 2 years (7). Vaccine-related seizure onset was defined as within 24 hours of inactivated vaccine and 5 to 12 days after a live attenuated vaccine (e.g., measles/mumps/rubella [MMR]). Epilepsy after vaccination occurred in 26 of 990 cases with data available on 23. Their critical phenotypic analysis distinguished 12 children who developed an epileptic encephalopathy, 3 who had a preexistent encephalopathy and 8 with benign (now termed self-limited) epilepsies. In their total cohort, 15 of 23 (65%) had a cause identified, including *SCN1A* mutations in 8 children with Dravet syndrome and 1 with genetic epilepsy with febrile seizures plus (GEFS+). Clinical or molecular genetic evidence for causation was present in four more individuals, and an additional two had neuronal migration disorders, which were also likely to have a genetic basis. One girl had a *PCDH19* mutation in accord with *PCDH19* parent groups who describe a significant proportion of girls having seizures triggered by vaccination (Julie Walters, BA, President PCDH19 Alliance, email communication 17 August 2015). Two patients had compelling autosomal dominant family histories of epilepsy including one with benign familial infantile epilepsy, in which febrile seizures are recognized to occur (8). These observations provide further evidence for an underlying genetic cause for which the vaccine triggers the initial seizure. Further, they emphasize that the outcome of vaccine-related seizures may be excellent in patients without encephalopathy (7).

Although most children in the cohort remained prone to fever-related seizures at follow-up, the vaccine-related seizures in the cohort with later epilepsy occurred at a lower body temperature of <38.5°C compared with all other children. Six of our original cases with "vaccine encephalopathy" were afebrile during their initial vaccine-related seizure in contradistinction to the typical fever-related onset of seizures in Dravet syndrome (4). Taken together, these findings suggest that the immune response activated by vaccination triggered a seizure without necessarily producing a high fever or even a fever at all.

A critical question is why seizures are associated with vaccination? The immune basis is not understood. In Dravet syndrome mouse models with a *Scn1a* mutation, seizure onset occurs in a developmental age window when Scn1a is first expressed (9). Temperature-inducing experiments only trigger seizures once Scn1a is expressed, suggesting that the first insult, whether that be fever or vaccination, will trigger seizures in an individual predisposed to have febrile seizures or specific genetic epilepsies.

A different approach to unraveling potential genetic factors associated with vaccine-related seizures was used in genome-wide association scans comparing Danish children with MMR-related febrile seizures, febrile seizures unrelated to vaccination, and controls (10). The authors identified two common variants at chromosomal loci distinctly associated with MMR-related febrile seizures and not with vaccine-unrelated febrile seizures; these loci harbored genes involved in the innate immune system. They also identified four loci implicated in febrile seizures more broadly. They postulated that MMR-related febrile seizures may involve a two-step pathway whereby the MMR-related febrile seizure variant triggers an immune response, while the general febrile seizure variants influence seizure susceptibility. They cautioned that the next steps involve the identification of the actual causal variants at the loci to determine if they confer risk for seizures with other vaccines and with live viral infections.

Vaccination has changed the health of our society affording untold benefits to billions of people, yet doubts remain about safety, particularly when seizures occur in close temporal proximity to vaccination. Controversies surrounding vaccination are beautifully articulated in a recent award-winning documentary by Sonya Pemberton called "Vaccines—Calling the Shots" or "Jabbed—Love, Fear and Vaccines." Fortunately, science is providing key insights into the underlying etiology of vaccine-related seizures, particularly those heralding the onset of epilepsy. Known genetic factors may explain the causation in monogenic diseases such as *SCN1A* or *PCDH19* epilepsies, or common variants may contribute to our understanding. What remains is to determine the underlying mechanism—how does the malfunctioning protein interact with the presumed immune response to vaccination to trigger a seizure or the onset of epilepsy?

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