

Current Literature

In Clinical Science



Vaccination and the Onset of Dravet Syndrome

Effects of Vaccination on Onset and Outcome of Dravet Syndrome: A Retrospective Study.

McIntosh AM, McMahon J, Dibbens LM, Iona X, Mulley JC, Scheffer IE, Berkovic SF. *Lancet Neurol* 2010;9:592–598.

BACKGROUND: Pertussis vaccination has been alleged to cause an encephalopathy that involves seizures and subsequent intellectual disability. In a previous retrospective study, 11 of 14 patients with so-called vaccine encephalopathy had Dravet syndrome that was associated with de-novo mutations of the sodium channel gene *SCN1A*. In this study, we aimed to establish whether the apparent association of Dravet syndrome with vaccination was caused by recall bias and, if not, whether vaccination affected the onset or outcome of the disorder. **METHODS:** We retrospectively studied patients with Dravet syndrome who had mutations in *SCN1A*, whose first seizure was a convulsion, and for whom validated source data were available. We analysed medical and vaccination records to investigate whether there was an association between vaccination and onset of seizures in these patients. Patients were separated into two groups according to whether seizure onset occurred shortly after vaccination (vaccination-proximate group) or not (vaccination-distant group). We compared clinical features, intellectual outcome, and type of *SCN1A* mutation between the groups. **FINDINGS:** Dates of vaccination and seizure onset were available from source records for 40 patients. We identified a peak in the number of patients who had seizure onset within 2 days after vaccination. Thus, patients who had seizure onset on the day of or the day after vaccination (n=12) were included in the vaccination-proximate group and those who had seizure onset 2 days or more after vaccination (n=25) or before vaccination (n=3) were included in the vaccination-distant group. Mean age at seizure onset was 18.4 weeks (SD 5.9) in the vaccination-proximate group and 26.2 weeks (8.1) in the vaccination-distant group (difference 7.8 weeks, 95% CI 2.6–13.1; p=0.004). There were no differences in intellectual outcome, subsequent seizure type, or mutation type between the two groups (all p values >0.3). Furthermore, in a post-hoc analysis, intellectual outcome did not differ between patients who received vaccinations after seizure onset and those who did not. **INTERPRETATION:** Vaccination might trigger earlier onset of Dravet syndrome in children who, because of an *SCN1A* mutation, are destined to develop the disease. However, vaccination should not be withheld from children with *SCN1A* mutations because we found no evidence that vaccinations before or after disease onset affect outcome.

Commentary

Imagine you have an adorable baby, the birth went well, and he/she is developing nicely; laughing, smiling, making eye contact, and playing. You are worried because you heard about complications from immunizations, but your pediatrician reassures you. In fact, all of your friends have immunized their children without problem.

After the injection, your baby has a fever and experiences a seizure. From that moment in time, your life is never the same nor is the life of your child or the whole family. No wonder many parents think that it was the vaccination itself that created this terrible situation. Wouldn't you?

Therefore, studies such as the McIntosh paper (1) have important implications. Several relevant questions arise: 1) How should doctors advise parents before vaccinations? What should be said to parents? Should all parents be warned about

the potential triggering of Dravet syndrome, a rare disorder affecting about 1 of 30,000? 2) How can we identify children that might be susceptible to developing Dravet syndrome? 3) Do all children with the *SCN1A* genetic mutation develop the full expression of the disease? 4) Can a vaccination be deferred or not given, thereby possibly preventing or delaying the onset or expression of Dravet syndrome? None of these questions have answers at this time, but prospective studies and treatment protocols are needed to try to find the answers. At present, retrospective chart reviews like the cited study are all we have, but, at least, it is a beginning.

The trouble (or the good news) is that Dravet syndrome (severe myoclonic epilepsy of infancy) is a very rare disease, and most cases are sporadic with a high rate of de novo sodium-channel gene (*SCN1A*) mutations. This means that the mutation most often appears spontaneously rather than being inherited. Onset age is around 6 months, with prolonged febrile or afebrile generalized clonic or hemiclonic seizures. This occurs, coincidentally, just at the same time as the vaccinations are commonly given. The Center for Disease Control (CDC) recommends that vaccinations are given at 2, 4, and 6 months. Affected children

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develop more or less normally until 1 to 4 years of age, when developmental regression begins, and other seizure types occur such as myoclonic jerks, absences, and partial seizures (2, 3).

The genetic mutation in *SCN1A* was described by Claes et al. (4) and has become one of the most useful and successful marker of genetically mediated epilepsies that has yet been determined. It is now known that several types of mutations exist and that these may determine the expression of the disease or phenotype. In a new study by Claes et al. (5), both missense mutations and truncation mutations were found to occur in Dravet syndrome and were approximately equal in frequency in this study. Missense mutation means that there is an amino acid substitution, and truncation means that there is a deletion. In the study by Zuberi et al. (3), truncated mutations accounted for earlier onset of myoclonic seizures and atypical absences, but not prolonged seizures. The authors concluded that "the phenotype is related to a variety of changes within the *SCN1A* gene." In other words, not all children with Dravet syndrome are equal.

Another interesting finding in the Zuberi study (4) is that GEFS+ (generalized epilepsy with febrile seizures plus) mutations on the *SCN1A* gene also can be found in relatives of children with Dravet syndrome. GEFS+ is generally a benign epilepsy syndrome and does not cause mental handicap. Almost all mutations in these patients are missense, none truncated. Other studies have also found that GEFS+ is more prevalent among relative of children with Dravet syndrome (Scheffer et al.).

The first step along the way to understanding whether vaccination can elicit Dravet syndrome or vaccine encephalopathy was a finding in 2006 by Berkovic et al. (7). There, it was discovered that most children who showed signs of a vaccine encephalopathy actually had the *SCN1A* (11/14) gene mutation and at the end were diagnosed with Dravet syndrome. The implication is that the vaccination was only the trigger in the inevitable onset of the disease, and it would have happened anyway.

The present study expands the population reported on in 2006 and finds that of patients who eventually were diagnosed with Dravet syndrome, more than 27% had a seizure 1 to 3 days postvaccination, and for 58% of these, it was the first seizure and symptom of Dravet syndrome reported.

Directly after the publication of the McIntosh paper (1), a similar retrospective chart review from Germany was published with essentially the same results (8), thus confirming and adding evidence to the findings of the McIntosh paper.

The test for the *SCN1A* mutation is now commercially available. The cost for the *SCN1A* deletion test at one company (which would confirm the diagnosis) is just over \$600 and takes 21 to 28 days to analyze (Athena Diagnostics, Worcester, MA). This test is relatively inexpensive and should be accessible for parents who are nervous about childhood vaccinations and the risks involved.

A prospective study could be conducted in a population of infants. Parents of children who test positive for *SCN1A* would have a choice of whether to defer the vaccination or not. The children could be followed up closely, and it could be determined if Dravet syndrome manifests itself at the same time anyway or is deferred or is never expressed. For those children with *SCN1A* mutation, analyses for missense or truncated mutations could be evaluated as well. Although we assume

that vaccinations, especially pertussis, will not elicit Dravet syndrome, only trigger it, it is still only a hypothesis and has not been proven. Maybe it will turn out that only children with, for example, truncated mutations are at risk.

Another problem is that children receive many different vaccinations between infancy and 18 months, which is coincidentally the debut interval for many catastrophic epilepsy syndromes in childhood. However, at least *SCN1A* can be tested for, while other syndromes cannot yet be predicted through a simple genetic test.

What should the clinician tell parents? If genetic testing in a controlled trial cannot be done, then it is wise for parents to go ahead with vaccinations anyway. The risk of contracting the illness being vaccinated against is not insignificant and in fact is much higher than the risk of Dravet syndrome. Of interest, it was estimated in 1979 that costs due to pertussis would be reduced by 61% if community vaccinations were instigated (9).

To add oil to the fire of the vaccination controversy as a whole, it has very recently been found that Swedish and Finnish children who were given Pandemrix (an H1N1 vaccine from GSK) have a higher risk of developing narcolepsy. The findings were just announced in the Swedish media and have shocked the whole nation because the government had assured the public in 2009 and 2010 that the vaccination was safe and had recommended that all children be vaccinated to prevent a pandemic (10, 11).

As much as we professionals understand that the risks of not being vaccinated are probably higher (9) than developing a vaccination encephalopathy, it is not easy to dismiss the danger of vaccinations and encephalopathy in the general population. Prudent clinical practice supports active vaccinations of children with pertussis and other vaccines.

by Elinor Ben-Menachem, MD, PhD

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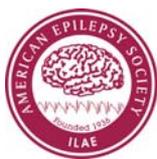
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