Effects of vaccination on onset and outcome of Dravet syndrome: a retrospective study

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Summary

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.

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Introduction

Claims of causal associations between vaccination and neurological disorders, most recently autism, have societal consequences for vaccination uptake and also have medicolegal implications.1 Despite extensive epidemiological studies showing no relation between vaccination and permanent neurological disease,2–4 perception of causality is hard to eliminate.

In a retrospective study, most patients with suspected so-called vaccine encephalopathy—a poorly defined disorder that causes seizures and intellectual impairment in infants, with onset after vaccination—had clinical features typical of the severe epileptic encephalopathy Dravet syndrome.5 Moreover, most patients had de-novo mutations of the sodium channel gene SCN1A, thus questioning the idea that the vaccination was the primary cause of the encephalopathy. We therefore concluded that in these patients Dravet syndrome was misinterpreted as a syndrome that had an acquired cause (vaccination) because the phenotype was not recognised and a family history of epilepsy was absent. Pertussis vaccination was usually suspected to be the cause of seizures and intellectual disability because the vaccination often causes minor distress (including fever and irritability, particularly with the old cellular preparation)6 and carries an increased risk of benign febrile seizures.6–7 The absence of family history, and severe illness in a previously healthy infant, reinforced the misconception that pertussis vaccination caused the encephalopathy.

Dravet syndrome (also known as severe myoclonic epilepsy of infancy; SMEI) is characterised by onset of seizures at around 6 months of age. Initial seizures are usually prolonged convulsions, either generalised or hemiclonic, often triggered by fever. Other seizure types that subsequently develop include myoclonic, partial, absence, and atonic seizures. From the second year of life, intellectual development in these infants begins to plateau or regress, resulting in intellectual disability.8 About 70–80% of children with Dravet syndrome have mutations in SCN1A, of which 95% are de novo.4,9 Diphtheria-tetanus-pertussis (DTP) vaccination, typically given at 2 months, 4 months, and 6 months of age, has...
been reported to precede the onset of Dravet syndrome or to apparently trigger further seizures in children who already have the disorder.8,12 In this setting, families typically blame vaccination for the illness. Further vaccination might be advised against by the physician or refused by the family.

Although our earlier report suggested that vaccine encephalopathy was not a real disorder,5 there remains a possibility, because of the apparent temporal association, that DTP vaccination might sometimes trigger the onset of Dravet syndrome. Reports from families of affected children might be subject to recall bias because families might suspect an association between the onset of Dravet syndrome and vaccination. If, however, the observation of the temporal association is valid, a gene–environment interaction might be occurring.

We aimed to assess, in patients with Dravet syndrome and a known mutation of SCN1A, whether there was a genuine temporal association of seizure onset with vaccination, by use of source records to avoid recall bias. We also assessed whether patients who had onset of Dravet syndrome shortly after vaccination had any specific clinical, molecular, or outcome differences that could suggest the disorder in these patients represents a separate entity. Such data might have important consequences for the advice given to parents regarding vaccination.

Methods

Patients

We included patients with Dravet syndrome from our study on infantile epileptic encephalopathies.10 The diagnosis of Dravet syndrome includes patients who were previously diagnosed with classical SMEI or the borderline variant (severe myoclonic epilepsy of infancy borderline), in which certain features deemed to be essential for a diagnosis of SMEI are absent.10 We sought validated source data (the date of the first seizure and the dates of vaccinations) for patients with Dravet syndrome who have a mutation in SCN1A and in whom the first seizure was a convulsion. We excluded patients whose first seizure was a myoclonic or absence seizure because the exact dates of these are hard to verify.

The study was approved by the Human Research Ethics Committee of Austin Health. Written informed consent was obtained from all patients or their parents at enrolment in our previous study.9

Procedures

The date of each first seizure was validated by use of hospital charts or files from the patients’ family doctor or specialist. Exact dates of each of the DTP vaccinations were obtained from original medical records or the child’s health-care booklet, which was retained by the parents. These booklets were stamped or signed and dated at the time of the vaccination by the health-care professional who gave the vaccine. Because the exact composition of vaccinations has changed over time, we documented whether the patients received whole-cell or acellular forms of pertussis vaccine.

From the source data we assessed the number of days between the first convulsive seizure and the previous vaccination. A day was defined as midnight to midnight because the date but not the time of vaccination was documented in the source data. The day of vaccination was day 0, and all seizures that occurred on day 0 occurred between the time of vaccination and midnight of the day of vaccination. Day 1 was from midnight of the day of vaccination to midnight of the next day. We separated patients into two groups according to whether seizure onset occurred shortly after vaccination (vaccination-proximate group) or not (vaccination-distant group).

We analysed the clinical characteristics and distribution of molecular lesions in the two groups to establish whether the vaccination-proximate group had a different outcome or other distinguishing clinical or molecular features compared with the vaccination-distant group. Intellectual outcome was classified, according to a detailed assessment of developmental milestones and present functioning of each patient, as normal intellect (documented normal educational achievement), mild intellectual disability (definite mild intellectual impairment), moderate intellectual disability (limited speech and cognition but able to do some aspects of daily living), or severe intellectual disability (limited or no speech and dependent for activities of daily living—ie, going to the toilet and dressing).13 Classification was done by assessors masked to mutation type or relation to vaccination. For binary analyses, we grouped together children with normal intellect and mild intellectual disability and compared them with those with moderate or severe intellectual disability. Intellectual regression was defined as prolonged (4 weeks or more) or permanent loss of skills and was coded as present or absent.

Numbering of SCN1A mutations was taken from the start codon ATG of the full-length SCN1A mRNA sequence (Genbank accession number AB093548). Mutations were divided into missense mutations or others from which markedly abnormal protein was predicted, including truncation, frameshift, and splice-site mutations. Such other mutations have been reported only in patients with Dravet syndrome or related severe epilepsies and never in control individuals.13 Missense mutations were classed as causative if they had been previously reported in Dravet syndrome or if they predict a non-conservative amino acid change in an evolutionarily conserved residue and are absent from single nucleotide polymorphism databases of healthy individuals. Certain missense mutations cause milder epilepsy syndromes and rarely some missense variants occur in healthy individuals.13

To establish whether outcome was worse in patients who received vaccination after seizure onset, we compared outcomes according to whether or not patients had received further vaccinations.
In a post-hoc analysis, we examined whether non-missense mutations were associated with earlier age at onset, and whether these mutations or earlier age at onset were associated with worse outcome.

Statistical analysis
Patients with missing data were excluded from the relevant analyses. Independent-sample t tests were done to examine differences in age at onset. Differences in other characteristics between groups were tested using the Fisher’s exact test. Statistical significance was tested at the 5% level using two-tailed tests. All analyses not stated as post-hoc were prespecified. The number of days used to define the vaccination-proximate group was calculated after viewing the summary data but before the analyses were undertaken.

Role of the funding source
The sponsor had no role in the study design, data collection, data analysis, interpretation of the data, or writing of the report, and was not involved in the decision to submit the paper for publication. AMM, JMc, IES, and SFB had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
We identified 127 patients with Dravet syndrome from our previous study,10 of whom had a confirmed mutation in SCN1A. Six of these patients were excluded because their first seizure was a myoclonic or absence seizure. Data for 84 of these 95 patients have been published previously.1,13,15–16

Validated data (ie, the date of the first convulsion and the vaccination dates) were obtained from source data and were available for 40 of the 95 patients, including six patients from our earlier report on vaccine encephalopathy. The 40 patients with validated data did not differ from the 55 patients without validated data in terms of mean age at onset, outcome, syndromic diagnoses, or mutation types (data not shown).

The 40 patients with validated data had a median age of 5·4 years (IQR 3·2–8·0 years; range 11 months to 27 years) at assessment. Mean age at seizure onset was 5·5 months (SD 1·9). The median age was 2·1 months (IQR 1·9–2·5) at the first vaccination, 4·3 months (4·1–4·8) at the second vaccination, and 6·8 months (6·2–8·7) at the third vaccination. Three patients had their first seizure before their first vaccination; the remaining 37 had their first seizure after at least one DTP vaccination. Inspection of these data showed a clear temporal peak (figure 1), which led us to classify children as vaccination-proximate if they had their first seizure on days 0 or 1, and vaccination-distant if their first seizure occurred 2 days or more after a vaccination. 12 of 40 patients had seizure onset either on the day of vaccination (n=5) or during the first day post-vaccination (n=7) and were thus defined as vaccination-proximate. The patients in the vaccination-distant group had seizure onset from day 2 to day 98 after vaccination (n=25) or before the first vaccination (n=3).

Of the 37 patients who had at least one vaccination before seizure onset, eight had their first seizure after

![Figure 1: Timing of first seizure and DTP vaccination](image-url)
the first immunisation (3 vaccination-proximate and 5 vaccination-distant), 16 after the second (7 vaccination-proximate and 9 vaccination-distant), and 13 after the third (2 vaccination-proximate and 11 vaccination-distant). The differences in proportions of patients in the vaccination-proximate group compared with the vaccination-distant group for each of the vaccinations was not significant (Fisher’s exact p=0·23). Whole-cell (as opposed to acellular) pertussis vaccine was given to four of 11 patients in the vaccination-proximate group and eight of 26 patients in the vaccination-distant group (Fisher’s exact p=0·27; data missing for one patient in the vaccination-proximate group and two in the vaccination-distant group).

The mean age at onset of Dravet syndrome 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 weeks; t(38)=3·03, p=0·004; table 1). Comparison of other clinical characteristics suggested that there was no difference between groups in the characteristics of the first seizure (documented fever, bilateral or unilateral convulsion, or status epilepticus), occurrence of other seizure types, presence of intellectual regression or intellectual disability, or syndromic diagnosis.

Analysis of the SCN1A mutations in the 40 patients with validated data revealed 12 missense and 28 other mutations (18 truncation, 9 splice site mutations, and 1 deletion of exons 21–26; figure 2). Two mutations (IVS4+1G>A and S1516X) were found in patients in both the vaccination-proximate group and two in the vaccination-distant group (webappendix).

From assessment of figure 1, one could argue that patients with their first seizure 2–5 days after vaccination should also be included in the vaccination-proximate group. Post-hoc, the comparison of vaccination-proximate and vaccination-distant groups was rerun using an extended definition of vaccination-proximate (seizure onset day 0–5). The mean age at onset was 20·5 weeks (SD 6·4) in the vaccination-proximate group and 26·4 weeks (8·7) in the vaccination-distant group (difference 5·9 weeks, 95% CI 0·9–11·0; p=0·02). Using this extended definition, seven of 17 patients in the vaccination-proximate group and nine of 23 in the vaccination-distant group had intellectual regression (p=0·0), and 12 of 17 patients in the vaccination-proximate group and 15 of 23 in the vaccination-distant group had moderate or severe intellectual disability (p=0·0).

We also assessed whether age at onset or mutation type was associated with worse outcome, irrespective of proximity to vaccination. 13 of 40 patients had normal intellect or mild intellectual disability (mean age at onset 21·3 weeks [SD 7·7]) and 27 of 40 patients had moderate or severe intellectual disability (23·1 weeks [8·4]; p=0·2). The mean age at onset was 21·9 weeks (8·6) for those with intellectual regression and was 25·2 weeks (8·0) for those without (p=0·2). There was no difference between patients with missense mutations and those with other mutations in age at onset (other 23·6 weeks [7·0] vs missense 24·5 weeks [11·0]; p=0·8), moderate or severe intellectual disability (other 20 of 28 vs missense 7 of 12; Fisher’s exact p=0·5), or occurrence of regression (other 13 of 28 vs missense 3 of 12; Fisher’s exact p=0·3).

Most children receive three sequential identical vaccinations. However, in our sample the onset of seizures resulted in exclusion of the pertussis component from subsequent vaccinations in some patients. In a post-hoc analysis, we investigated the association between vaccination after seizure onset and intellectual disability. Complete vaccination data for the first year were available in 37 of 40 patients, 12 of whom had normal or mildly

| First seizure | Vaccination-proximate (n=12) | Vaccination-distant (n=28) | p |
|---------------|-----------------------------|---------------------------|---|
| Age at onset (weeks) | 18·4 (5·9) | 26·2 (8·1) | 0·004 |
| Presence of fever* | 4 (33%) | 10 (37%) | 1·0 |
| Initial convulsion type† | | | |
| Bilateral | 7 (58%) | 18 (69%) | – |
| Unilateral | 5 (42%) | 8 (31%) | – |
| Status epilepticus§ | 5 (45%) | 11 (41%) | 1·0 |

| Subsequent seizure types | | |
|---------------------------|---------------------------|---|
| Tonic-clonic or secondarily generalised | 12 (100%) | 28 (100%) | – |
| Tonic | 3 (25%) | 5 (18%) | 0·7 |
| Atonic | 2 (17%) | 3 (11%) | 0·6 |
| Absence | 8 (67%) | 20 (71%) | 1·0 |
| Myoclonus | 10 (83%) | 25 (89%) | 0·6 |
| Hemiclonic | 11 (92%) | 23 (82%) | 0·7 |
| Focal¶ | 11 (92%) | 25 (89%) | 1·0 |
| Status epilepticus§ | 11 (92%) | 26 (93%) | 1·0 |

| Intellectual outcome | | |
|----------------------|---------------------------|---|
| Regression | 6 (50%) | 10 (36%) | 0·5 |
| Intellectual disability | | | |
| None | 0 | 1 (4%) | 0·7** |
| Mild | 3 (25%) | 9 (32%) | – |
| Moderate | 3 (25%) | 9 (32%) | – |
| Severe | 6 (50%) | 9 (32%) | – |

| SCN1A mutation type | | |
|---------------------|---------------------------|---|
| Missense | 2 (17%) | 10 (36%) | 0·3 |
| Other | 10 (83%) | 18 (64%) | – |
| Truncation (nonsense, frameshift) | 8 | 10 | – |
| Splice site | 1 | 8 | – |
| Intragenic copy number variation | 1 | 0 | – |

Data are mean (SD) or number (%). SMEI=severe myoclonic epilepsy of infancy. SMEB=severe myoclonic epilepsy of infancy borderline. *A temperature of greater than 38°C was regarded as febrile. †Details unavailable for one patient. ‡Details unavailable for two patients in the vaccination-distant group. §A seizure lasting at least 30 min. ¶Does not include hemiconic seizures. **2×2 analysis: no or mild intellectual disability versus moderate or severe intellectual disability.

Table 1: Clinical features, outcome measures, and type of SCN1A mutation

See Online for webappendix

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impaired intellect and 25 of whom had moderate or severe intellectual disability (table 2). 15 of 37 patients had pertussis vaccinations after seizures began, and there was no evidence that subsequent vaccination was associated with a worse intellectual outcome (Fisher’s exact p=0.5).

Intellectual regression occurred in 14 of 37 children; six had further pertussis vaccination and eight did not. Further pertussis vaccination was administered in nine of 23 patients without intellectual regression. Subsequent pertussis vaccination was not associated with intellectual regression (no further vaccinations vs one or more further vaccinations; Fisher’s exact p=1.0).

Discussion

About one-third of patients with Dravet syndrome had disease onset less than 2 days after vaccination, and the mean age at onset in these patients was significantly lower than that of patients whose disease onset was vaccination-distant. Universal vaccination in infancy is an emotive issue, in which science, societal views, and social policy are sometimes poorly aligned.1 At present, there is much attention on the debate regarding vaccination and autism;16–19 this attention is similar to the earlier intense debate regarding the role of pertussis vaccination and so-called vaccine encephalopathy. We previously reported a retrospective analysis in which 12 of 14 patients with presumed vaccine encephalopathy in fact had previously unrecognised Dravet syndrome, 11 of whom had mutations in SCN1A.1 This showed that vaccination was wrongly blamed as an acquired cause of a genetic disorder,20,21 and the hypothesis that vaccination was the causal factor in our cohort could be rejected. However, the possibility that vaccination triggered the onset of Dravet syndrome, causing a temporal shift (ie, brought forward an inevitable onset),22 or resulted in worse neurological outcome in these patients could not be excluded.

Recall bias can be a major factor in reporting of catastrophic disorders, and our impression was that certain cases of Dravet syndrome that were not clearly temporally associated with vaccination were nevertheless attributed to vaccination. Here, by examining a cohort of patients with Dravet syndrome who were not selected according to temporal relation to vaccination, we have confirmed the previous clinical reports that the onset of Dravet syndrome might occur shortly after vaccination.8,12 In our cohort, in which recall bias was minimised by reliance on source records, 30% of patients with Dravet syndrome who had SCN1A mutations had seizure onset shortly after vaccination.

We used a data-driven approach to identify days 0–1 as the at-risk period. The period of apparent vulnerability to onset of epilepsy after DTP vaccination has not been clearly defined, although 24–72 h periods are generally used.23–27 Our data was precise regarding the date, but not the hour, of vaccination and seizure onset. Because immunisations were likely to have been given in working hours, the at-risk period seems to be within 40 h of vaccination.

The mean age at disease onset was 7.8 weeks earlier in the vaccination-proximate group than in the vaccination-distant group, but all other clinical and outcome measures did not differ between groups (table 1). The mean age at onset in the vaccination-distant group was 26 weeks, which is similar to that quoted for patients with Dravet syndrome (5.5–6.0 months).18–20 Our findings show that, although vaccination might sometimes seem to trigger the onset of Dravet syndrome, there is no evidence that patients in the vaccination-proximate group had a different disorder from those in the vaccination-distant group. In particular, the similarity in clinical and outcome measures between patients in the vaccination-proximate group and those in the vaccination-distant group is not consistent with vaccination itself affecting the severity of
the disorder. Using a different approach in a population cohort, Goodman and colleagues 22 found evidence for a temporal shift of onset (but not of frequency) of infantile spasms in previously normal children after DTP or diphtheria and tetanus vaccination.

Molecular lesions also did not seem to differ in their type (missense versus other) or distribution within the protein between the vaccination-proximate and vaccination-distant groups (figure 2). The same mutations occurred in both groups on two occasions, further highlighting the similarity of the groups.

Despite the absence of significant difference, we wondered whether the higher number of non-missense mutations in the vaccination-proximate group could explain the earlier age at onset, but analysis of age at onset with respect to mutation type did not support this suggestion. We also examined whether earlier age at onset or presence of non-missense mutations were associated with intellectual disability or regression, and no associations were found.

Seizure onset in Dravet syndrome commonly occurs in the setting of fever. Only one third of patients had fever documented with the initial seizure, suggesting that vaccination might work through an alternative mechanism to trigger seizure onset earlier than might have occurred otherwise.

There are several limitations to this study. To study a homogeneous cohort, we assessed only patients with Dravet syndrome and SCN1A mutations who had been referred to the Epilepsy Research Centre, Melbourne, Australia. This approach might have resulted in some bias in the study. Also, our findings might not apply to the 20–30% of patients with Dravet syndrome who do not have SCN1A mutations. Because of the problem of recall bias, we chose to include only patients with validated vaccination and onset data. This limited the number of patients we could include in the analyses, and thus type 2 errors might have occurred. Finally, because our study was not a prospective evaluation with random assignment of vaccination, we cannot exclude the possibility that patients in the vaccination-distant group had an artificially later age at onset because vaccination occurs at fixed times, typically at around 2, 4, and 6 months. However, this is unlikely because the mean age at onset in the vaccination-distant group was similar to that reported for patients with Dravet syndrome overall (i.e., 6 months), whereas disease onset was at a mean of 18-4 weeks in the vaccination-proximate group.

There is increasing interest in examining gene-environment interactions in clinical research. Our study design and absence of a control group of patients with Dravet syndrome who did not have DTP vaccinations precluded us from examining a gene-environment interaction. However, our observation of an environmental effect (vaccination) temporally shifting the age at onset of an age-specific genetic neurological disease with no apparent effect on outcome suggests that Dravet syndrome would be an ideal model, both clinically and in experimental animals, with which to formally assess and examine the basis of such an interaction. If vaccination was withheld, the patients in the vaccination-proximate group would be expected to have had disease onset with the next substantial environmental trigger, be it fever, infection, or another stressor.

We therefore conclude that there is no rational basis for withholding DTP immunisation for potentially lethal childhood diseases for fear of causing Dravet syndrome or injuring the brain by a direct or presumed immune-mediated mechanism. The finding that onset of seizures occurred after the first, second, or third vaccination argues against a major role for immune sensitisation in which an initial immune challenge (i.e., vaccination) has no effect but subsequent challenges have increasing effects. Outcome was not influenced by vaccination after clinical onset (table 2), and thus vaccination does not seem to cause brain damage, although this analysis was post hoc and would ideally require confirmation in a prospective study.

Contributors
AMM and SFB developed the hypotheses and conceived the study. JMc and IES compiled and analysed the clinical data. LMD, XI, and JCM did the molecular analyses. AMM did the statistical analyses. JMc wrote the first draft and all authors critically evaluated the manuscript.

Conflicts of interest
JCM, IES, and SFB have acted as consultants to Bionomics, which has licensed testing of the SCN1A gene. JCM has been an unpaid consultant for and has received payment for preparation and presentation of a virtual grand round from Athena Diagnostics. IES has been a consultant and speaker for Athena Diagnostics, is a member of the Janssen-Cilag Asian Oceanic scientific board and the UCB SV2 advisory board, has received honoraria from Athena Diagnostics and the UCB Pediatric workshop, has patents pending for genes not relevant to this study, has received payment for development of educational presentations including service on speakers’ bureaus from Athena Diagnostics, and has received travel and accommodation expenses from Athena Diagnostics and UCB. AMM, JMc, LMD, and XI have no conflict of interest.

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