Characteristics of the initial seizure in familial febrile seizures

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Abstract

Complex seizure characteristics in patients with a positive family history were studied to define familial phenotype subgroups of febrile seizures. A total of 51 children with one or more affected first degree relatives and 177 without an affected first degree relative were compared for history of complex characteristics of the initial febrile seizure. No difference was found in the frequency of febrile status epilepticus (OR = 1.1 (95% confidence interval (CI) 0.3 to 4.3)), multiple type (OR = 0.6 (CI 0.3 to 1.2)), and focal characteristics (OR = 0.4 (CI 0.2 to 1.2)). The presence of any complex characteristic (OR = 0.5 (CI 0.3 to 1.0)) was higher in those without an affected first degree relative, although differences did not reach significance. The familial type of febrile seizures is not associated with complex characteristics of the initial febrile seizure. Complex seizure characteristics are unlikely to help in discriminating phenotype subgroups for genetic studies of febrile seizures.

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Although the genetic basis of febrile seizures is still unknown, several findings suggest a genetic origin. Febrile seizures are known to aggregate in families; 18 to 40% of affected children have affected relatives, and monozygotic twin concordance varies between 19% and 69% depending on the sampling method of the study.[1–6] A polygenic aetiology is suggested in some families, in addition to an autosomal dominant inheritance pattern observed in others.[6 7] One study found different inheritance patterns depending upon whether the patients had suffered recurrent febrile seizures.[8] A positive family history of febrile seizures is one of the major risk factors for febrile seizure recurrence; if first degree relatives are affected, the recurrence risk is increased and may rise up to 80%.[2–5 9] Clearly, the frequency of febrile seizure recurrences is an important phenotype feature of children with a familial type of febrile seizures. An increasing number of genes are identified for epileptic disorders, but no genes for febrile seizures specifically have been localised up until now. An important step towards the localisation of genes involved in febrile seizures will be the dissection of the heterogeneous group of children with febrile seizures into subgroups of patients with a more homogeneous phenotype.

We examined whether familial febrile seizures can be characterised by complex seizure characteristics. Characteristics of the initial febrile seizure were compared between children with one or more affected first degree relatives and children without an affected first degree relative.

Patients and methods

Children who consecutively visited the Sophia Children's Hospital in Rotterdam or the Juliana Children's Hospital in the Hague between 1994 and 1996 with a febrile seizure were considered for inclusion. They were selected from the prospective febrile seizure registration, established at the paediatric department of the Sophia Children's Hospital since 1988. The paediatric department of the Juliana Children's Hospital joined this registration in 1994. All patients in this registration visited the febrile seizure outpatient clinic within two to four weeks after a febrile seizure. As well as routine patient follow up, baseline characteristics of the patients were registered, including the family history. A febrile seizure was defined according to the National Institute of Health consensus for febrile seizures, excluding any seizure caused by an underlying abnormality and excluding any seizure occurring after a previous non-febrile seizure.[10] Children with an unknown family history were excluded from the analysis. Children of non-white origin were excluded to obtain a genetically homogeneous study sample.

Children were included in the case group if they had one or more first degree relatives affected with febrile seizures: parents, brothers, and sisters. The referent group consisted of all children who had no first degree relatives affected by febrile seizures.

DATA COLLECTION

The following data were studied: baseline characteristics, including age at the initial febrile seizure (age at onset); sex; and the presence of complex characteristics of the initial febrile seizure. A seizure was defined as complex if it lasted 30 minutes or longer (febrile status epilepticus) and/or if the seizure recurred within 24 hours (multiple type) and/or if the seizure had a focal onset or a postictal Todd's paresis of facial muscles or limbs (focal characteristics).[1 11 12] Seizure characteristics were determined based on the history given by the child's parents or other witnesses of the seizure, or on the documentation in the

Table 1 Baseline characteristics and characteristics of the initial febrile seizure

	Cases (n = 51)	*Referents (n = 177)*	*OR (95% CI) univariable*	*p Value*
Baseline characteristics				
Median age at onset (25th to 75th centiles in years)	1.3 (1.0 to 2.2)	1.5 (1.2 to 2.2)	0.8 (0.5 to 1.1)	0.19
Female	19 (37%)	73 (41%)	0.8 (0.4 to 1.6)	0.61
Initial seizure characteristics				
Febrile status epilepticus*	3 (6%)	9 (5%)	1.1 (0.3 to 4.3)	0.89
Multiple type†	11 (22%)	56 (32%)	0.6 (0.3 to 1.2)	0.14
Focal characteristics‡	5 (10%)	27 (15%)	0.4 (0.2 to 1.2)	0.11
Any complex characteristic	14 (27%)	72 (41%)	0.5 (0.3 to 1.0)	0.07
Number of complex characteristics§				
0	36 (71%)	97 (55%)	Reference category	–
1	9 (18%)	52 (29%)	1.5 (0.9 to 2.4)	0.11
2	5 (10%)	20 (11%)	0.7 (0.4 to 1.2)	0.21
3	–	–	–	–

*Missing values: 3 (6%) *v* 19 (11%).
†Missing values: 3 (6%) *v* 14 (8%).
‡Missing values: 12 (23%) *v* 72 (41%).
§Analysed as a continuous variable: OR = 0.7 (0.4 to 1.1) p = 0.14.

patient's chart. If characteristics of the initial seizure were unknown, they were considered missing values.

For the analysis, second and further degree relatives were not taken into account. Siblings and parents with epileptic disorders, but without a history of febrile seizures, were considered not affected.

STATISTICAL ANALYSIS

The relation between the characteristics of the initial febrile seizure (febrile status epilepticus, multiple type, and focal characteristics) in the case group and the control group was estimated using logistic regression analysis. Odds ratios (ORs) were used as the measure of association; associations were statistically significant ($p < 0.05$) if the 95% confidence interval (CI) of the OR did not include the value 1. SPSS 6.0 for Windows was used for the analysis.

Results

Of all 478 children who had visited one of the two participating hospitals because of a febrile seizure between 1994 and 1996, 240 children were of non-white origin. For 10 of the remaining eligible children, the family history was unknown; thus, 228 children entered the study.

Of these 228, 51 (22%) children had at least one affected first degree relative and were included in the case group: 14 (27%) of the 51 children had one or more affected siblings, 31 (61%) had one affected parent, and six (12%) had one affected parent and one or more affected siblings. The referent group comprised 177 (78%) of 228 children without a first degree relative affected by febrile seizures.

Table 1 shows the baseline characteristics and the characteristics of the initial febrile seizure of the cases and the referents. Using logistic regression, no difference was shown in age at onset or sex. Febrile status epilepticus did not differ between the two groups; multiple type and focal characteristics were counted more frequently in the referent group; the presence of any complex characteristic was observed more frequently in the referent group, although differences did not reach significance ($p = 0.07$). The number of complex characteristics for each seizure did not show a difference between the case and the referent group.

Discussion

This study shows that the familial type of febrile seizures is unlikely to be associated with complex characteristics of the initial seizure. Thus, defining a phenotype subgroup associated with complex seizure characteristics may be unhelpful in genetic studies to localise genes involved in febrile seizures. The results suggested even higher frequencies of complex seizure characteristics in the referent group, although differences were not statistically significant. These results are supported by a study that showed no difference in "seizure severity" in familial versus non-familial febrile seizures. In the previous study, no further specification was made on how seizure severity was defined and whether complex seizure characteristics were considered.[13] Another study of familial febrile seizures suggested that the proportion of complex febrile seizures was higher among multicase (familial) compared with single case (non-familial) probands; statistical significance, however, was not reached.[6] The results of the present study are in accordance with these previous studies.

A large population based study of 2609 relatives (parents, siblings, children, nieces, nephews, and half-siblings) of 421 children with febrile seizures investigated the risk for the development of febrile seizures in siblings. As well as frequent recurrent seizures, complex seizures in the proband were associated with an increased risk of febrile seizures in siblings, which may suggest that complex seizures are associated with a familial predisposition.[1] In a recent study of 398 first degree relatives of 129 children with febrile seizures, the risk of febrile seizures in siblings was increased when the proband had had recurrent febrile seizures.[14] Unfortunately, complex characteristics were not considered in the analysis.[14] These two studies used a different strategy to investigate phenotype subgroups which may be helpful to study the hereditary basis of febrile seizures. Their approach has been based on studying a

sample of the *relatives* of the proband. Thus, their results can not easily be compared with ours. Both previous studies[1 14] suggested that recurrent febrile seizures might be characteristic of hereditary febrile seizures, and one of them[1] also suggested that complex seizure characteristics might help to delineate a subgroup worthy of genetic study.

The limitation of the present study is the high number of missing values for focal seizure characteristics. This is likely to be due to the relative difficulty of recognising a focal seizure feature. In a study assessing the accuracy of the classification of complex characteristics of febrile seizures, experienced paediatric neurologists most often showed disagreement about assessment of focal seizure characteristics. They disagreed less about multiple and prolonged characteristics.[11]

In conclusion, we provided no evidence for an association between familial febrile seizures and complex characteristics of the initial febrile seizure of the proband. This does not exclude the existence of other clinical features—that is, characteristics of the seizure which are specific for patients with familial forms of febrile seizures. Complex febrile seizure characteristics, however, are unlikely to help in discriminating phenotype subgroups for genetic studies of febrile seizures.

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