AN EPIDEMIOLOGICAL STUDY OF FEBRILE SEIZURES WITH SPECIAL REFERENCE TO FAMILY HISTORY AND HLA LINKAGE

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ABSTRACT

One hundred and forty four cases of febrile seizures, 95 simple (typical) and 49 complex (atypical); were studied and compared for clinical and epidemiological data and family history of febrile and afebrile seizures. Major results were: maximum age of onset below three years (75%) in both simple and complex groups, male preponderance, respiratory infection as the commmonest etiology (69.4%) and maximum seizure onset within 24 hours of fever (73%).

The familial prevalence of all seizures was 29.1%, 23.2% in the simple and 40.8% in the complex group ($p<0.01$). The familial prevalence of febrile seizures was 20%; similar in both groups. The familial prevalence of afebrile seizures was 13.9%; 6.3% in simple and 28.6% in complex group ($p<0.01$). The commonest relative was a sibling (13.2%). The prevalence in parents was 4%. Families with two additional members with history of seizures revealed complex seizure patterns in two-thirds of index cases. There was no correlation between family history of seizures and age at onset or sex. No clear inheritance pattern emerged and polygenic inheritance is likely.

One third of eighteen families had siblings with identical segregation of parental HLA-A and B haplotypes. Five families showed the presence of HLA All. This small though adequate sample size did not reveal an HLA marker for febrile seizures.

Key words: *Febrile seizures, Family studies, HLA linkage.*

Febrile seizures affect approximately 5% of children in the age group of 6 months to 5 years(1). Although febrile seizures are innocuous and have a benign course, they generate parental anxiety leading to enquiries on possibility of recurrence, prognosis and risk to other siblings. The risk of future epilepsy is negligible in children with simple febrile seizures as compared to those with complex seizures. A higher risk is also seen in those with prior neurological deficits or family history of afebrile seizures(2).

Familial predisposition to febrile seizures has long been recognized. A positive family history has been documented in many studies(2), varying from 2-58% (mean 17%). The frequency in siblings has been reported as 9-22% and in parents 8-14% in various studies(3,4). Concordance rates of 31-81% have been reported among monozygotic twins(5,6). The mode

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of inheritance of febrile seizures is not clear. Frantzen(3) reported autosomal dominant inheritance. Tsuboi(7) and Baraitser(8) suggest polygenic inheritance.

Although there are many reports on epidemiology, familial prevalence of febrile and afebrile seizures and risks of epilepsy, no genetic markers have been investigated. A number of childhood disorders of believed polygenic inheritance have been subjected to HLA-linkage studies to identify such a marker, notable among these being HLA B 27 positive ankylosing spondylitis(9). HLA–linkage has been studied in other childhood seizure forms, such as the Lennox-Gestaut syndrome (HLA-B 7)(10) and infantile spasms (no significant association)(11).

The present study of febrile seizures in children was conducted to analyze epidemiological data; to analyze and compare the prevalence of febrile and afebrile seizures in families of index cases with simple (typical) and complex (atypical) febrile seizures; study pedigrees for possible mode of inheritance and finally; study families with two or more siblings affected for segregation of parental HLA haplotypes among siblings. No studies of HLA-linkage in families with febrile seizures have been conducted to date.

Material and Methods

Children with simple and complex febrile seizures were prospectively enrolled in the study over one year conforming to standard clinical definitions(1). Data regarding age at onset, sex, precipitating illnesses, time of onset, pedigree charts up to three generations and history of febrile and afebrile seizures among first and second degree relatives of index cases were recorded. Grandparents were interviewed wherever possible with home visits, if required, for elicitation of familial incidence. The limitations were geographic in accessibility, memory failure, ignorance or death of grandparents. Epidemiological data and family incidence were compared in the simple and complex febrile seizure groups. Familial prevalence with individual epidemiological factors as variables were also compared in both groups.

Eighteen families with two or more siblings with febrile seizures; simple and complex, were studied for HLA-linkage between HLA haplotype and disease susceptibility gene. Ten to twelve ml of heparinized blood was drawn from all subjects under aseptic conditions. Tissue typing was carried out by standard NIH microlymphocytotoxicity test(12) for specificities of the A locus and 15 specificities of the B locus using a set of 118 well defined sera. Phase contrast microscopy was used to identify the viable and non-viable cells. Haplotypes of the siblings and parents were deduced from HLA typing results. Nijenhuis' formula as described by de Vries *et al.*(13) was used for the statistical analysis.

Results

Of the 144 index cases of febrile seizures, 95 (66%) were simple and 49 (34%) were complex. The age at presentation of both simple and complex seizures is shown in *Table I.* Five per cent presented at less than 6 months and 5.5% at more than 5 years. The percentage of cases presenting at different ages in the simple and complex groups were similar.

Male predominance (1.9 : 1) was noted; more so in the simple group (2.2 : 1) than in the complex group (1.45 : 1). The predisposing illnesses included fever with upper respiratory infection (70%), diarrhea (8.3%) and otitis media (8%). Seizures occurred within the first 24 hours of fever in

TABLE I—*Epidemiological and Family History Data*

Parameter	Simple (n = 95)	Complex (n = 49)	Total (n = 144)
1. *Age at onset* (mo)			
<18	29 (30.5)	21 (42.9)	50 (34.7)
18-36	43 (45.3)	15 (30.6)	58 (40.3)
>36	23 (24.2)	13 (26.5)	36 (25.0)
2. *Positive family history*			
(all seizures types)	22 (23.2) *	20 (40.8) *	42 (29.1)
3. *Family history of febrile sizures*			
Sibling	14 (14.7)	5 (10.2)	19 (13.9)
Parents	4 (4.2)	2 (4.2)	6 (4.2)
First degree relative	1 (1.1)	3 (2.8)	4 (2.8)
Total	19 (20.0) +	10 (20.4) +	29 (20.2)
4. *Family history of febrile sizures*			
Sibling	1 (1.1)	2 (4.1)	3 (2.1)
Parents	1 (1.1)	5 (10.2)	6 (4.2)
First degree relative	4 (4.2)	7 (14.3)	11 (7.6)
Total	6 (6.3) ‡	14 (28.6) ‡	20 (13.9)

Figures in parentheses are percentages.
*p<0.01; + p = NS; ‡ p<0.01.

73% of cases. The percentage in the simple and complex groups were similar (75 and 69.3%, respectively).

The epidemiological and family history data are summarized in *Table I*. A positive family history of all seizure types was significant in the two groups (23.3% in the simple and 40.8% in the complex group) (p<0.01). History of afebrile seizures in the family for simple and complex groups (6.3 and 28.6%, respectively) was also statistically significant (p<0.01). There was no significant difference; however, in the family history of febrile seizures in the two groups. There was no significant difference in familial prevalence of febrile or afebrile seizures in relation to sex of the proband or age at onset of febrile seizures in both simple and complex groups.

Table II shows the relationship between number of family members involved and type of seizure in the index case. Where families with more than two members involved were studied, it was found that 66% of these had index cases presenting with complex seizures. The comparative figures for families with less than two affected members was 33%.

There were 17 instances of two siblings having febrile seizures without any other family member being involved. One-fifth of these had a history of consanguinity.

TABLE IV—*HLA Haplotypes in 18 Families*

Family	Parents		Children			Nijenhuis statistics					
No.	Father	Mother	1	2	3	Father			Mother		
						D	d	θ^2d	D	d	θ^2d
*1	ab	cd	ad	ad		2	1	1	2	1	1
2	ab	cd	bc	ad		0	1	1	0	1	1
3	ab	cd	bd	ac		0	1	1	0	1	1
4	ab	cd	bd	bc		2	1	1	0	1	1
*5	ab	cd	ac	ac		2	1	1	2	1	1
6	ab	cd	ad	ac		2	1	1	0	1	1
*7	ab	cd	ad	ad		2	1	1	2	1	1
8	ab	cd	bc	ac		0	1	1	2	1	1
9	ab	cd	ad	bc	bd	1	1.5	0.75	1	1.5	0.75
*10	ab	cd	ad	ad		2	1	1	2	1	1
11	ab	cd	bd	bc	ac	1	1.5	0.75	1	1.5	0.75
12	ab	cd	ac	ad		2	1	1	0	1	1
13	ab	cd	bc	ad		0	1	1	0	1	1
14	ab	cd	ac	bc		0	1	1	2	1	1
15	ab	cd	ac	bd		0	1	1	0	1	1
*16	ab	cd	ac	ac		2	1	1	2	1	1
17	ab	cd	ad	bc		0	1	1	0	1	1
*18	ab	cd	ac	ac		2	1	1	2	1	1

ab represent paternal haplotypes.
cd represent maternal haplotypes.
*Identical HLA haplotypes are observed in the sibs in these families.
D = observed segregation value.
d = expected segregation value.
θ^2d = variance associated for each value of D.

Tsuboi(7) and Baraitser(8) that the disorder is probably polygenic. These and other limitations account for the wide variation of 2-58% in the familial prevalence of febrile seizures in earlier studies(2). Our finding of 20.2% lies somewhere in between; Sehgal and Bela reported a prevalence of 10%(14). A large recent study by Verity *et al.*(15) in which a cohort of British children were followed prospectively from birth, reported family history of febrile seizures in 18.4%. Our figure is in agreement with that reached by Verity(15).

No consistent pedigree pattern emerged in the 42 cases with positive family history. Seventeen families had two siblings with the disorder with no other family members being involved. It becomes tenuous to conclude autosomal recessive inheritance as skipped generation involvement could have been present. Great-grandparents would almost never be avail-

able for interview. There is also no marker for heterozygosity in febrile seizures. To illustrate this discrepancy, a representative pedigree of 5 cases in the study is shown in the *figure*. It is difficult to conclude if the febrile seizure gene is dominant or recessive as there is no marker for heterozygosity in the middle generation.

Table I reveals a significant difference ($p<0.01$) in the prevalence of family history of all types of seizures between index cases of simple and complex febrile seizures. Most studies(2) have not analyzed this distinction. Verity *et al.* reported a family history of all seizure types in 25.9% which is in close agreement with the 29.1% in the present study. Our study is also in agreement with Verity's study over the markedly increased prevalence of family history of all seizure types in the complex group over the simple group.

Family history of febrile seizures in the present study did not differ in the simple and complex groups, but family history of afebrile seizures/epilepsy was significantly higher ($p>0.01$) in the complex group (*Table I*). The study of Verity *et al.*(15) is the only one that has analyzed these differences, the family history of afebrile seizures being similar in the two groups, (7.2% in simple and 8.3% in complex); which is at variance with our results. The same study reported family history of febrile seizures to be 14.5% in the simple and 33.4% in the complex groups; which is also at variance with the present study in which the figures were similar (*Table I*). These differences may be explained by noting that in 62 cases that were included in that study, family history was not documented and could have altered the results.

It is evident from the present data that the total seizure prevalence and that of afebrile seizures in the family are higher in the complex seizure group. The index case is more likely to have had a complex seizure if more than two family members are affected (*Table II*).

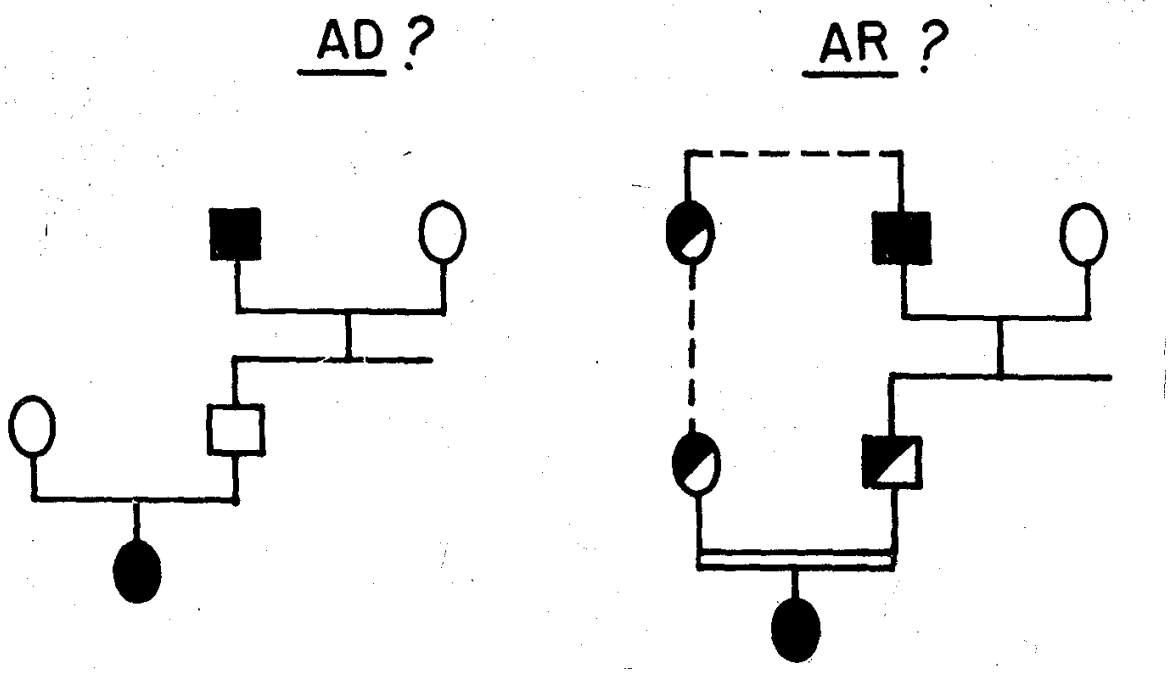

Fig.. Five cases with the same pedigree reveals how a consanguinous AR pedigree could be similar to an AD pedigree with skipped generation.

Epidemiological factors such as age at onset and sex have not been analyzed by previous workers for simple and complex seizures with reference to family history. We found no significant differences and are in agreement with Verity *et al.*(15).

A recent meta-analytic review on predictors of recurrence has found that a family history of febrile seizures is even more strongly associated with a recurrence risk in the same individual than a family history of unprovoked seizures(16). The present study has not addressed the problem of recurrence risks in the index cases. A large, prospective study with pedigree recording needs to be undertaken for better appreciation of the mode of inheritance of febrile seizures.

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