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Some Aspects of the Genetics of Febrile Convulsions

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Summary

Scott-Emuakpor AB and Longe AC. Some Aspects of the Genetics of Febrile Convulsions. *Nigerian Journal of Paediatrics*, **1985: 12:49.** A prospective study of the inheritance pattern of febrile convulsions was carried out among the families of 70 children who presented with the condition at the Children's Emergency Unit of the University of Benin Teaching Hospital, over a period of 12 months. A retrospective study involving the families of 87 others seen over a period of 2 years was also carried out. Although no clear-cut pattern emerged, it was felt that, on the basis of the available data, an autosomal dominant mode of inheritance was the most plausible. The following conclusions and projections about febrile convulsions in Benin City were also made:

(*a*) febrile convulsions constitute approximately 5.8% of all paediatric emergency room admissions in Benin-City.

(*b*) one-eighth of parents of patients with febrile convulsions would have had the condition themselves;

(*c*) 50% of the full siblings of affected children stand the risk of developing febrile convulsions, if their mothers also had them and

(*d*) a third of all patients with febrile convulsions will have at least, one recurrence in 5 years.

Introduction

No clear-cut definition of febrile convulsion exists. Thus, Livingston[1] describes it as generalized seizures, of brief duration, occurring soon after an elevation of temperature in a child between the ages of 6 months and 5 years, with no evidence of meningitis or encephalitis, and with normal electroencephalogram (EEG) after the patient has been afebrile for at least, one week. Ellenberg and Nelson[2] consider it is febrile convulsion, if the first seizure ever experienced was accompanied by fever and occurred between the ages of 1 month and 7 years. For the purpose of this study, we have defined febrile convulsion as a generalized seizure occurring in association with elevation of temperature in a child aged between 6 months and 6 years, with no evidence of intracranial infection or metabolic derangement.

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The frequency of febrile convulsions in the Nigerian population is not well established despite the very common occurrence of such seizures. Inadequate reporting of cases appears to be prominent among the reasons for this. However, in developed countries, a frequency of about 5% is generally accepted for febrile convulsions[3,4].

Several reports exist on the heritability of febrile convulsions. In his review, Pratt stated that there is a "considerable inherited tendency to febrile convulsions and in many cases, the (hereditary) predisposition is limited to convulsions precipitated by fever"[5]. Frantzen *et al*[6] summarizing their findings, concluded that the inheritance of febrile convulsion is compatible with transmission by a single dominant gene with incomplete penetrance. Although observations of familial occurrence of febrile convulsions have been made[7], no scientific study of the genetics of this entity exists in Nigeria. This study was therefore, designed to fill this void.

Materials and Methods

One hundred and four patients with the provisional diagnosis of febrile convulsion, out of a total of 1207 children admitted to the Children's Emergency Unit of the University of Benin Teaching Hospital (UBTH), over a period of twelve months (August 1, 1982 to July 31, 1983) were investigated to exclude other conditions that might mimic febrile convulsion. A spinal tap was done on each of these 104 patients and the cerebrospinal fluid (CSF) analyzed for glucose and protein. Cell count and morphology, gram stain and culture for bacteria were also carried out on all the CSF samples while blood glucose, electrolytes and calcium levels were determined in each case.

Of these 104 patients, only 70 met our strict definition of febrile convulsion. Thus, the frequency of febrile convulsion among our patients was 70 (5.8%) out of 1207. These 70 had normal values for CSF and blood investigations. Of the remaining 34, 29 were initially excluded because of clear evidence of associated drug ingestion (alcohol or kerosine), cloudy CSF suggestive of meningitis, or clinical evidence of severe malnutrition and other chronic diseases. The remaining 5 were subsequently excluded because laboratory results suggested a diagnosis of meningitis in 2, hypoglycaemia in one, while further information on two others placed them outside the age criteria for the diagnosis of febrile convulsion.

The 70 patients who satisfied our diagnostic criteria constituted the probands for the prospective aspect of this study. A complete family history was obtained from the parents of each of these patients and this was constructed into a pedigree. Because of inaccuracies in the history beyond first and second degree relatives, each pedigree was limited to the proband, full and half siblings, maternal and paternal uncles and aunts and maternal and paternal full first cousins. In this way, every family was ascertained solely through a proband and each proband was ascertained once.

In order to obtain information in patients whose first febrile convulsion occurred 5 to 6 years prior to the beginning of the prospective part of the study, case-notes of patients who had febrile convulsions in 1977 and 1978 were retrieved. Eighty-one of such case-notes were retrieved, but only 53 home follow-ups were possible because of movement and untraceable addresses. From these 53 home follow-ups, data was collected retrospectively on 87 children with febrile convulsions. Care was taken to ensure that only convulsions precipitated by fever was discussed, and this was done rather willingly by the mothers, who were the providers of the bulk of the information in this study. Statistical analysis was by means of the chi-squared method.

Results

The characteristics of the 70 patients who were studied prospectively are presented in Table I. It will be observed that the peak

TABLE I

Characteristics of 70 Patients with Febrile Convulsions

Age of Probands (mon)	*No of Cases*	*Sex*		*Order of Convulsion at Time of Presentation*				
		M	*F*	*1st*	*2nd*	*3rd*	*4th*	*5th*
6–12	12(17.1)	9	3	6	4	1	0	1
13–24	23(32.9)	14	9	12	10	0	1	0
25–36	14(20.0)	9	5	11	1	1	0	1
37–48	5(7.1)	0	5	3	1	0	1	0
49–60	10(14.3)	5	5	3	3	2	2	0
61–72	4(5.7)	3	1	1	0	1	0	2
73–84	2(2.9)	1	1	0	0	1	0	1
Total	70(100.0)	41 (58.6)	29 (41.2)	36 (51.4)	19 (27.1)	6 (8.6)	4 (5.7)	5 (7.1)

Figures in parentheses = percentages of total

age for febrile convulsion was between 13 and 36 months, with about 53% of the patients involved. There was a preponderance of males among the probands (ratio about 3:2). About one-half (51.4%) of the 70 presented with their first febrile convulsion, 27.1% presented with a second febrile convulsion, 8.6% presented with a third febrile convulsion, 5.7% presented with a fourth and 7.1% presented with more than a fourth febrile convulsion at the time of presentation.

Febrile convulsions among near relatives of probands

Of the 140 parents of the probands, 18 (12.9%) had febrile convulsions as children (Table II). The difference from the frequency of 5.8% among the population studied was statistically significant ($X^2=9.6$; $p<0.01$). In one family, both father and mother had febrile convulsion and in 16 families, only the mothers had febrile convulsion. Thus, of the 70 mothers of our probands, 17 (24.3%), had febrile convulsion indicating a clear-cut preponderance of mothers.

Thirty-seven (21.6%) of 171 full siblings and 15 (40.5%) of 37 half siblings (36 of these 37 were paternal) had febrile convulsions. These frequences were significantly higher than the 5.8% among the population studied ($p<0.001$ in each case). The sex distribution of the affected sibs (both full and half) was about equal.

There were 569 paternal first cousins of which 32 (5.6%) were affected and there were 474 maternal first cousins of which 45 (9.5%) were affected. Thus, only the risk to maternal cousin was significant ($X^2=6.8$; $p<0.01$) when compared to the study population frequency. No difference between the sexes was observed among affected first cousins. There was no history of febrile convulsion among all 235 paternal uncles and aunts. However, among the 272 maternal uncles and aunts, 11 (4.0%) were affected.

An analysis of febrile convulsions among relatives of probands in the 16 families with history of maternal febrile convulsion is summarized in Table III. It will be observed that of the 38 full sibs of probands in this group, 19 (50%) were affected and of the 16 half sibs, only

5 (31.3%) were affected. These two values are each significantly different from the population frequency ($p<0.001$).

Recurrence of febrile convulsions

The findings on recurrent febrile convulsions in 87 children who were identified in the retrospective study as having had febrile convulsion 5 years previously, are presented in Table IV. Of 10 children who had their initial febrile convulsion below the age of 12 months, 8 (80%) had at least, one recurrence 5 years later. Of these 8, 2 had their recurrences within the first 6 months of the first episode, a total of 4 within 12 months, 5 within 2 years and 7 within 3 years. The recurrence rates for all the other age groups

TABLE II

Febrile Convulsions Among Near Relatives of 70 Probands

Relation	*Total No of Cases*	*No of Affected Individuals*			*Percent of Total*
		M	*F*	*Total*	
Parents	140	1	17	18	12.9
Full sibs	171	17	20	37	21.6
Half sibs	37	8	7	15	40.5
Paternal cousins	569	16	16	32	5.6
Maternal cousins	474	22	23	45	9.5
Paternal uncles/aunts	235	0	0	0	0.0
Maternal uncles/aunts	272	6	5	11	4.0

TABLE III

Febrile Convulsions Among Relations of Probands in 16 Families in which Mother of Proband was affected

Relationship	*Total No. of Cases*	*Affected Individuals*			*Percent of Total*
		M	*F*	*Total*	
Full sibs	38	10	9	19	50.0
Half sibs	16	4	1	5	31.3
Paternal cousins	119	3	3	6	5.0
Maternal cousins	108	6	5	11	10.2
Maternal uncles/aunts	62	3	1	4	6.5

TABLE IV

Recurrences of Febrile Convulsion in 87 Children*

Age of Onset (mon)	*No of Cases*	*Recurrence within*[a]				
		6 months	*12 months*	*24 months*	*36 months*	*60 months*
6–12	10	2	4	5	7	8
13–24	13	1	5	5	6	7
25–36	24	0	2	6	6	8
37–48	17	0	0	1	4	4
49–60	15	0	1	1	1	2
61–84	8	1	1	1	1	1
Total	**87**	4	13	19	25	30

* Retrospective Study

a Cumulative

are shown in the Table. The older the age of onset, the lower the probability of having a recurrence. Thirty (34%) of the 87 patients with febrile convulsions had experienced at least, one recurrence within 5 years of the initial episode.

Discussion

Several authors have suggested that febrile convulsions occur with increased frequency among family members of febrile convulsive patients.[5-11] This suggestion cannot as of now, be verified with any degree of certainty for Nigeria because of lack of information as to the frequency of febrile convulsions in the general population of children. In this study, the frequency among the population of 1207 studied was 5.8%. Because of our strict diagnostic criteria for this condition which affects every socio-economic class and because the children's emergency room is more or less, a "walk-in" clinic, this frequency is likely to be near to the population frequency.

Employing the 5.8% frequency, this study has shown that febrile convulsions occur with increased frequency among first degree relatives of febrile convulsive patients in Nigeria. The first degree relatives in this study were the parents, full-sibs and half-sibs. The study of Familusi and Sinnette[7] also showed familial clustering. However, our studies cannot be strictly compared to theirs because different criteria for diagnosing febrile convulsions were employed. For example, infants under 6 months of age and those over 6 years were included among their patients. Also, apart from including patients with overt kwashiorkor, a number of their patients had metabolic derangements such as acidosis, hyponatraemia, hypochloraemia, hypokalaemia, hyperelectrolytaemia and significant hypoglycaemia.

The frequency of 12.9% found among parents of our probands was largely due to maternal febrile convulsions. This discrepancy between maternal and paternal febrile convulsions is contrary to the sex-ratio found among

the other categories of relatives and it may be partly explained by a possible ignorance of paternal past medical history.

The finding that the risk to half-sibs was greater than that to full-sibs was unexpected. We are aware that full-sibs have half of their genes in common, whereas half-sibs have only a quarter of their genes in common. If this condition has a heritability of 97% as suggested by Tsuboi,[10] then, one would expect full-sibs to be at greater risk of developing febrile convulsions than half-sibs. Before this paradox can be fully explained, it is necessary to have available, (*a*) a correct history of paternal febrile convulsion since 36 of the 37 half sibs were paternal (*b*) a correct history of febrile convulsions in the maternal side of the half-sibs and (*c*) an analysis of febrile convulsions among relatives of probands in the 16 families with history of maternal febrile convulsion. It was not possible to obtain the first two pieces of information in this study. The third piece of information was however, available and it suggests that in a family where the mother has a history of febrile convulsion, the risk to the full siblings of her febrile convulsive child is 50%, whereas the risk to the half siblings is 31.3%.

The mode of inheritance of febrile convulsions has been a subject of considerable debate. Some workers have postulated an autosomal recessive mode of inheritance[12] while others have postulated a single autosomal dominant gene with reduced penetrance.[6 13] There have also been some suggestions of a polygenic mode of inheritance,[8] but no reports of sex-linked inheritance has been suggested.

The present study may be interpreted in two ways. In the first place, 21.6% of full-sibs had febrile convulsions. The fact that the probands are not included in this estimate has corrected for the "error of ascertainment." The value of 21.6% is not significantly different from the 25% that would be expected among offsprings of parents who are heterozygous for an autosomal recessive gene. Thus, it may be postulated on the basis of this data that febrile convulsion is transmitted by an autosomal recessive mode of inheritance. If we however, exclude the 17 families in which at least, one parent had febrile convulsions, we will be left with 53 families where there is no history of parental febrile convulsions. In these 53 families, there were 129 full siblings of probands, out of which 16 were affected (frequency of 12.4%). For autosomal recessive inheritance, it is in this group (where no parent is affected) that we would have expected about 25% risk to siblings of probands. The observed value of 12.4% (after correcting for error of ascertainment) is significantly different from the expected 25%. Thus, an autosomal recessive mode of inheritance does not appear likely. The data may also be interpreted by studying the families in which one parent had febrile convulsions. There were 16 such families, all with the mother affected. The risk to full siblings is 50%, indicating an autosomal dominant mode of inheritance. The fact that the value of 50% was obtained suggests a complete penetrance, but this cannot be stated with certainty until several generations of febrile convulsive families are analyzed and the behaviour of the gene, if it is indeed a single gene, studied.

It is also important to stress the contribution of mothers to the heritability of febrile convulsions. Usually, it is in extra-chromosomal or cytoplasmic inheritance that maternal influence is so pronounced. Thus, the possibility of extra-chromosomal inheritance cannot be discarded.

One of the values of undertaking this study, is to provide empirical data for the purposes of counselling. In Nigeria, counselling of patients and family members has not been given a prominent place in the management strategy of disease entities. One of the major reasons for this is because the data base is lacking for carrying out counselling effectively. Fortunately, it is our belief that the data obtained in the present study contain the basis for such counselling.

The conclusions and projections that appear to have emerged from this study include the following:

(*a*) febrile convulsions constitute approximately 5.8% of all paediatric emergency admissions in Benin City;

(*b*) the peak incidence of febrile convulsions is between the ages of 13 and 36 months; there is a slight but insignificant preponderance of males with febrile convulsions among our probands;

(*c*) about $\frac{1}{8}$ of parents of febrile convulsive patients would have had febrile convulsions themselves,

(*d*) if a child has febrile convulsions, the risks to his relations are as follows; full siblings 21.6%, maternal cousins 9.5%, paternal cousins 5.6%, full siblings 50% if the mother also had febrile convulsions and maternal cousins 10.2%, if the mother also had febrile convulsions.

(*e*) the younger the age of onset of febrile convulsions, the greater the probability of recurrence;

(*f*) about $\frac{1}{3}$ of all patients with febrile convulsions will have at least, one recurrence within 5 years; the role of these recurrences in the development of later seizure disorder is not known;

(*g*) the mode of inheritance of febrile convulsions appears to be as an autosomal dominant entity, although autosomal recessive and extra-chromosomal mode of transmission cannot be completely ruled out.

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