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Aetiological Aspects of Febrile Convulsions

Pregnancy and Perinatal Factors

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Wallace, S. J. (1972). *Archives of Disease in Childhood*, **47**, 171. **Aetiological aspects of febrile convulsions: pregnancy and perinatal factors.** The birth histories of 132 patients admitted to hospital with convulsions in association with febrile illnesses are compared with those of 180 of their sibs. Patients experienced significantly more often threatened abortion, maternal medication during pregnancy, caesarean section, and moderately low birthweight. Male patients had a significant increase in fetal distress, and, in specified circumstances, in neonatal feeding difficulties. Female patients were born significantly more often to very young or elderly mothers. At least one significant factor was recorded in 61% of patients. It is concluded that an abnormal pregnancy or birth history predisposes to febrile convulsions.

In the Newcastle survey of 896 children, it was found that 5·9% had a history of convulsions between the ages of 1 month and 5 years (Miller *et al.*, 1960). In this age group, the majority of seizures are associated with feverish illness (Peterman, 1946; Thom, 1942). However, only 11% of children admitted to hospital while febrile have convulsions (Friderichsen and Melchior, 1954). This suggests that fever may be only one of a number of causative factors which result in a 'febrile convulsion'. In the present study, the possible significance of abnormalities of pregnancy, labour, and delivery, and the neonatal period which could have caused brain damage are examined as predisposing factors to fits occurring in association with fever. A comparison is made between the histories of children admitted to the Royal Hospital for Sick Children, Edinburgh, on account of 'febrile convulsions' and those of their sibs who had not suffered from convulsive disorders.

Children Selected for Study and Methods of Investigation

The children are divided into two categories:

(A) Patients, males 83, females 49, total 132.

(B) Sibs, males 91, females 89, total 180.

The patients were aged more than 3 months and less than 7 years on admission to hospital. All were febrile, or had evidence of active infection. Though no parent had previously requested advice on account of any suspected neurological abnormality, the history or signs suggested that such an abnormality had existed before the first fit in 31 cases. The admission was precipitated by a first fit in 122 cases, and by a second or third fit in association with a febrile illness in 10 cases. All sibs aged 1 year or more at the last occasion that the mother was seen, who had no history of a fit, and on whom it was possible to get the relevant information, are included.

While the patient was in hospital, detailed histories of the pregnancies, labours, and deliveries resulting in the births of the patient and his sibs, and an account of their neonatal periods were obtained from each mother. In the cases of the 91 patients and 107 sibs who were born in the Maternity Departments of Edinburgh hospitals, or, in Bangour General Hospital, the mothers' maternity records and the infants' neonatal progress sheets were scrutinized. Satisfactory information was obtained about the pregnancy in 132 patients and 179 sibs, the labour and delivery in 132 patients and 180 sibs, and the neonatal period in 129 patients and 178 sibs.

In the comparison of abnormalities of pregnancy, the children were subcategorized as in Table I.

For labour and delivery, the same subcategories were used with the addition of gestation defined as: i—less than 38 weeks; ii—38 weeks or more. In the neonatal period, further subcategorization for: (a) type of delivery: i—caesarean section, ii—forceps or breech; iii—spontaneous vertex; and (b) birthweight: i—less than 2·5 kg; ii—2·5 kg, less than 3 kg; iii—3 kg or more, was included. Differentiation according to

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TABLE I

(A) Male or female	
(B) Maternal age at birth	i. less than 20, 30 or more, years ii. 20, less than 30, years
(C) Place of birth	i. Hospital in Edinburgh group ii. Home iii. Elsewhere
(D) Birth order	i. 1st or more than 3rd ii. 2nd or 3rd
(E) Social class	i. 1 to 3 ii. 4 and 5

social class was omitted in the neonatal period because the numbers in the final subcategories were too small.

In relation to the pregnancy, comparison between patients and sibs was made for the presence of the following (Table II): bleeding in the first and second trimesters, bleeding in the third trimester, pre-eclamptic toxaemia, maternal urinary infection, administration of drugs other than iron, gestation of under 38 weeks. Factors during the labour and delivery which were compared were: the type of onset of labour, the length of the labour, the presence of fetal distress, the type of delivery, and the administration of a general anaesthetic (Table III). The following abnormalities of the neonatal period were assessed: birthweight in relation to the 10th centile, the use of active resuscitation, the method of oxygen administration, the use of chemical stimulants, the presence of apnoeic attacks, abnormal blood chemistry (with raised serum bilirubin considered separately), drowsiness, floppiness, the use of an incubator, and, whether or not feeding was satisfactory (Tables IV and V).

In each final subcategory, the expected values for the presence or absence of an abnormality or specified factor were calculated using a null hypothesis. The expected values were summated, alongside the observed values. The χ^2 test of significance was then applied.

In addition, the birthweights were compared with those expected for sex, gestation, maternal height, and birth order (Tanner and Thomson, 1970).

Results

Significant differences were found between the sex distributions in the patients and sibs and between the maternal ages at birth in the case of females. 83 of 132 patients and 91 of 180 sibs were male ($\chi^2 = 4{\cdot}7$, $P < 0{\cdot}05$). 22 of 49 female patients, and 22 of 88 female sibs were born to mothers aged less than 20 years, or 30 or more years ($\chi^2 = 5{\cdot}8$, $P < 0{\cdot}02$). The differences between patients and sibs were not significant for maternal age in males, or for birth order in either sex. When place of birth was compared, hospital deliveries were not significantly more common in patients than in their sibs. These results are summarized in Table VI.

The antenatal period results are shown in Table II. 13 patients and 1 sib had a history of bleeding in the first or second trimester of pregnancy ($\chi^2 = 8{\cdot}6$, $P < 0{\cdot}005$). 48 mothers of patients and 20

TABLE II

Findings in Antenatal Period

Factors Investigated	Patients		Sibs		χ^2	P
	Observed	Expected	Observed	Expected		
Bleeding in 1st and 2nd trimesters:						
Present	13	7·6	1	6·4	8·6	<0·005
Absent	119	124·4	178	172·6		
Bleeding in 3rd trimester:						
Present	5	6·1	6	4·9		
Absent	127	125·9	173	174·1	0·5	NS
Pre-eclamptic toxaemia:						
Present	28	25·9	25	27·1		
Absent	104	106·1	154	151·9	0·4	NS
Urinary infection:						
Present	13	11·4	11	12·6		
Absent	119	120·6	168	166·4	0·5	NS
Drugs other than iron:						
Given	48	34·4	20	33·6		
Not given	84	97·6	159	145·4	14·0	<0·0005
Gestation:*						
<38 wk	11	14·1	19	15·9		
38 wk +	121	117·9	160	163·1	1·5	NS

*An excess of sibs was born before 38 weeks' gestation.

TABLE III

Findings Related to Labour and Delivery

Factors Investigated	Patients		Sibs		χ^2	P
	Observed	Expected	Observed	Expected		
Onset of labour:						
Pitocin drip + ARM*	12	10·3	13	14·7		
ARM only	20	17·7	19	21·3	1·1	NS
Spontaneous	100	104	148	144		
Length of labour:						
>24 hr	12	12·3	17	16·7		
24 hr or less	120	119·7	163	163·3	0·01	NS
Fetal distress (males):						
Present	15	9·9	4	9·1		
Absent	68	73·1	87	81·9	6·2	<0·02
Fetal distress (female):						
Present	3	2·5	3	3·5	Numbers too small	
Absent	46	46·5	86	85·5		
Delivery:						
Spontaneous vertex	110	114·2	161	156·8		
Forceps or breech	12	12·4	16	15·4	7·0	<0·05
Caesarean section	10	5·4	3	7·6		
General anaesthetic:						
Given	13	9·4	9	12·6		
Not given	119	122·6	171	167·4	2·6	NS

*ARM = artificial rupture of membranes.

mothers of sibs received drugs other than iron during their pregnancies ($\chi^2 = 14·0$, P <0·0005). Table VII shows the numbers of mothers receiving specified types of drugs. 12 mothers of patients, and 5 of sibs received diuretics ($\chi^2 = 6·3$, P <0·02). Barbiturates were given to 14 mothers of patients and 3 mothers of sibs ($\chi^2 = 11·8$, P <0·001). An excess of mothers of patients received antibiotics, folic acid, antiemetics, and antidepressives, but the total numbers involved were too small for statistical analysis.

The differences between the pregnancies of mothers giving birth to patients and sibs were not significant for bleeding in the third trimester, pre-eclamptic toxaemia, urinary infection in pregnancy, and prematurity. There were relatively more sibs than patients born before 38 weeks' gestation.

The findings referring to labour and delivery are summarized in Table III. Fetal distress was found significantly more often in male patients than in male sibs. The fetal heart rate was more than 160, or less than 120 / minute in the labours of 15 patients and 4 sibs ($\chi^2 = 6·2$, P <0·02). 10 patients and 3 sibs were delivered by caesarean section ($\chi = 7·0$, P <0·05). Induction of labour, prolonged labour, fetal distress in females, and the use of general anaesthetic were all recorded slightly more often in patients than sibs, but the excess was not significant.

Details of abnormalities occurring in the neonatal period are given in Tables IV and V. Fig. 1 and 2 show the birthweights as compared with centiles given by Tanner and Thomson (1970). 24

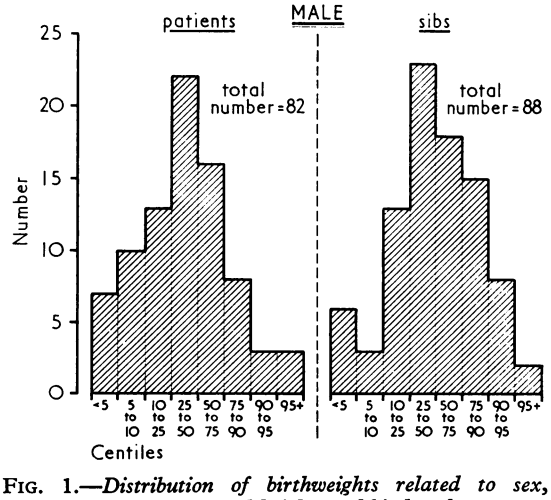
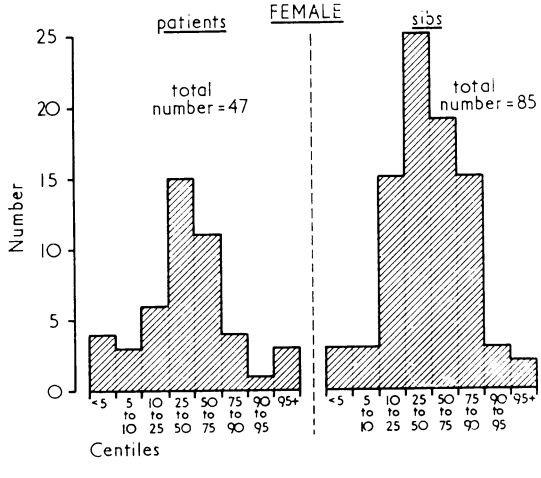


FIG. 1.—*Distribution of birthweights related to sex, gestation, maternal height, and birth order.*

TABLE IV
Findings in Relation to Neonatal Period

Factors Investigated	Patients		Sibs		χ^2	P
	Observed	Expected	Observed	Expected		
Birthweight:						
<10th centile	24	16·7	15	22·3		
>10th centile	105	112·3	158	150·7	6·4	<0·02
Active resuscitation:						
Given	36	32·9	28	31·1		
Not given	93	96·1	150	146·9	0·8	NS
Resuscitation with oxygen (face mask):	27	25·1	27	28·9		
Positive pressure	1	1	0	0	Numbers too small	
Intubation	7	5·4	0	1·6	for full evaluation	
No oxygen given	94	97·5	151	146·5		
Resuscitation with chemical stimulants:						
Given	9*	7·3	4†	5·7		
Not given	120	121·7	174	172·3	0·9	NS
Apnoeic attacks:						
Present	1	0·4	3	3·6	Numbers too small	
Absent	128	128·6	175	174·4		
Abnormal blood chemistry, excl. raised serum bilirubin:						
Present	1	0·4	0	0·6	Numbers too small	
Absent	128	128·6	178	177·4		
Serum bilirubin >10 mg/100 ml:						
Present	5	3·2	4	5·8	Numbers too small	
Absent	124	125·8	174	172·2		
Drowsiness:						
Present	9‡	7·7	2	3·3	Numbers too small	
Absent	120	121·3	176	174·7		
Floppiness:						
Present	9	5·7	0	3·3	Numbers too small	
Absent	120	123·3	178	174·7		
Nursed in incubator:						
Present	8	6·4	7	8·6		
Absent	121	122·6	171	169·4	0·53	NS

*All were term. †One out of four term. ‡5 females, 4 males.



patients and 15 sibs weighed at birth less than the 10th centile for sex gestation, maternal height, and birth order ($\chi^2 = 6·4$, P $<0·02$). Active resuscitation, chemical stimulation, and, intubation were not required significantly more often in patients. No significant excess of children with feeding difficulty defined as poor sucking, drowsiness during feeds, inability to take the expected quantity, or poor swallowing ability, was noted when the whole group of patients was compared with all the sibs. However, of the term males born in Edinburgh hospitals, 9 patients and 2 sibs fed unsatisfactorily in the neonatal period ($\chi^2 = 4·3$, P $<0·05$). There was also

FIG. 2.—*Distribution of birthweights related to sex, gestation, maternal height, and birth order.*

TABLE V

Findings in Relation to Early Feeding

Groups Investigated from Feeding Aspect	Patients		Sibs		χ^2	P
	Observed	Expected	Observed	Expected		
All patients and sibs:						
Feeding satisfactory	107	108·9	168	166·1		
Feeding unsatisfactory	22	20·1	10	11·9	0·5	NS
Males: term, born in Edinburgh hospitals, spontaneous delivery:						
Feeding satisfactory	36	39·2	41	37·8		
Feeding unsatisfactory	9	5·8	2	5·2	4·3	<0·05
Females: term, born in Edinburgh hospitals, spontaneous delivery:						
Feeding satisfactory	24	—	36	—		
Feeding unsatisfactory	1	—	2	—		
Males: gestation <38 wk:						
Feeding satisfactory	5	—	10	—		
Feeding unsatisfactory	2	—	2	—		
Females: gestation <38 wk:						
Feeding satisfactory	0	—	8	—		
Feeding unsatisfactory	4	—	0	—		
Males: term, abnormal delivery:						
Feeding satisfactory	10	—	9	—		
Feeding unsatisfactory	1	—	1	—		
Females: term, abnormal delivery:						
Feeding satisfactory	4	—	7	—		
Feeding unsatisfactory	2	—	0	—		

TABLE VI

General Findings

Factors Investigated	Patients		Sibs		χ^2	P
	Observed	Expected	Observed	Expected		
Sex:						
Males	83	73·6	91	100·4		
Females	49	58·4	89	79·6	4·7	<0·05
Maternal age at birth (females only):*						
Young, old, mothers	22	15·7	22	28·3		
Mothers in 20's	27	33·3	66	59·7	5·8	<0·02
Place of birth:						
Edinburgh hospitals	91	85·6	107	112·7		
Home	24	25·5	40	38·5	2·0	NS
Elsewhere	17	20·9	32	28·1		
Birth order:†						
First, more than 3rd	78	71·7	89	95·3		
Second, third	54	60·3	92	85·7	2·1	NS

*Males: equal distribution between the groups.

†Females showed a greater trend towards first and later than third birth order, but the difference between patients and sibs is still not significant.

an apparent excess of prematurely born female patients and female patients delivered other than spontaneously by the vertex with feeding difficulties. The numbers of female patients and female sibs in these two groups are too small for statistical evaluation. Other abnormalities of neonatal behaviour recorded in the history were also too small for statistical analysis. 7 patients required intubation and one was given oxygen by positive pressure. A face mask alone was used in

TABLE VII

Type of Drug Given in Antenatal Period, and, Numbers of Patients and Sibs Involved

Type of Drug	Patients	Sibs
Diuretic	12	5
Barbiturate	14	3
Epanutin	2	2
Sulphonamide	8	9
Antibiotic	6	3
Folic acid	5	3
Antiemetic	7	0
Antidepressive	3	0
Others*	5	0

*The following were each given to only one mother: thyroxine, purovarine, digoxin, prednisolone, unspecified analgesic for headache.

the other 27 patients receiving oxygen, and in all sibs thus resuscitated. Apnoeic attacks occurred in 1 patient and in 3 sibs. Abnormal blood chemistry (hypocalcaemia) was found in 1 patient and in none of the sibs. Serum hyperbilirubinaemia occurred in 5 patients and in 4 sibs. There was some excess of patients who suffered from drowsiness and pathological hypotonia compared with the sibs. 9 patients and 2 sibs were reported to be drowsy, and 9 patients, but no sibs, to be hypotonic.

Comparison of the number of adverse factors found significantly more often in patients than in sibs is shown in Table VIII. 23% of patients and 3% of sibs had had more than one significant abnormality.

TABLE VIII

Number of Significant Abnormalities Sustained by Patients and Sibs

No. of Abnormalities	Patients	Sibs
One abnormality	49	34
Two abnormalities	19	4
Three abnormalities	9	1
Four abnormalities	3	0
Total with significant abnormalities	80	39

Discussion

A convulsion occurring in association with fever is a manifestation of neurological disease. It seems reasonable to postulate that a child who has previously experienced damage to the nervous system could be predisposed to seizures if other adverse circumstances such as an acute infection were to supervene.

The present study attempts to define the importance of abnormalities of the birth history by comparing the children who had their first convulsion when febrile with their sibs. The use of sibs for comparison reduces the influence of family history as another aetiological factor.

A history of threatened abortion is elicited more often than expected in children with neurological abnormality. Ingram (1964) reports such a history in 3 of 30 children with congenital hemiplegias, and, in 4 of 43 mature, and 7 of 34 premature diplegics. Drillien (1968) found it significantly in excess in children with mental handicap and epilepsy when these were compared with controls. The inference is that those patients in this study whose mothers had bleeding in the first and second trimesters were predisposed to central nervous system disorders.

Elucidation of the effect of drugs given in pregnancy is difficult. The mothers received drugs other than iron more frequently in their pregnancies with patients than with sibs, but this may simply indicate more ill health in the former instances. However, examination of the types of drugs given shows that those known to have an effect on the central nervous system, i.e. barbiturates, antidepressives, and antiemetics, were frequently implicated (Table VII). It seems possible that these agents have adverse effects on the developing cerebrum. Diuretics were given significantly more often to mothers of patients. In altering electrolyte balance, and, in the case of thiazides, carbohydrate metabolism, they could adversely affect the fetal environment during brain maturation.

When compared with matched controls, mature diplegic infants are found to have a statistically significant excess of problems during labour and delivery, and in the neonatal period (Drillien, Ingram, and Russell, 1962). The present finding that fetal distress is significantly commoner only in males probably reflects the increased vulnerability of this sex to the birth process. That caesarean section was necessary more often in patients suggests that problems arose, and were resolved early in labour. The incidence of forceps and breech delivery, considered separately or together, was marginally higher in sibs than in patients.

Despite relative sparing of the brain, undernourished, small-for-dates babies are known to be predisposed to abnormal neurological states (McDonald, 1965). The patients did not show an increase in birthweights below the 5th centile, but there is a significant excess of those weighing less than the 10th centile. It is inferred that some of these patients suffered from mild intrauterine undernourishment. Nutrition of the brain is then likely to have been suboptimal. As a

consequence, permanent anatomical abnormalities may have resulted (Dobbing, 1970).

Resuscitation by any method was required after birth more commonly in patients. The use of intubation implies actual, or potential, severe hypoxia, such as might be associated with neurological sequelae. It is remarkable that no child in this series showed neurological signs of sufficient severity to cause concern to the parents.

Difficulty in feeding is a symptom of many illnesses in the neonatal period. None of the term male patients who fed poorly was reported to have evidence of cardiovascular, gastrointestinal or infective illnesses. It is, therefore, thought likely that poor feeding in these cases was a symptom of neurological disorder.

Lilienfeld and Pasamanick (1954) compared 396 epileptic children born in hospital with matched controls. Of the white population 39% epileptics and 25% controls had at least one abnormal prenatal or paranatal factor. The percentage of sibs who had a single perinatal abnormality in the present study is comparable with these controls. These authors conclude that a relation exists between certain abnormal prenatal and paranatal states and epilepsy. Lennox (1960b) compared 1,647 epileptic children with 933 controls. He found that 21% of patients and 8·8% controls had some difficulty at birth. Prolonged labour and instrumental delivery were six times commoner, 'injury to brain' three times commoner, and twins twice as common in epileptics as in controls. In those epileptics with a positive family history, the incidence of difficult births was 19·9% in comparison with 30·1% in those with a negative family history. In a study of monozygotic twins, he found that if there was a known brain lesion present in one twin before the first fit, the twins had a dissimilar pattern for epilepsy, but that if no brain lesion had been present, the twins had similar epileptic patterns (Lennox, 1960a). From these studies, Lennox concludes that difficulties at birth make an important contribution to the development of epilepsy. Ounsted, Lindsay, and Norman (1966) have investigated the relation of birth injury to temporal lobe epilepsy. Definite birth injury occurred in 10 of 35 cases and possible birth injury in a further 7 cases. It is suggested that birth injury can lead to a lesion which potentiates seizures, and that these seizures, often 'febrile convulsions', lead to epileptic brain damage selectively in Ammon's horn. These authors found that the risk of sibs developing fits was smaller if the patient had sustained some insult, but, in this context, they did not separate 'birth injury' from other insults. McDonald (1965), in her study of infants with birthweights of less than 1·8 kg, found, when children with cerebral palsy or mental defect were excluded, 7·7% of those surviving more than six months had fits. It seems likely that very small babies have an increased liability to epilepsy when this percentage is compared with 5·9% of children in the Newcastle survey who had fits (Miller *et al.*, 1960). However, babies of very low birthweight were not overrepresented either in the present study or in the children with temporal lobe epilepsy investigated by Ounsted *et al.*

Lennox (1949), comparing the birth histories of children with epilepsy and children who convulsed only when febrile, found no difference between the groups unless children under 5 years were considered separately. Then, 38% of epileptics and 27% of children with febrile convulsions had abnormal birth histories. Millichap (1968), on review of the literature on febrile convulsions, finds, in 19 series where abnormalities of birth are recorded, the average incidence to be 17%. The range varies from 34% to 3%. The number of adverse factors sought must influence whether the birth history is, or is not, found to be abnormal.

In the present investigation, 80 (61%) of the patients and 39 (22%) of the sibs had at least one of the abnormalities of the antenatal or perinatal period which was found significantly more frequently in the patients. Though 25 (51%) female and 55 (66%) male patients were affected, the difference between the sexes is not significant ($\chi^2 = 3·0$). More than one abnormality was found in 31 (23%) patients and 5 (3%) sibs. In conclusion, it is suggested that in up to 61% of children in whom a first convulsion occurs with a febrile illness, an abnormal pregnancy or perinatal history may have predisposed to the attack, by causing brain damage and a lowered convulsive threshold.

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