THE VALUE OF INVESTIGATIONS, THE SIGNIFICANCE OF PERINATAL AND FAMILY HISTORIES AND THE PREVALENCE OF SIDE EFFECTS TO PHENOBARBITONE IN CHILDREN WITH RECURRENT SEIZURES

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SYNOSIS

A retrospective study involving 50 children with recurrent seizures was carried out. There were 26 patients with recurrent febrile fits and 24 patients with epilepsy. 50% of patients with epilepsy presented initially like typical febrile fits but later developed non-febrile fits on follow up. 15 out of 26 or 57% of patients with recurrent febrile fits had significant perinatal insults such as prematurity, cord prolapse, breech presentation, forceps delivery and neonatal jaundice.

30% of patients with recurrent febrile fits had positive family history of febrile fits. Only 8% of epilepsy group had positive family history of epilepsy. Although 14 out of 45 patients studied had hyponatreamia, only 2 had levels below 125 mmol/1. 26 out of 38 had low bicarbonate, only 4 had levels below 15 mmol/1. Serum calcium levels were normal in all 37 cases studied. Serum magnesium, phosphate, potassium, urea and glucose were normal in all 45 cases studied. 46 patients had CSF studied and were normal in all of them. All 50 cases had normal skull X rays.

51% of patients developed adverse effects to phenobarbitone. The commonest side effect was behavourial problems (42.8%). 18.3% of patients had drowsiness which were usually transient. Skin eruptions were present in 14.3% and 6 out 7 cases were severe. GIT symptoms were prominent in 8.2% of patients. 25% of patients who developed adverse effects stopped the drug and they belonged to the behavourial problems and skin eruptions groups.

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INTRODUCTION

In the paediatric ward, the commonest neurological disorder encountered is seizure. When a child presents to us with recurrent seizures, a series of investigations would be carried out to elicit the underlying cause. Our routine workout would include a lumbar puncture, serum urea, electrolytes, bicarbonate, glucose, calcium, phosphate, magnesium, skull xray and an EEG.

The aims of this study are to establish

1) the significance of perinatal and family histories
2) the yield of biochemical and radiological investigations
3) the prevalence and severity of side effects to phenobarbitone, our first line drug for seizures.

METHODS

A retrospective study was conducted on 50 children chosen at random when they presented for follow up at our specialist out patient clinic between July and October 1985. All the patients had at least two seizures and 49 of them had been on phenobarbitone. All patients were asked regarding side effects to phenobarbitone during follow up.

The patients were categorised accroding to their clinical presentations and EEG findings.

Definitions:

1) A febrile seizure is an event in infancy or childhood usually occurring between 3 months and 5 years of age associated with fever but without evidence of intracranial infection or defined cause (1). Recurrent febrile fits were who had more than one episode of fits associated with fever
2) Epilepsy group consisted of patients who had recurrent non febrile seizures (2). They may or may not have definite EEG findings. 20 out of 24 cases of epilepsy presented as grand mal seizures, while the remaining 4 had focal seizures each lasting from 1 min to 30 min.

Statistical analysis was carried out using Chi-square test.

RESULTS

There were 26 patients with recurrent febile convulsions and 24 patients with epilepsy. 7 of the latter group had inconclusive EEG pattern. The reason for a relatively high percentage of epilepsy was because most of them were being followed up for much longer period. The mean duration of follow up for recurrent febrile fits was 1 year 7 months, while that of the epilepsy group was 3 years 4 months.

Sex Distribution

TABLE 1: SEX DISTRIBUTION

Sex	Epilepsy	Rec Feb Fits	Total
Male	15	17	31
Male	15	17	32
Female	9	9	18
Total	24	26	50

There were 64% males and 36% females in the sample studied. Male to female ratio was 1.2:1.

Fever

TABLE 2: DISTRIBUTION OF TEMPERATURES

Temp	37.5	37.5-37.9	38.0-38.4	38.5-38.9	39 C
Epilepsy	7 + (4)	1	8	1	3
Rec F F	0	3	8	9	6

There were 4 patients in the epilepsy group where fever was said to be present in the histories but could not be verified in the hospital. 13 out of 24 or 1/2 of patients with epilepsy presented with fever. By and large their temperature tend to be lower grade. Those with higher temperatures at presentation are more likely to be febrile convulsions. All those who presented with fever and fits later developed recurrent non febrile convulsions and are classified under epilepsy.

23 out of 26 in the recurrent febrile fits group had documented fever above 38 C, compared with 12 out of 24 in the epilepsy group. 15 out of 26 (58%) of patients with recurrent febrile fits had temperatures above 38.5 C as compared with 4 out of 24 (17%) in the epilepsy group.

Perinatal History

In the recurrent febrile fits group there were 4 patients with history of prematurity with gestation of 32 to 35 weeks. Their birth weight ranged from 2.35 kg to 3.2 kg. Another 2 patients from this group were delivered by emergency LSCS, one for cord prolapse and the other for breech presentation. 4 other patients had assisted forcepts delivery; three for prolonged labour, one for poor maternal effort. 7 patients had neonatal jaundice, 3 of them had serum bilirubin between 15 and 19 mg%; 4 had milder jaundice (serum bilirubin<15 mg%). A total of 15 out of 26 (57%) had a significant perinatal history. 2 patients with NNJ were also preterm babies.

Only one patient with epilepsy had severe jaundice with serum bilirubin of more than 20 mg% needing an exchange blood transfusion.

Family History

TABLE 3: FAMILY HISTORY IN RECURRENT FITS

Family History	Feb Fits	Epilepsy	Total
Epilepsy Group	9	2	11
Recurrent Feb Fits	8	3	11
Total	17	5	22

Of the 24 patients with Epilepsy, 2 had a family history of Epilepsy and 9 had a family history of febrile fits (1 had family history of both febrile fits and epilepsy). So 11 out of 24 patients or 46% had positive family history of seizures.

Of the 26 patients with recurrent febrile fits, 8 out of 26 or 30% of patients had a positive family history of febrile fits. There were 2 patients who had positive family history for both febrile fits and epilepsy. 3 had family history of epilepsy. So 11 out of 26 or 42% had positive family history of fits.

Biochemical Investigations

Serum Sodium

Serum sodium levels were done in 45 patients. 13 of these were less than 130 mmol/1. 5 out of 15 in epilepsy and 8 out of 17 in recurrent febrile fits group had

hyponatraemia. Only 2 had level below 125 mmol/1 which could trigger convulsions.

TABLE 4: DISTRIBUTION OF SODIUM LEVELS

$NA^+ < 130$ MMOL/L		$NA^+ > 130$ MMOL/L	
Epilepsy	**Rec Feb Fits**	**Epilepsy**	**Rec Feb Fits**
Total 5	8	15	17

Majority of these (11/13) were below 18 months of age. Since most of the study group were below 18 months of age during the investigation, the chance of finding a hyponatreamia amongst this group is not statistically higher.

Serum Bicarbonate

The serum bicarbonate levels were done on 38 patients. 26 of these were below 21 mmol/1. The range was 11 to 21 mmol/1. Only 4 had levels below 15 mmol/1 which was the cutoff point used clinically when deciding correction.

TABLE 5: BICARBONATE LEVELS

	$HCO3 < 21$ MMOL/L		$HCO3 > 21$ MMO/L		
	Epilepsy	**Rec Feb Fits**	**Epilepsy**	**Rec Feb Fits**	**Total**
Total	7	19	8	4	38

Low bicarbonate level appeared more frequently in the recurrent febrile fits group as compared with the epilepsy group and that was statistically significant ($p<0.05$) with continunity correction.

Others

Serum calcium levels were estimated in 37 patients. Serum phosphate, magnesium, potassium, urea, and glucose were estimated in 45 patients. All the results were within normal limits.

Cerebrospinal Fluid

46 patients had lumbar puncture done. All CSF results were normal.

Skull X-ray

50 patients in this study had skull X ray done and all were reported as normal.

Electroencephalograms

All 26 patients with recurrent febrile fits had normal EEG. 17 patients with epilepsy had definite epileptogenic foci while 7 others had non-specific EEG changes. All the EEG were carried out at least 1 month after the acute illness.

CT Scan of Head

Only 8 patients had CT scan done and only 1 was abnormal showing hemiatrophy of 1 cerebral hemisphere.

Drug Therapy: Side Effects of Phenobarbitone

49 patients were on long term phenobarbitone. Duration of therapy ranged from 2 months to 7 years till present study. The mean duration was 1 year 3 months. Side effects were reported in 25 patients (51%). 12 patients had 1 side effect; 4 patients had 2 side effects and 4 patients had 3 side effects.

TABLE 6: SIDE EFFECTS OF PHENOBARBITONE

Type	No.	Remarks
1. Behavourial	21	3 More Naughty 8 Hyperactive 4 Short Attention Span 2 Poor Memory 4 Poor School Performance
2. Drowsiness	9	8 Transient 1 Persisent
3. Skin Rashes	7	4 Erythema Multiforme 2 Extensive Macular 1 Transient Rash over Neck
4. Gastrointestinal Symptoms	4	2 Abdominal Discomfort 1 Transient Vomiting 1 Poor Appetite
5. Others	1	1 Excessive Weight Gain

The commonest side effect was behavourial problems which occurred in 21 out of 48 patients or 42.8%. Drowsiness occurred in 18.3%, skin reactions in 14.3% and GIT symptoms in 8.2% of patients. 25% of the above patients discontinued phenobarbitone because of side effects. These patients belonged to the behavioural and skin rashes groups.

SUMMARY OF RESULTS

Fever

As many as 1/2 of patients with epilepsy presented initially as fever with fits. By and large the temperature were below 38.5 C. In other words, a child presenting with fever and fits may not be easily catergorised until longer period of follow-up is made which may or may not reveal recurrent nonfebrile fits with or without EEG changes.

Perinatal History

Amongst the group with recurrent febrile fits, a high proportion 15/26 or 57% had significant perinatal history. This tends to suggest that perinatal insults had predisposed them to recurrent febrile fits or something underlying predisposed them to both perinatal insults and recurrent febrile fits. In contrast only 2/24 in the epilepsy group had significant perinatal insults. The difference in proportion between the two groups is statistically significant at $p<0.05$.

Family History

30% of recurrent febrile fits group had positive family history of febrile fits. Only 8% of epilepsy group had positive family history of epilepsy. But 35% of epilepsy group had positive family history of febrile fits.

Sodium

Although 13/45 (29%) had hyponatraemia by definition, only 2 had levels low enough to cause fits. Majority of these 11/13 were below 18 months of age. Since most of the study group were below 18 months of age the chance of finding a hyponatraemia amongst this group is not statistical significant.

Bicarbonate

Although 26/38 (68%) had low bicarbonate levels by

definition, only 4 had a significantly low level clinically i.e.<15mmol/1. Low bicarbonate level appeared to be more frequently in the recurrent febrile fits than epilepsy group and the difference in proportion is statistically significant at $p<0.05$ with continuity correction.

Others

Magnesium, phoshpate, potassium, urea and glucose were all normal in 45 cases studied. Serum calcium levels were normal in all 37 cases studied.

CSF

All 46 CSF were normal. This has inherent bias because those with abnormality would be labelled as meningitis or encephalitis and would not be included in the study.

SXR

All 50 skull X rays were normal.

Side Effects of Phenobarbitone

Side effects of phenobarbitone were reported in 51% of patients. The most common side effect was behavioural changes which accounted for 42.8% of cases. Complaints of drowsiness were usually transient and subsided with time. Gastrointestinal symptoms were mild and tolerable. 6 patients had severe skin reactions which necessitated cessation of phenobarbitone. 25% of patients had to stop phenobarbitone due to behavioural problems or skin reactions.

DISCUSSION

Fever and Fits

Although by definitions febrile fits (1) and epilepsy (2) are different entities, clinical experience and this study shows that they are not easily categorised at presentation. As many as 1/2 of patients with epilepsy presented like a typical febrile fit initially. The final diagnosis will be apparent only after follow up reveal nonfebrile fits or EEG changes which are compatible with epilepsy.

Perinatal History

From our study 57% of patients with recurrent febrile fits had significant perinatal history. This seems to indicate that these unfavourable factors had predisposed them to febrile seizures or something underlying had predisposed them to both perinatal insults and recurrent fits. Further prospective study on this group of high risk children may reveal more conclusive results. Wolf (3) also found that those infants who sustained perinatal insults have increased risk of developing febrile convulsions.

Family History

In our study, 30% of our patients with recurrent febrile fits had positive family history of febrile fits. 35% of patients with epilepsy had positive family history of febrile fits was surprising. The possible reasons for this results could be error in recall and the social stigmata attached to the diagnostic label epilepsy. Another reason is some of their siblings who were labelled as febrile fits at first presentation may not have sufficient follow up period to manifest nonfebrile fits. Only about 8% of patients with epilepsy have positive family history of epilepsy. Tsuboi (4) reported 17% of parents and 22% of siblings of febrile seizures probands affected. Even higher proportions of siblings were affected (30%) if one parent was affected. In Rochester, Minnesota, siblings, offspring, and also second degree relatives of febrile convulsion probands were at a two to threefold increase in risk for convulsions with fever (4).

The increased frequency of febrile seizures among both parents and siblings of febrile convulsion probands suggests that familial factors, most likely genetic, are important in this disorder. Inheritance patterns have been felt to be consistent with a single gene dominant trait (5) or recessive trait (6) or to be polygenic (4).

Biochemical Investigations

The yield of biochemical investigations was varied. 28% of patients had hyponatreamia which was proportionally distributed amongst the two groups. Most of these had values lying between 126 to 129 mmol/1 which were not low enough to cause fits. Only 2 out of 45 or 4.4% had serum sodium levels below 125 mmol/1. 68% of patients had low bicarbonate levels and they were unevenly distributed amongst the two groups. There is a definite higher proportion of patients in the febrile fits group with low bicarbonate levels as compared with the epilepsy group. The difference was statistically significant for $p<0.05$. This finding should be interpreted with caution as the laboratory estimation for serum bicarbonate has wide variation with coefficient of variation of the region of 10%. Secondly the difference points to the view that a patient with fits and fever is more prone to low bicarbonate than those with fits only. Since patients in the febrile fits group are generally younger than the epilepsy group, the difference in the bicarbonate may simply reveal that younger children are more prone to acidosis. This study is unable to address the problem of whether acidosis is the cause of febrile fits or the consequence of fits.

Serum calicum levels were normal in all 37 cases and serum phosphate, magnesium, urea, glucose were all normal in 45 cases studied. CSF were normal in all 46 cases studied. These findings seem to suggest that these investigations were not useful. On the other hand those patients with abnormal results may have been categorised as other diseases and therefore not included in this retrospective study. The impression is that the other diseases are very rarely encountered. Rutter and Smales (6) found routine screening tests unhelpful in typical febrile convulsions.

Skull X Ray

Skull X ray were normal in all 50 patients studied even though 1 had hemiatrophy of brain. This finding is in keeping with other studies. Skull X rays done in 4 medical centres in U.S.A. spaced between 1960 to 1975 where 487 cases studied and all were normal (7). So skull X ray is one test which can be omitted in our routine tests unless other clinical findings warrant it.

Side Effects of Phenobarbitone

Our study showed a surprising high prevalence of side effects to phenobarbitone. 51% of our study group developed some adverse effects to the drug and 25% of cases were severe enough for us to stop the drug. The use of phenobarbitone in a continuous way is still controversial. The therapeutic benefits of the drug have to be balanced against the adverse effects of the drug. The most common side effect was behavourial problems which was similar to other studies. In other studies as many as 20—40% of children (8,9) had behavourial problems compared with

42.8% in our study. There is no evidence that children who tolerate phenobarbitone will suffer adverse effects on intellectual development or school performance.

At the present time, it does not seem reasonable to suggest treating all children who have febrile convulsions with continuous phenobarbitone therapy since this would involve treating 2 to 4% of all children under 5—6 years of age. It would be more reasonable to treat those who are at higher risk. These would included children who have their first febrile fit at a young age (< 15 months); who at the time of their 1st febrile fit have significant abnormalities or neurological examination or developmental delays by history; who have complex febrile seizures and children who had a positive family history of non-febrile fits.

More recently the use of intermittent administration of anticonvulsants are gaining popularity as it produced comparable results without the side effects of chronic therapy. Knuden and Vestermark (10) studied 195 children of whom 83 completed 1 year of intermittent rectal diazepam therapy and 73 completed 1 year of continuous phenobaritone therapy. The recurrence rate of febrile fits was similar in the two groups (about 15%), and well below the expected for an untreated population. Intermittent high dose phenobarbitone (15 mg/kg/day) has showed to be as effective as continuous therapy (11), but it may produce somnolence, lethargy and other behavourial manifestations. Although valpropic acid is shown to be effective in prevention of recurrence, the rare but severe complications of toxic hepatitis and pancreatitis will make one hesitant to use it to treat a relatively benign condition. Liver functions should be monitored periodically in patients on prolonged valproic acid therapy.

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