THE NATURAL HISTORY OF INFANTILE SPASMS

BY

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The claim of Sorel to have improved the outlook for children with the syndrome of infantile spasms ('lightning spasms') and mental retardation by the use of corticotrophin (Sorel and Dusaucy-Bauloye, 1958; Sorel, 1959) has aroused widespread interest, and first reports have been enthusiastic (Low, 1958, 1959; Stamps, Gibbs, Rosenthal and Gibbs, 1959). Cortisone has also been said to be effective (Low, 1958; Dunermuth, 1959; Cox and Martin, 1959). It is now clear that these hormones produce some beneficial effect, but for a more precise assessment of their efficacy it is important to know the natural history of the disorder. In this paper we describe the clinical and electroencephalographic (E.E.G.) findings in 30 patients who have been followed up for periods varying from two to six years without the administration of hormones. They form a basis for comparison of the results of hormone treatment in 20 other patients (Bower and Jeavons, 1961).

Material

Thirty patients whose spasms began before the age of 12 months have been followed by clinical and E.E.G. examinations at approximately six-monthly intervals for a minimum of two years and a maximum of six years. Apart from the early examinations of a few of the older patients, which were made by the referring paediatricians, all clinical assessments were made by one of us (B.D.B.); and all E.E.G. records were interpreted by the other (P.M.J.). The clinical features of 20 of the patients have been described previously (Bower and Jeavons, 1959) and those of the remainder are similar. The numbers in each aetiological group are shown in Table 1. The symptomatic group consists mainly of children with a definite history suggesting prenatal or perinatal brain damage who had been mentally retarded afterwards, and one child with tuberose sclerosis. Patients in the cryptogenic group, by contrast, had had an uneventful life with normal development until the onset of the spasms, and investigations gave no clue to the aetiology of their cerebral insult. In two patients developmental and birth history were paradoxical and they are therefore classified as 'doubtful'.

All patients were treated with one or more of the commonly used anticonvulsant drugs, for it is difficult to withhold them in such a distressing epileptic disorder even though there is general agreement that barbiturates, primidone, the diones, and drugs of the phenytoin group are ineffective. In our patients they had a negligible short-term effect and in all probability had no long-term effect, unless it was to suppress the major and focal fits which at times complicate infantile spasms.

Fourteen patients were at some time given a short course of a drug of the tetracycline group, but it is doubtful if this treatment produced any long-term benefit. Spasms were decreased in number or abolished in 11 of the 14 patients so treated, but in nine a relapse occurred shortly after the treatment was stopped; there was no clinical or E.E.G. evidence of more than temporary benefit in these nine patients, by comparison with the patients not given such treatment. In only two patients, therefore, could tetracyclines be given the credit for cure, and we think it more probable that administration of the drug coincided with natural cessation of the spasms.

There is therefore good reason to believe that the progress of all 30 children approaches that of the untreated case.

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Nos.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>15</td>
</tr>
<tr>
<td>Prenatal or perinatal trauma or anoxia</td>
<td></td>
</tr>
<tr>
<td>Tuberose sclerosis</td>
<td>13</td>
</tr>
<tr>
<td>Measles encephalitis</td>
<td>1</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>13</td>
</tr>
<tr>
<td>Doubtful</td>
<td>2</td>
</tr>
</tbody>
</table>

TABLE 1

AETIOLOGY
and less severe in the individual patient. For instance, several of those shown in Fig. 1 as having spasms at 30 months, or later, merely had infrequent head nods. Five patients initially showed major or focal fits in addition to spasms, and three of these continued to have major fits over a long period. Five other patients developed major fits during the follow-up period.

It is of interest to compare the epilepsy in the symptomatic group with that in the cryptogenic group, and Table 2 shows the numbers of patients in each main group who at each age period still had spasms. It will be seen that there is little difference between the two groups. This suggests that age is a much more important factor than aetiology in determining the prognosis of the spasms once a patient develops them. Presumably some maturation factor is responsible for the inhibition of this type of epilepsy as the patient grows older and for the rarity of its onset after the age of 2 years.

There is one difference relating to the spasm in the two main groups. Six patients in the symptomatic group showed a lateralizing feature in the spasm; the head was flexed partly to one side, or the amplitude of limb movement was greater on one side than on the other. No patient in the cryptogenic group showed this feature.

**E.E.G. Findings.** The scoring system, designed to separate the characteristics of hypsarrhythmia from those of non-hypsarrhythmic epilepsy, which was used in our previous study (Bower and Jeavons, 1959) was used again. Details are given in the Appendix. A hypsarrhythmic record scores 13-30 points. All records scoring 2-12 points were previously classified as 'non-hypsarrhythmic epilepsy'. However, we now label a record scoring 9-12 points as 'modified hypsarrhythmia', as it shows more organized epileptic activity than a truly hypsarrhythmic record and yet has some chaotic features. This category corresponds to hypsarrhythmia types 1 and 2 of Thiébaut, Sacrez, Röhmer and Isch-Treussard (1955). A record scoring 2-8 points shows centrencephalic or focal epilepsy, but is well organized. The total number of records taken and scored in the present study was 167.

Twenty-five patients had their first E.E.G. examination before the age of 12 months and our E.E.G. discussion is limited to these patients. All their first records were abnormal. The score was in the hypsarrhythmic range in 13, in the modified hypsarrhythmic range in four, and in the epileptic range in eight. Further E.E.G. examinations were carried out, as far as possible at six-monthly intervals; all 25 were followed to the 30-36 month age period,
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and 23 to the 36-42 month period. Fig. 2 shows the number of patients with records in each E.E.G. category in each six-monthly age period.

It will be seen that there was an improvement in the E.E.G. up to the age of 42 months, just as there was an improvement in the epilepsy. In the 30-36 month period 10 records (over one-third) were normal, eight were epileptic, two showed modified hypsrrhythmic, and only three were frankly hypsarrhythmic. In the 36-42 month period the proportions were similar. There was a close correlation between individual clinical and E.E.G. improvement. Fifteen of the 25 lost their spasms during follow-up; 10 of these 15 had a normal E.E.G. at the next and all subsequent examinations. The remaining five showed (non-hypsarrhythmic) epileptic E.E.G. abnormalities and three of these patients had occasional major fits after the spasms had ceased. The E.E.G.s of the eight whose spasms continued were abnormal (five showed hypsrrhythmicia or modified hypsarrhythmia and three were epileptic).

Comparing the scores in the symptomatic and cryptogenic groups, we found that on average the scores in the former group were higher than those in the latter, both initially and throughout the subsequent six-monthly periods. Moreover, the cryptogenic group tended to produce normal records earlier.

Since six children in the symptomatic group showed a focal element in their spasms, one might expect a higher incidence of lateralized focal E.E.G. abnormality in this group. Four of these six children showed such abnormalities. However, 12 of the 25 children showed focal E.E.G. abnormalities at some time, and five of them belonged to the cryptogenic group. The foci often changed to the opposite side in subsequent E.E.G. records and, since disappearance, reappearance and ‘wandering’ of foci are quite common features of the E.E.G.s of epileptic children in general, their presence in our patients is probably not important. They do not necessarily indicate localized cerebral change, though they may be significant in association with clinical lateralization.

Mentality. Unfortunately there was no corresponding general improvement in mentality (Fig. 3). The mental level was graded in each case as gross retardation (corresponding to amnesia), moderate retardation or normal. The abilities of two patients at the age of 12 months illustrate the two categories of mental retardation:

Gross Retardation. A. was unable to sit or hold his head up. He could not grasp an object even when put into his hand. He could not recognize his mother and appeared blind. There was no response to voice, and he did not vocalize spontaneously. Movements were aimless, generalized, and incoordinate.

Moderate Retardation. J. could sit and stand unaided, and retained an object if placed in the hand. However, he was not interested in his surroundings; he only fixed with his eyes for a few seconds and showed

![E.E.G. Diagram](attachment:image.png)

Fig. 2.—Number of patients with E.E.G.s in various categories (<12-48 months).
little emotional response to social overture. He did not laugh, and smiled only briefly and occasionally. Vocalization consisted of only two or three sounds. He showed the relatively slight motor retardation commented upon by Illingworth (1955).

At 12 months, 16 patients were grossly retarded and 13 were moderately retarded; one had died. Twenty-eight of the 30 patients have now reached the age of 42 months; 11 are grossly retarded, 12 moderately retarded, one patient is mentally normal, and four patients have died. The remaining two patients are 36 months old and in view of their past history it is most unlikely that their state will change in the next six months; one is grossly retarded and one is mentally normal. In Fig. 3 they are therefore treated as if they were 42 months old. The two patients who have regained normal mentality were both in the cryptogenic group, had a low E.E.G. score on their first record (4 and 5), and their second and subsequent E.E.G.s were normal. They lost their spasms early (at 7 and 20 months). One received tetracycline.

Comparing the two groups, both at 12 months and subsequently, there is a great preponderance of grossly retarded children in the symptomatic group (Table 3). Even though patients in the cryptogenic group may be grossly retarded shortly after the onset, some pass into the moderately retarded category within a few months. Only two children in the cryptogenic group were grossly retarded at 12 months and both were only moderately retarded at 42 months. The improvement in this group was maintained after this age in the older patients reviewed. For instance, three children in the cryptogenic group are now over 5 years of age. All three are pleasant children, relatively obedient, able to communicate with short sentences, and have no neurological deficit. They are probably all mildly retarded, but two attend a normal school. By contrast, the four in the symptomatic group who are over 5 years old are grossly retarded and obviously ineducable.

**Mortality.** Four patients died, one at 5 months and the others at between 2½ and 3½ years. Two were in the symptomatic group and two in the cryptogenic group.

**Discussion**

Apart from the reports of Gibbs, Fleming and Gibbs (1954) and Livingston, Eisner and Pauli (1958) there is little detailed information in the literature about the prognosis of patients with infantile spasms. Most authors agree that in general the spasms tend to diminish with age, the E.E.G. pattern becomes more organized and may become normal, but the mental retardation usually persists unaltered. Of our surviving patients 57% were free of spasms at 3½ years and this compares with 43% at 3-4 years, reported by Gibbs et al. (1954). Livingston et al. (1958) report that less than 1% of their patients with minor motor epilepsy (equivalent to infantile spasms) still had spasms after 5 years of age. Only eight

**Table 3**

**MENTAL ASSESSMENTS AT 12 AND 42 MONTHS IN THE TWO MAIN GROUPS**

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>At 12 Months</th>
<th></th>
<th>At 42 Months</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gross</td>
<td>Moderate</td>
<td>Dead</td>
<td>Gross</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cryptogenic group</td>
<td>2</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Symptomatic group</td>
<td>13</td>
<td>2</td>
<td>0</td>
<td>10*</td>
<td>3</td>
</tr>
<tr>
<td>Doubtful aetiology</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>13</td>
<td>1</td>
<td>12</td>
<td>12</td>
</tr>
</tbody>
</table>

* One patient only 36 months old.
of our patients have reached this age so we cannot compare our figures with theirs.

The E.E.G.s of our patients during follow-up appear to be less abnormal than those of Gibbs et al. (1954). Of our patients, at 3-3½ years, 19% had typical or modified hypsarrhythmia, compared with 53% of their patients at 3-4 years; and at these ages 47% of our patients and 20% of theirs had normal records.

Both Gibbs et al. and Livingston et al. show that it is rare for these patients to survive this form of epilepsy with normal intelligence. The latters' figure for mental normality is 1·8%, and ours (in a much smaller series than theirs) is 7·7%. Burnett, Gibbs and Gibbs (1958) show that the prognosis is much better if the initial E.E.G. is normal. It is of interest that the two patients in our series who became mentally normal each had only one abnormal E.E.G. and this had a low score. Of our patients, 44% were grossly retarded and, although details of the severity of the mental defect are not given in the above publications, it is clear that gross retardation was fairly common, for in each series 23% were institutionalized.

The mortality rate in our series (13% of 30 patients) is similar to that of Gibbs et al. (11% of 103 patients) up to the age of 3 years. Livingston et al., however, found that by 6 years only 3·7% of 622 patients had died.

Our patients show definite prognostic differences in the symptomatic and cryptogenic groups, and this is not commented upon by previous authors. The patients in the symptomatic group were initially more severely retarded, some had spastic diplegia or hemiplegia, and microcephaly was common, in contrast to the cryptogenic group. It is therefore not surprising that, in view of this clear evidence of more severe brain damage in the symptomatic group, they should show no mental improvement during follow-up, whereas there is a slight tendency for the cryptogenic group to improve. Although the numbers followed to the age of 6 are small, the clear-cut difference in mental level in the two groups at that age confirms this prognostic difference. By contrast, the two groups behaved similarly with regard to the rate of disappearance of spasms, although there is perhaps a tendency to earlier disappearance in the cryptogenic group after 2 years. The E.E.G.s are more chaotic in the symptomatic group at all ages.

**Summary**

Thirty infants with the syndrome of infantile spasms and mental retardation occurring before the age of 1 year have been followed by clinical and E.E.G. examinations for periods of two to six years. None were treated with corticotrophin or steroids.

There was a steady reduction in the number still having spasms and at 3 years over half the patients were free of them. Focal or major fits occurred in one-third of the total and did not show the same tendency to disappear with age.

The E.E.G.s became more organized and at 3-3½ years more than one-third were normal. Hypsarrhythmia was rare by this age but was found even at 6 years.

Mental improvement was much rarer and only two patients became mentally normal.

The mortality rate was 13% by 3½ years.

There was little difference between the symptomatic and cryptogenic groups with regard to the rate of disappearance of spasms and E.E.G. improvement. Mental retardation, however, was less severe in the cryptogenic group even at 1 year and this group showed a slight but definite general improvement later, whereas none occurred in the symptomatic group.

Our thanks are due to the consultant physicians of the Children's Hospital, Birmingham, and the consultant paediatricians of the Birmingham Region for allowing us to examine their patients; to Professor D. V. Hubble for encouragement and advice; and to Mrs. Trilloe, Miss D. J. Campbell, Miss M. E. Dyas and Miss A. E. Hill for their skilful performance of E.E.G. examinations on these difficult patients.

**REFERENCES**


It is notoriously difficult to analyse and describe the records of young children and therefore a scoring system (based on examination of 180 records) was devised to enable more precise comparison to be made between different cases and to assess change in the same case. The scoring system is designed to give maximum marks to utterly chaotic tracings and minimum marks to highly organized epileptic records. The records are divided into nine grades:

Grade 1: Complete chaos, with total asynchrony, no organized discharges and no normal background activity. Score 12 points

Grade 2: Chaos, with some discernible synchronous bursts. The bursts were of chaotic make up, and the episodic nature could only be seen by reducing the gain. Score 8 points

Grade 3: Mainly chaotic, but with more bilaterally synchronous activity than Grade 2. Score 6 points

Grade 4: Bursts of chaotic make-up, some bilaterally synchronous discharges and a little normal background activity. Score 4 points

Grade 5: Discharges mainly bilaterally synchronous, but some showing a chaotic make-up. Some normal activity. Score 3 points

Grade 6: Bilaterally synchronous epileptic discharges (centrencephalic). No chaos. Normal background activity. Score 1 point

Grade 7: Focal epileptic discharges. No chaos. Normal background activity. Score 1 point

Grade 8: Non-specific abnormality. Score 1 point

Grade 9: Normal. Score Nil

The grading is made on the overall appearance of the record, and it is therefore not possible to give illustrations of the different grades.

In addition to being given a grade score the different components of hypsarrhythmia are scored as follows:

(a) Amplitude. High voltage is probably the most common finding, at times being over 900 microvolts.
   Voltage normal or up to twice normal for age: Score 1 point.
   Voltage two to four times normal for age: 2 points.
   Voltage over five times normal for age: 4 points.

(b) Bursts of very chaotic make-up, containing delta waves from 0.75 c/s to 3 c/s, with spikes of varying site and amplitude: score 2 points.

(c) Bursts of slow or rapid spikes appearing simultaneously in all regions: score 2 points.

(d) Focal spikes: score 1 point each for left, right, or posterior.

(e) Completely random spikes: score 4 points

(f) Completely random delta: score 2 points.

Normal background activity scores minus 1 point.

Using the above method a completely hypsarrhythmic record scores 13-30 points; modified hypsarrhythmia scores 9-12 points; an epileptic record of centrencephalic type and a focal epileptic record scores 2-8; a normal or non-specific record scores 0 or 1 point respectively.
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