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Hereditary Components in Epileptic Patients

Electroencephalogram Family Studies

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The electroencephalograms of 80 families of epileptic patients were compared with those of 30 normal control families. Abnormal family EEGs were not only encountered in patients with centrencephalic seizures but also in patients with psychomotor epilepsy. One half of all patients with focal sharp wave or spike discharges were found to have another family member with an abnormal EEG. Abnormal family EEGs were more frequently encountered in female than in male patients. Mothers of epileptic patients had a significantly higher percentage of electroencephalographic abnormalities than fathers, regardless of the type of seizure the patient was experiencing. Patients whose seizures started between the ages of 6 and 15 years usually had a genetic component to their illness, as demonstrated by electroencephalographic abnormalities in one parent and at least one sibling.

The question of the relative importance of heredity in the causation of epileptic seizures is still unresolved. A widely held current assumption is that a genetic predisposition exists for idiopathic or centrencephalic epilepsy, but the role of heredity is regarded as negligible in the production of focal seizures.[1] The reasons for the acceptance of genetic factors in patients with centrencephalic epilepsy lie mostly in the results of the electroencephalographic studies by Lennox and co-workers,[2] Harvald,[3] and, most recently, Metrakos and Metrakos.[4] There is therefore relatively little disagreement about the first part of the mentioned assumption. The second part, namely, that hereditary factors are negligible in patients with focal seizures is, however, not as well documented. The difficulty arises from that large segment of epileptic patients who have psychomotor or temporal lobe seizures. These seizures are by definition of a focal nature but a definite structural lesion of etiologic significance cannot be demonstrated in a great number of instances. Previous electroencephalographic studies by Rodin and Whelan,[5] as well as Bray and Wiser,[6,7] on relatives of patients with temporal foci showed the rather frequent occurrence of similar abnormalities in other family members who are clinically healthy. This, as well as a report by Barslund and Danielsen[8] on the occurrence of psychomotor epilepsy in a pair of monozygotic twins, raises the question of a genetic component for some of the patients with this seizure type. The present study was undertaken for two main reasons: (1) to investigate the relative importance of genetic factors in psychomotor epilepsy, and (2) to ascertain the clinical characteristics of epileptic patients in whom hereditary factors can be shown to exist on the basis of family electroencephalograms.

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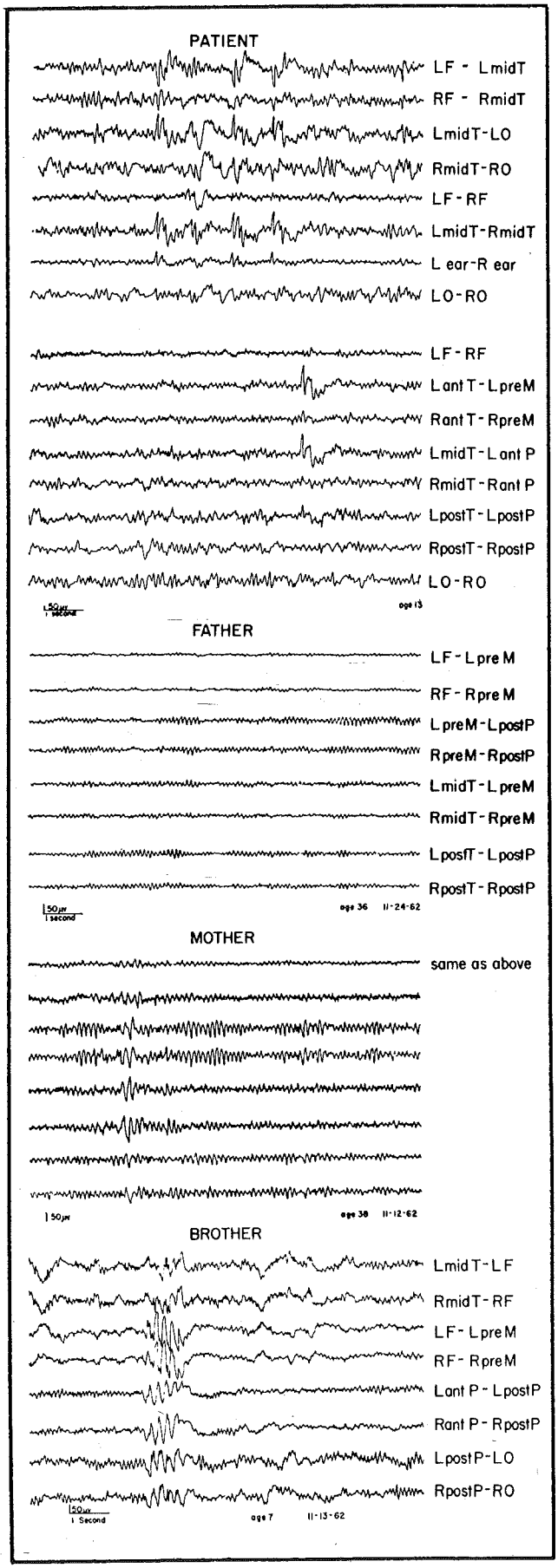
Methods

EEGs of families of epileptic patients, psychiatric patients, and normal controls were systematically collected from 1958 on. By December 1964, EEGs of 110 families of epileptic patients had become available as well as EEGs of 22 families of psychiatric patients and 30 normal control families. Nineteen electrodes were used in monopolar and bipolar connections. The length of recording time was at least 25 minutes, photic stimulation was used in all instances, and hyperventilation was used in all individuals above the age of 6 years. The tracings were initially interpreted on a routine basis by the senior author as they accumulated over the years. In order to avoid bias, the records of these families were subsequently thoroughly shuffled and reinterpreted on a blind basis by the coauthor. At the time of reinterpretation only the age of the individual was known. The electroencephalographer had therefore no knowledge of whether he was dealing with the recording of an epileptic or psychiatric patient or with the recording of a relative or normal control individual. Records of 674 persons were reinterpreted in this manner and the results of the two interpretations compared. It was observed that approximately 75% agreement existed between the two raters. The recordings on which there was disagreement were then jointly reviewed by both authors, again on a blind basis (except for the age) and a common decision regarding normality or type



1. Patient's EEG shows left temporal sharp wave focus; clinical temporal lobe epilepsy is present. Father has normal EEG; mother, slight diffuse bursts; brother, definite diffuse bursts with small spike components. Both parents and brother are clinically healthy.

of abnormality was made. Records were regarded as being abnormal when they showed one, or a combination, of the following characteristics: (1) focal slow wave activity, that is, frequencies less than 7 cycles/sec (symmetrical bioccipital slowing was regarded as normal in children); (2) generalized paroxysmal activity; (3) marked diffuse activity with frequencies below 7 cycles/sec unless the individual was less than 10 years of age; and (4) marked mixture of frequencies without prominent background rhythm. Low voltage fast or desynchronized records were regarded as normal. Borderline tracings were regarded as normal rather than abnormal. For statistical analysis of the data, only the results of the waking EEG were used because the majority of relatives, especially the adults, did not fall asleep during the recording. The data were then reassembled into family units and separated again into families of epileptics, psychiatric patients, and normal controls. The charts of the epileptic patients were then reviewed and charts were retained for statistical analysis for only those families of patients for whom the diagnosis was unequivocal and for whom both parents and practically all the siblings had been recorded. This reduced the number of families of patients with epilepsy to 80.

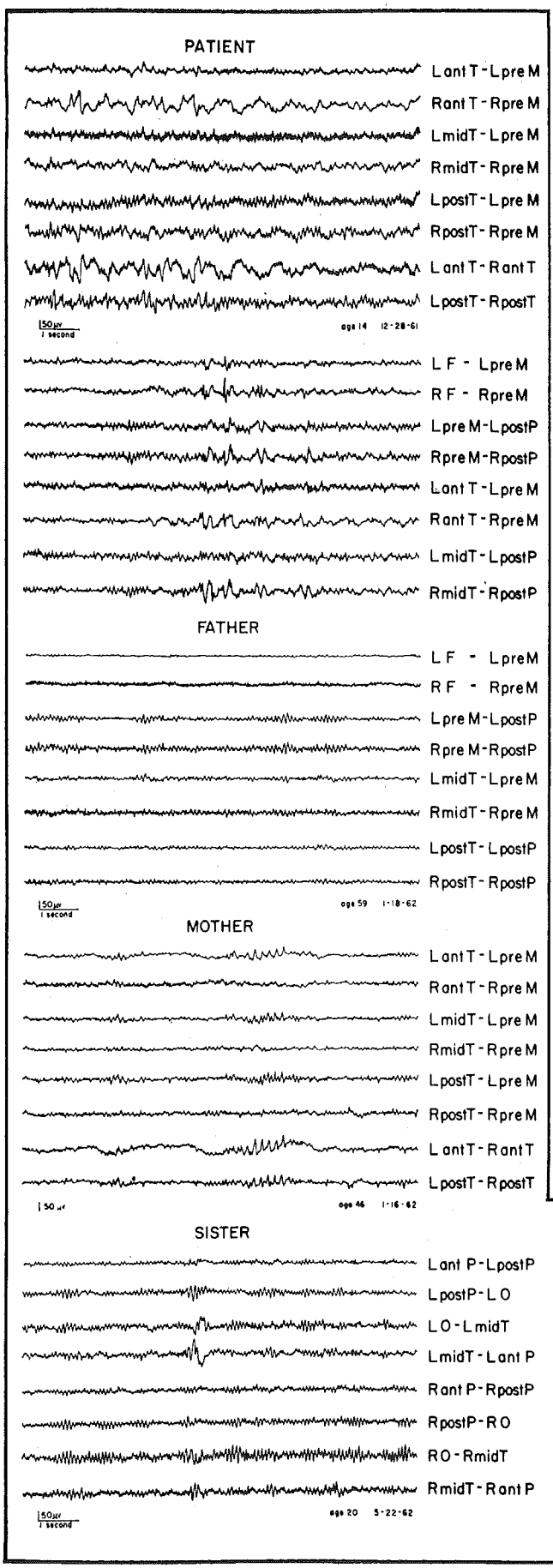
Table 1.—Percentages of EEG Abnormalities in Families of Epileptic Patients and Controls

	Epilectic Patients		
	This Series	Harvald Series*	Controls
Patient abnormal	90%	91%	....
Fathers abnormal	25%	24%	26%
Mothers abnormal	41%	45%	30%
Siblings abnormal	34%	36%	....
Children abnormal			21%†

*Data from Harvald.[8]
†$P < 0.05$.

Results

The findings of the statistical evaluation of the charts of families of psychiatric patients will be presented elsewhere and only the results from the epileptic and normal control population will be shown here. A comparison of our results with those obtained by Harvald in Denmark is shown in Table 1. The table also contrasts the findings in the epileptic population with those of our normal control families. Harvald had no data on control families. It can be seen that a close agreement exists between the Detroit and the Copenhagen series. It can also be seen that mothers had a higher percentage of electroencephalographic abnormalities than fathers. This difference is statistically significant ($P < 0.05$) for the epileptic but not for the



2. Patient, right anterior temporal slow wave activity and clinical temporal lobe epilepsy. Father, normal; mother, slight left anterior temporal slow wave activity; sister, left midtemporal slow wave activity; another sister, diffuse bursts. Parents, sisters clinically healthy.

Table 2.—Comparison of Findings in Patients With Temporal Lobe Epilepsy and Patients With Nonfocal Grand Mal Epilepsy

	Temporal Lobe Epilepsy	Nonfocal Grand Mal Epilepsy
Fathers abnormal	27%	30%
Mothers abnormal	58%	45%
Siblings abnormal	33%	46%
Potential exogenous etiology	40%	30%
Family history of epilepsy	27%	15%
Family history of epilepsy or isolated seizures, or both	50%	35%

control population. There were no differences in the percentages of abnormalities of the fathers between the epileptic and control population and the difference in the percentages for the mothers did not reach statistical significance. The difference in percentages of abnormalities of the siblings was, however, statistically significant ($P < 0.05$).

From the total sample of epileptic patients, two groups of 20 patients were then selected. One group had clear clinical evidence of temporal lobe epilepsy and the other group had clinical nonfocal grand mal epilepsy. Table 2 presents a comparison of electroencephalographic and clinical findings between these two groups. None of the differences in the percentages were large enough to be statistically significant. It is of interest to note that in the group with temporal lobe epilepsy more than half of the mothers had abnormal EEGs. The clinical classification gives, therefore, no reliable indication about the presence or absence of underlying genetic concomitants.

As a next step, two groups were formed on the basis of electroencephalographic criteria only. Patients who had focal temporal sharp waves were contrasted with patients who had diffuse spike wave bursts. Table 3 presents the results. It is apparent that mothers had again a high abnormality rate in both groups. Statistically significant differences appeared, however, only in relation to the abnormality rate of the siblings and the family history of epilepsy or isolated seizures, or both. The group with spike wave bursts showed a higher per-

Table 3.—Comparison of Findings in Patients With Focal Sharp Waves and Patients With Generalized Spike Waves

	Focal Sharp Waves	Generalized Spike Waves
Fathers abnormal	25%	35%
Mothers abnormal	43%	50%
Siblings abnormal	31%	55%*
Potential exogenous etiology	40%	25%
Family history of epilepsy	15%	30%
Family history of epilepsy or isolated seizures, or both	35%	70%*

*$P < 0.05$.

centage for those two variables. The difference in the variable "family history of epilepsy" did not reach statistical significance because of the smaller numbers involved. In the group with spike wave bursts, all families contained at least one family member (apart from the patient) with an abnormal EEG. In the group with focal sharp waves, 12 of the 20 families had at least one member with a pathological EEG. Inasmuch as more than half of the families of patients with focal sharp waves contained a family member with an abnormal EEG, the presence of a focal pattern in the patient does not automatically exclude the possibility of a genetic component in the patient's illness.

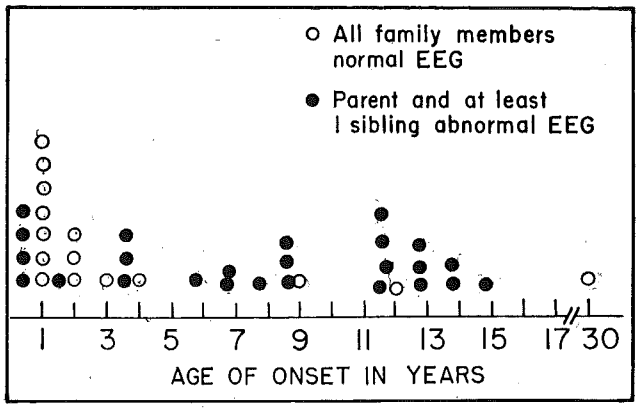
The types of electroencephalographic abnormalities encountered in the families varied considerably and different types of abnormalities could at times be found within a given family unit. The relatives of patients with focal sharp waves or slow waves could have either focal slow waves or diffusely disorganized patterns with or without diffuse bursts. Figure 1 presents an example of one family and Fig 2 demonstrates the phenomenon in a second family to indicate its fairly common occurrence.

Having established that the presence of focal electroencephalographic abnormalities or of psychomotor seizures gives no reliable indication of the presence or absence of a genetic component in the patient's illness, it was of interest to determine whether a group of patients could be identified in whom heredity can be assumed to play some role, as contrasted with a group in whom no hereditary factors are apparent from the EEG. The patient material was therefore divided into two groups. One consisted of families in whom all members except for the patient had normal EEGs and the other of families in whom at least one parent and one of the siblings had an abnormal EEG. Fifteen families for whom the patient was the only child were eliminated for this part of the study. Of the remaining 65 families, only 16 (25%) were found where all relatives had normal recordings. There were 28 (43%) families who fulfilled the criteria for the second group. Table 4 presents the results. The significant findings were that in group 1 there was a predominance of males, the mean age of onset of the illness was lower, and there was a positive history of insult to the central nervous system in two thirds of the cases. Family history of epilepsy did not differentiate the two groups. A focal seizure pattern was encountered in four fifths of group 1 but also in one half of group 2. Figure 3 presents a more detailed breakdown of the findings in regard to age at onset of the illness in the two groups. The overwhelming majority of patients whose seizures started between 6 and 15 years of age had evidence for a genetic component. The age at onset of patients whose family had normal EEGs tended to cluster around the first two years of life.

Table 4.—Relationship of EEGs of Family to Clinical Findings in Patient

	All Family Members Except Patient Had Normal EEG	At Least 1 Parent and 1 Sibling Had Abnormal EEG
Male sex	87%	57%*
Mean age, yr	11.5	14.9
Mean age at onset of illness, yr	4.6	8.2*
Seizure pattern focal	81%	53%†
Potential exogenous etiology	62.5%	14%*
Family history of epilepsy	18%	11%

*$P < 0.05$.
†$P = 0.06$.



3. Onset of epilepsy in patients whose parents and siblings have normal EEGs occurs mostly during first two years of life. Onset in patients with genetic concomitants occurs any time during childhood and adolescence but clusters predominantly between the ages of 6 and 15 years.

Comment

The findings indicate that abnormal genetic mechanisms are not only present in centrencephalic epilepsy but can also be demonstrated in patients whose seizures have focal characteristics. About one half of all patients with psychomotor seizures or temporal sharp waves had mothers whose EEGs were abnormal. The distribution of the age at onset of the disorder in relation to family electroencephalographic findings showed quite clearly that patients who start with seizures between the ages of 6 and 15 are very likely to have a genetic component to their illness. The cluster between 11 and 15 years of age is of special importance because this is the age group where psychomotor epilepsy frequently makes its first appearance. All individuals shown in Fig 3 had a psychomotor element to their seizure patterns. There were four patients in this series who had temporal lobectomies in an attempt to relieve their seizures. In all four instances the mothers likewise had focal temporal abnormalities in their EEGs. The patients' seizures

were improved postoperatively but not one has become completely seizure-free.

The data suggest that patients with psychomotor epilepsy can be divided into at least two groups. In one group, it is the sole expression of acquired neurological disease (trauma, tumor, infection, etc) and in another, it is accompanied by a genetic component. The focal electroencephalographic findings in these patients, and their relatives, might then be viewed not as indications of focal structural pathology but merely as the partial expression of a more diffuse disturbance of cerebral electrical events. It would be of great interest to compare the long-term neurosurgical results of temporal lobectomies between these two groups. The two groups cannot be separated at present on the basis of the electroencephalographic findings of the patient or on the basis of the clinical history but only through EEGs of parents and siblings or children of the patient. However, female sex or an age of onset between 6 and 15 years, or both, would favor the placing of the patient into the group with genetic components.

The study also showed that electroencephalographic abnormalities are more frequently transmitted through the mother than the father and that genetic factors can be demonstrated in the large majority of female epileptic patients. This is in agreement with the observations of Harvald. There were altogether only two female patients in the group of 16 where the rest of the family had normal EEGs.

The fact that a genetic *component* can be demonstrated by electroencephalography in a large number of epileptic patients should not be misinterpreted as indicating that the patient's illness is, therefore, primarily caused by this component. A convulsive seizure is not the direct result of the presence of an abnormal interictal EEG. The immediate cause of the seizure lies in those mechanisms that permit the spread of excessive electrical activity to other parts of the central nervous system or to the musculature, or both. The mechanisms responsible for spread of excessive electrical activity, which results in the clinical seizure, are at present not demonstrable by the usual electroencephalographic techniques. Inasmuch as the vast majority of relatives of patients with epilepsy are clinically healthy it would appear that the mechanisms of spread of abnormal electrical activity are not inheritable to the same extent as the dysrhythmic EEG itself. This concept would reconcile the electroencephalographic observation that large numbers of individuals have abnormal tracings with the clinical observation that the incidence of overt epilepsy in the families of patients is relatively low.

The observation that a considerable proportion of seemingly healthy individuals carry focal or diffuse electroencephalographic abnormalities has to be taken into account when the EEG is used as a diagnostic tool. Electroencephalographic abnormalities may antedate the patient's complaint and bear little or no evidence to the symptom for which the help of the physician is sought. The medicolegal implication of this finding is also obvious. The physician is frequently confronted with a case of minor head injury and an EEG showing mild abnormalities. The record may then be introduced as evidence that the patient had indeed suffered cerebral trauma and should be compensated accordingly. If one has only the patient to deal with it may be impossible to distinguish in a number of instances between constitutional and acquired electroencephalographic abnormalities, unless they are of a very gross nature. The situation can clarify itself immediately if other family members are available for recordings. If it can be shown by this technique that all other members of the family have normal EEGs, the patient's abnormality is likely to be due to an exogenous event. If several other family members show, however, abnormalities that are similar to those of the patient, it appears probable that the patient's EEG pattern did not result from trauma but is due to constitutional factors.

The tests for statistical significance were performed by Patricia Phillips.

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