The Detection of Carriers in Hereditary Myoclonic Epilepsy

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The syndrome of myoclonic epilepsy, first recognized by Unverricht (9), is characterized by the occurrence in childhood of typical epileptic seizures, followed several years later by the development of myoclonus, insidious mental deterioration, and death in early adulthood. Myoclonus may be defined as an irregular muscular contraction varying from a slight tremor to a generalized seizure. Lundborg (8) first recognized the hereditary nature of myoclonic epilepsy and postulated an autosomal recessive mode of inheritance.

Electroencephalograms of relatives of individuals afflicted with epilepsy were recorded by Lennox (5) who observed a significantly greater incidence of cerebral dysrhythmia in near relatives of epileptics than in the general population. This author suggested that cortical dysrhythmia, an underlying physiological manifestation of epilepsy, might be a dominant trait, and that the dysrhythmic parent of an epileptic might be the carrier of the gene for the disease. Although Lennox did not identify the type of epilepsy present in his cases, it is probable that his study was not concerned with myoclonic epilepsy. Lennox (7) found that concordance in monozygotic twins was typical with respect not only to the occurrence of seizures but also to the types of seizure and EEG pattern. This author (6) also noted that brain wave patterns were identical in 85% of the pairs of a large group of normal monozygotic twins, and with respect to abnormality in 61% of the pairs of a group of epileptic monozygotic twins.

Grinker, Serota, and Stein (2) recorded EEG's in a female sibling, the mother and a son of an affected female patient. Dysrhythmia was noted in each of these individuals; the paternal aunt and paternal grandmother had myoclonic epilepsy. Although a dominant gene would seem to be responsible for the syndrome in this family, the authors did not comment on the fact that myoclonic epilepsy is usually transmitted by an autosomal recessive gene (2, 3, 4, 8).

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Delay, Fischgold, Pichot and Verdeaux (1) were the first to obtain EEG's of relatives of patients afflicted with a recessive type of myoclonic epilepsy. In the family on which they reported, the electroencephalographic pattern typical of this disorder was noted in three normal siblings as well as the patient, but the tracings of both parents were considered normal.

Watson and Denny-Brown (10) also have recorded EEG's of relatives of patients with a recessive type of myoclonic epilepsy. The family in this study included a nor-

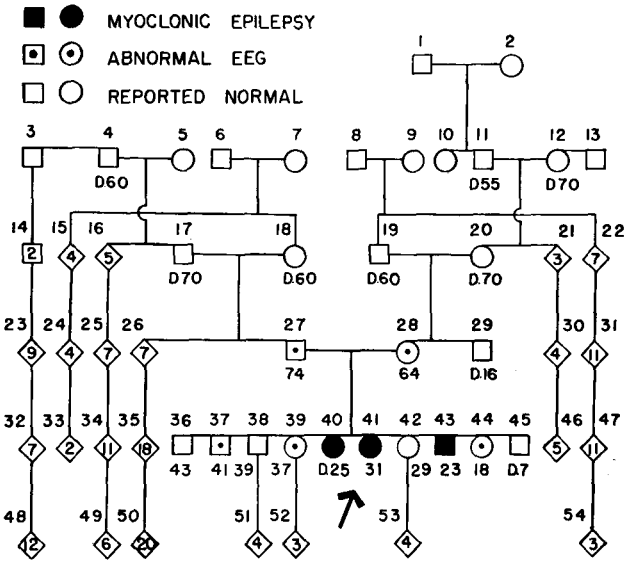

Fig. 1. Pedigree of a Negro family showing an autosomal recessive inheritance of myoclonic epilepsy. The reference number of each member is above the symbol; the number beneath the symbol is the age or age at death of the member. The arrow marks the propositus, 41. The number within the symbol is the number of members, if more than one, represented by a single symbol

mal brother and sister, each of whom had a dysrhythmia similar to that in the affcted brother.

Harriman and Millar (3) recorded the EEG's of a father and eleven offspring, of whom three were affected. The ages of the offspring ranged from 2 to 23. Harriman and Millar, however, did not publish EEG tracings and stated only that the EEG's of the unaffected members of the family were normal.

It is possible that the childhood seizures in both parents of the patients reported by Watson and Denny-Brown might represent a sign of heterozygosity.

Procedure

Three patients suffering from myoclonic epilepsy, members of a Negro sibship of 10, were seen at the Charity Hospital of Louisiana from 1942 to 1957. Of the three epileptics, one had died and another was no longer accessible. However, their EEG's at the time of admission were available. The third affected sibling, three unaffected siblings, and the parents were examined and EEG tracings were recorded.

Results and Discussion

The pedigree (Fig. 1) is of a Negro family of 10 siblings, 8 of whom are alive (at the present time). One unaffected member (no. 45) died of diphtheria at the age of

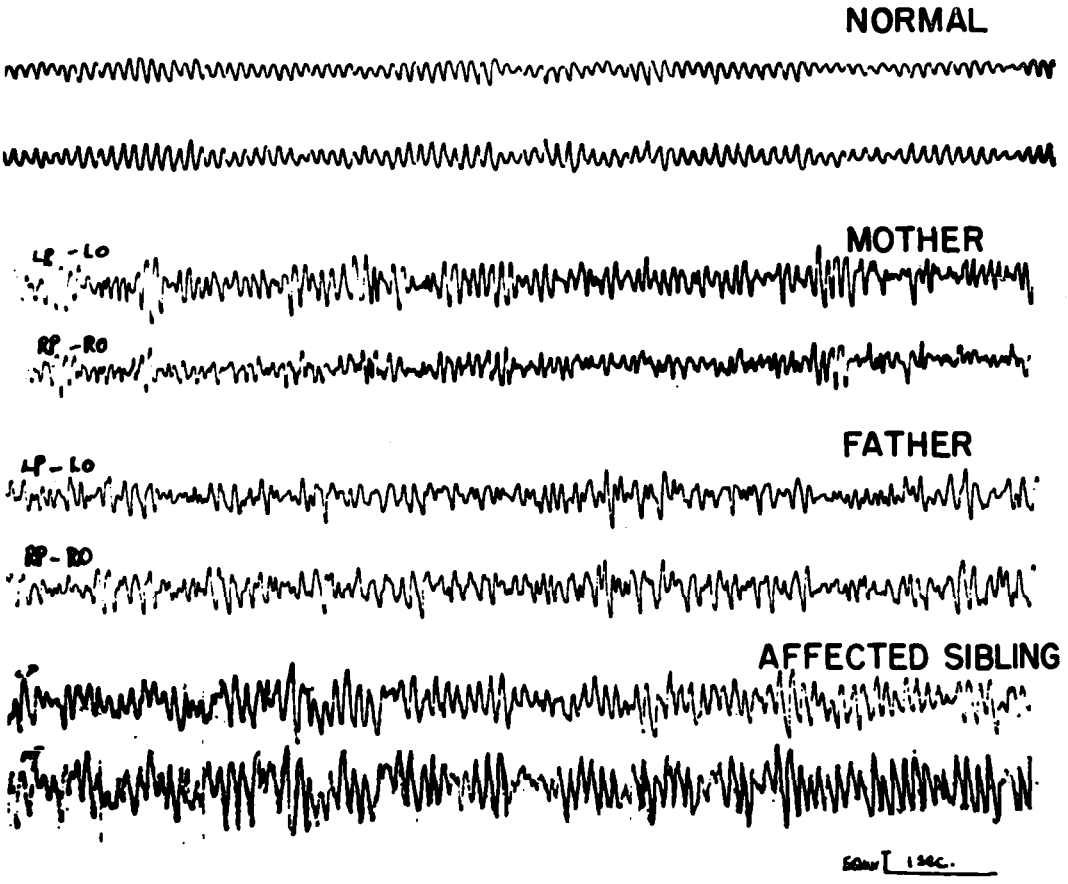

Fig. 2. Electroencephalograms showing spike discharges compared with the normal: a normal individual unrelated to this family, mother of the propositus (no. 28), father (no. 27), and the propositus (no. 41)

seven, and an affected member (no. 40) died at the age of twenty-five. The disorder was present in two of the 8 living siblings. Both parents were descendants of families from the same parish (i. e., county) in southwestern Louisiana and no relatives of the family other than those reported ever had been known to have the same or any related condition. Consanguinity of the parents on a first or second cousin level did not exist, but a more distant relationship cannot be excluded because ancestors of both parents lived in the same locality.

The findings of physical and neurological examinations of the parents and three unaffected siblings were within normal limits.

Spike discharges are evidenced in electroencephalograms (Fig. 2) of the mother, father, two affected siblings, and three siblings who showed no clinical evidence of the disease. Abnormalities of this type (Fig. 2) occur in epileptics and relatives of epileptics, although not restricted to the myoclonic type. The character of these records, however, suggests that the disturbance is of the so-called " idiopathic " type in which electrical abnormalities are not focal but generalized over the entire cerebral cortex.

Interpretation

A recessive gene for myoclonic epilepsy seems to be expressed in the following manner:

Genotype	*Phenotype*
MM	clinically normal with normal EEG
Mm	clinically normal with abnormal EEG
mm	myoclonic epilepsy with abnormal EEG

From our observations the mm genotype could be 100% penetrant for myoclonic epilepsy with an abnormal EEG. The Mm genotype seems to have resulted in an abnormal EEG in the heterozygous parents, cases nos. 27 and 28. If the abnormal EEG is associated with heterozygous carriers, one might expect an abnormal EEG among two out of three of the normal siblings of case no. 41. All three clinically normal siblings showed abnormal EEG patterns. It would seem that the abnormal EEG found in these siblings could identify them as heterozygotes.

This interpretation is compatible with the findings of Watson and Denny-Brown (10), who noted that the type of dysrhythmia in siblings was similar to the type in their cases. No history of childhood seizures, noted in the cases by these authors, was obtained from the probable heterozygotes in our study. However, our interpretations are incompatible with the work of Delay and others (1) and Harriman and Millar (3). Although the Mm genotype could be 100% penetrant for the abnormal EEG, in our study and in the work of Watson and Denny-Brown (10), when these results are pooled with the study of Delay and Harriman, the penetrance is

about 55%. The advisability of pooling these data may be questioned because Delay and Harriman may have been dealing with another type of myoclonic epilepsy in which the gene does not produce cerebral dysrhythmia in the heterozygote.

Summary

Three cases of hereditary myoclonic epilepsy have been observed among ten siblings in a Negro family. Electroencephalograms of the parents, three normal siblings and two of the three affected siblings have been recorded and all show abnormalities of a similar type. These are of a generalized nature revealing no focal damage. This type of abnormality has been observed in an affected male and two normal siblings by Watson and Denny-Brown.

The autosomal recessive mode of inheritance observed in the present study is consistent with the transmission most frequently reported in myoclonic epilepsy. We believe that abnormal electroencephalographic patterns are associated with this gene and that these patterns may be useful in the detection of heterozygous carriers.

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RIASSUNTO

Su dieci membri di una fratria di una famiglia negra sono stati osservati tre casi di epilessia mioclonica ereditaria. Sono stati registrati gli EEG dei genitori, di tre siblings normali e di due dei tre siblings affetti e tutti presentano delle anormalità dello stesso tipo. Tali anormalità sono di natura generale e non presentano danni locali. Watson e Denny-Brown hanno osservato questo tipo di anormalità in un maschio affetto ed in due siblings normali.

Il modo di trasmissione autosomico recessivo che è stato osservato in questa ricerca si accorda con il modo di trasmissione più frequentemente osservato nell'epilessia mioclonica. Si pensa che le tracce elettroencefalografiche anormali siano associate a questo gene e che tali tracce possano essere utili nella ricerca dei portatori eterozigotici.

RÉSUMÉ

Trois cas d'épilepsie myoclonique héréditaire ont été observés parmi 10 siblings d'une famille nègre. Les EEG des parents, de trois siblings normaux et de deux des trois siblings atteints ont été étudiés: tous présentent des abnormalités similaires. Ces dernières sont d'une nature généralisée, sans troubles locaux. Ce genre d'abnormalité a été observé par Watson et Denny-Brown chez un mâle atteint et deux siblings normaux.

La transmission autosomique récessive observée dans cette recherche s'accorde avec la transmission le plus fréquemment observée pour l'épilepsie myoclonique. Nous croyons que les abnormalités de l'EEG sont associées à ce gène et qu'elles peuvent être utiles dans le dépistage des conducteurs hétérozygotiques.

ZUSAMMENFASSUNG

Drei Fälle von vererblicher myoklonischer Epilepsie werden unter 10 neger Siblings beobachtet. Die EEG der Eltern, und von drei normalen Siblings und zwei der drei behaftete Siblings werden untersucht: alle zeigen ähnlichen Abnormalitäten. Diese sind allgemeinen, mit keinem örtlichen Leid. Diese Art Abnormalität wird bei Watson und Denny-Brown in einem männlichen behaftetem und zwei normalen Siblings beobachtet.

Die in dieser Untersuchung beobachtete rezessive autosomische Art Vererbung stimmt mit der in myoklonischer Epilepsie häufigst beschriebener Art Vererbung. Wir glauben dass das abnormales EEG mit diesem Gen in Verbindung steht, und dass dieses nützlich sein kann um heterozygotischen Träger aufzudecken.