

Genetic aspects of childhood epilepsy

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SINCE ancient times, genetic factors have been known to contribute to the manifestation of epileptic seizures. Although a large number of investigators have attempted to delineate the role of genetic influence more precisely, our present understanding of the topic is still insufficient. Only a small proportion of epileptic conditions are caused by monogenic inborn errors of metabolism. The genetic background of the vast majority of the epilepsies cannot be explained by single gene theories; it requires models allowing for a polygenic disposition. Attempts to formulate more or less globally valid polygenic models have not yet been successful. All that can be said with certainty is that the pathogenesis of epilepsy is multifactorial.¹

Until the present time, most studies of the genetics of epilepsy have concentrated on the obvious symptom, the epileptic seizure.² This is still the case, although it has been known for decades that "the clinically observed phenotypes of epilepsy represent only the tip of the iceberg,"³ the basis of which is constituted by a complex and much more widespread phenomenon: the so-called convulsive liability. Instead of dealing with the "iceberg's tip," it should be more productive for the following review to focus attention on this more fundamental phenomenon.

During recent decades, electroencephalographic (EEG) research has made important contributions to our understanding of the genetically determined convulsive liability. Already in the early days of clinical electroencephalography, it could be shown that EEG symptoms of an increased convulsibility can be detected in up to 40% of healthy relatives of epileptic patients.⁴ Even at the present time, the EEG is the only

tool to detect carriers of a genetic liability to convulsions.

EEG PATTERNS

Four EEG patterns may be regarded as "markers" of an increased liability to convulsions.

1. *Bilateral synchronous spikes and waves during rest and hyperventilation.* This pattern is prototypical of the corticoreticular epilepsies. In siblings of children with bilateral synchronous spikes and waves, analogous findings could be detected in up to 13% as compared to a maximum of 2.9% in controls (Figure 1).⁵

The spike-wave incidence in the siblings is distinctly age-dependent. Specifically, the age distribution of positive findings shows a bimodal character with peaks in the 3- to 6-year age range and in 15-year-old siblings. The pattern of inheritance of spikes and waves is still not known in detail. The hypothesis of an autosomal dominant inheritance of a so-called "centrencephalic" trait, originally presented by Metrakos and Metrakos,⁶ is unlikely in the light of present knowledge. It must be stressed that these authors did not differentiate between spikes and waves elicited by photic stimulation and those occurring spontaneously.

Since that time it has been proved that these phenomena are genetically different.^{7,8} Neuropharmacologic studies have suggested different physiologic processes underlying these two phenomena.⁹ Considering the relatively high frequency in the general population as well as the distinct age-dependency, a determination of spikes and waves by polygenes is most likely. Moreover, there are good reasons to assume underlying heterogeneity as suggested by their bimodal distribution in siblings.⁵ If spikes and waves occur during early childhood, they are statistically associated

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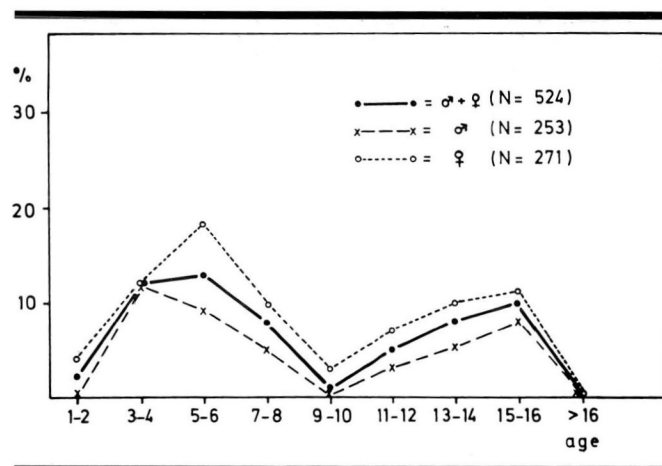


FIGURE 1. Bilateral synchronous spikes and waves during rest and/or hyperventilation in siblings of children with this pattern.⁵

with the 4 to 7 Hz rhythm anomaly.¹⁰⁻¹² Children positive for 4 to 7 Hz rhythms are more likely to manifest spikes and waves, especially if they are photosensitive as well; so it is clear that spikes and waves obviously do not represent an independent genetic phenomenon.

2. Photosensitivity. Photosensitivity is defined as the occurrence of irregular spikes and waves during intermittent photic stimulation (photoparoxysmal response). The familial occurrence of photosensitivity has been known for three decades.¹³ In siblings of photosensitive probands, positive findings could be obtained in up to 40%.⁸ Distribution was distinctly age-dependent with a maximum between the fifth and the fifteenth year of life; and, as is shown in Figure 2, girls were more often positive than boys.

The distribution of positive findings was bimodal. In brain-healthy children between 1 and 16 years of age, an average incidence of 7.6% was obtained.⁸ The pattern of genetic transmission cannot be deduced from the available data. Probably, this phenomenon is also due to polygenic effects.

3. 4 to 7 Hz rhythms. The EEG pattern is characterized by runs of bilateral synchronous, monomorphic 4 to 7 Hz rhythms. This pattern is prevalent in epilepsies of early childhood, but also in febrile convulsions, predominantly in children aged 2 to 6 years.¹⁴ In epilepsies with an unfavorable course, however, the rhythms can persist until puberty and adulthood. According to follow-up studies, they can change into frontal midline theta rhythms during late adolescence.

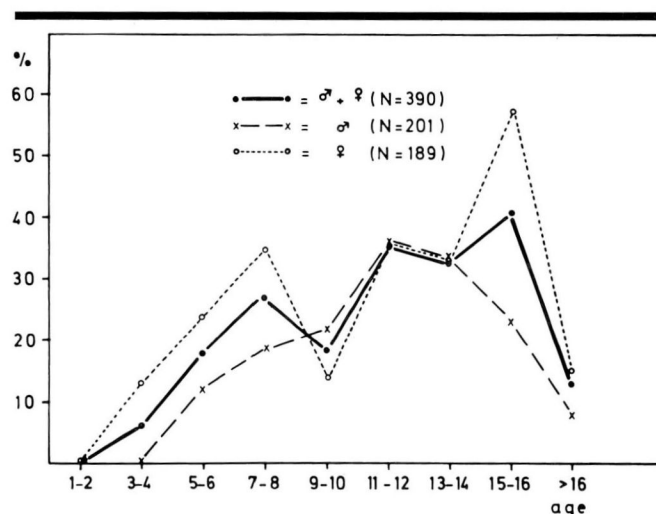


FIGURE 2. Photoparoxysmal response in siblings of photosensitive children.⁸

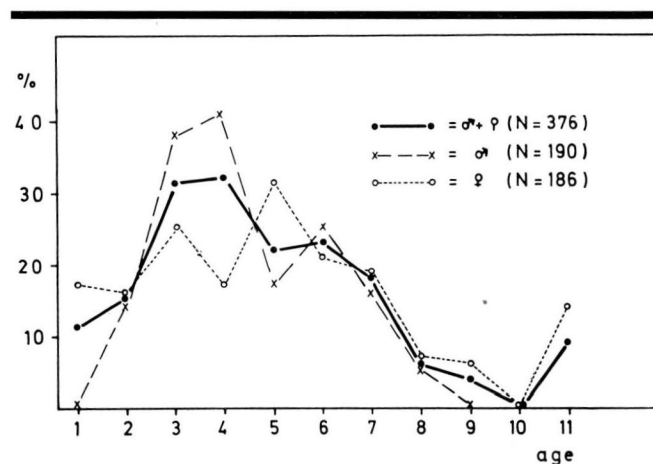


FIGURE 3. 4 to 7 Hz rhythms in siblings of children with this pattern.¹⁵

Studies of siblings clearly demonstrate that the pattern is transmitted in families.¹⁵ Siblings of positive probands were again positive in up to 30% of cases with obvious age-dependency (Figure 3).

Siblings of negative probands, on the other hand, showed 4 to 7 Hz rhythms in only 2% of cases. In all, the relatively high frequency of 4 to 7 Hz rhythms in the general population, and their age- and sex-dependency, are compatible with a polygenic trait.

4. Focal sharp waves.¹⁶ Genetic determination of

centrotemporal sharp waves, characteristic of benign partial epilepsies of childhood, has been proved by family studies and observations of twins.¹⁷⁻¹⁹ Regarding the pattern of genetic transmission, Bray and Wiser¹⁷ as well as Heijbel et al¹⁸ concluded from family studies that the EEG trait might be transmitted by an autosomal dominant gene with age-dependent penetrance. According to our own findings, however, this hypothesis has to be reconsidered. As can be shown by family studies, transmission of the pattern is independent from other genetic EEG patterns.^{5,8,15} In healthy children, the pattern can be detected in about 1% to 2%. From these data, and from the cumulative incidence of epileptic seizures as well as the proportion of benign partial epilepsies among all epilepsies of childhood, it can be calculated that only a minority of carriers of centrotemporal sharp waves experience seizures. Possible conditions which may augment a carrier's risk of contracting seizures are discussed below.

DISCUSSION

So far we have addressed four EEG patterns which can be interpreted as markers of a genetically determined convulsibility. The pertinent genotypes may interact to decrease the seizure threshold, thus increasing the risk of clinically manifest seizures. Even in the general population, these genetic properties are widespread; they follow different patterns of age- and sex-dependence. It is probable that they do reflect polygenic effects, except, possibly, for centrotemporal sharp waves. Therefore, on the basis of EEG findings alone, genetic convulsibility is not a homogeneous condition, but is determined by a complex of different sets of polygenes. A single major gene has not yet been identified.

If, as stated above, different EEG patterns are frequently detected in the general population, and if only a minor proportion of these carriers suffer from epileptic seizures, the question arises as to which conditions may effectively increase the risk of clinical manifestation. Primarily, two mechanisms have to be considered. One very plausible explanation is that of an interaction of a transmitted liability with exogenous factors. In this case, an exogenous event would strike an individual who is otherwise at insignificant genetic risk.^{20,21} A second possible mechanism is an inherently genetic interaction of different heritable dispositions. If the different markers of an increased convulsibility are widespread in healthy populations, and genetically

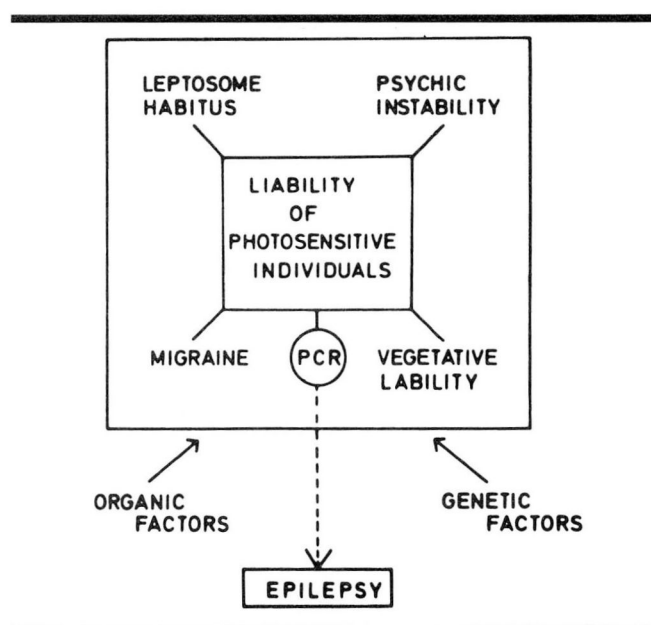


FIGURE 4. The constitution of photosensitive individuals and its relation to epilepsy.

independent, it follows that occasional coincidences of these factors must occur with a certain probability in some individuals. Such a coincidence may boost the resulting convulsive liability, and may shift the individual towards and finally beyond the threshold of clinically manifest symptoms.

Photosensitivity may serve as an example. This phenomenon is relevant not only to the pathogenesis of epilepsy. Only a minor proportion (about 3%) of all photosensitive individuals are at risk of manifesting seizures. On the other hand, complaints of a so-called vegetative liability, such as vasomotor headaches, abdominal pains, syncopal attacks, enuresis, and anorexia nervosa are more frequent in photosensitive persons.²² Migrainous children, too, are more often photosensitive.²³ Photosensitivity is a peculiar, age-dependent symptom of a very widespread "constitutional" diathesis (see Figure 4).

Convulsibility is only one of its aspects. The interaction, however, with other genetic factors boosts the convulsibility and may lead to an eruption of epilepsy. This mechanism can be detected by multivariate analyses of EEG findings in children with febrile convulsions, and in siblings of children with primarily generalized seizures.^{11,12} If photosensitivity and 4 to 7 Hz rhythms coincide in one individual, as a chance occurrence—not to be confounded with genetic linkage—

the result is an increase in the risk of bilateral synchronous spikes and waves at rest or hyperventilation. These, however, certainly are "near-seizure" EEG phenomena. In other words, the risk of epileptic seizures, which is insignificant in children who are only photosensitive or only positive for 4 to 7 Hz rhythms, will distinctly increase if the proband is positive for both of these patterns. This is a paradigmatic and well-documented example of a co-action of genetic risks, which, though mutually independent and each in itself almost insignificant, can result in seizures.

Genetic findings in benign partial epilepsies represent another example of interacting heritable factors. The pertinent sharp-wave pattern reflects a widespread genetic liability which leads to clinical seizures in only a minority of its carriers. In an effort to identify supporting risk factors, we studied 41 cases who were all positive for the typical sharp-wave patterns. In order to exclude sporadic cases, we required at least one sibling with analogous findings. Clinical symptomatology was not considered in selecting this sample. In the present context, some results merit discussion.²⁴

The clinical presentation of children with genetically transmitted focal or multifocal sharp waves is highly variable. Apart from rolandic seizures, we observed febrile and afebrile tonic-clonic seizures, atypical benign partial epilepsies with atypical absences, nodding and atonic-astatic seizures,²⁵ and in rare cases, even complex partial seizures and spike-wave absences. Some of the patients showed definite symptoms of perinatal brain lesions. Last but not least, different degrees of mental handicap were observed, especially in children with multifoci, even if they were not clinically seizure-affected. It follows from these findings that focal sharp waves transmitted in families are in no way specific of rolandic seizures, and that, naturally, this trait can also occur in brain-damaged children.

Like the clinical symptomatology, the EEG foci also show a great variability, with changing location uni- or bilaterally. Apparently, not the location of the sharp waves but the typical wave form is the main characteristic of benign focal discharges. Occipital sharp-wave foci, typically blocked by opening the eyes, are a definitely age-dependent symptom with maximum occurrence during the first 7 years of life. In our series,²⁴ however, neither clinical nor EEG findings showed any indication that this pattern represented an independent genetic phenomenon. Conditional on age, up to 79% of seizure-affected probands of our series manifested corticoreticular EEG patterns (spikes and waves at rest or hyperventilation, photoparoxysmal response,

4 to 7 Hz rhythms) simultaneously with focal sharp waves or successively during the course.

It is well documented by family studies that focal sharp waves and corticoreticular EEG patterns are transmitted independently.^{5,8,15} On the other hand, a genetic disposition which is widespread in the normal population needs nothing more than pure chance to coincide with other genetic properties. At least in part, such consideration may also explain the significantly increased incidence of febrile convulsions in children with rolandic seizures observed by numerous authors.¹⁶ It must be assumed that the coincidence of different liabilities may boost the risk of clinical manifestation. We must expect such coincidences, i.e., such factorial sets, to be rather the rule than an exception in epileptic populations.

The findings mentioned are prototypical of a pathogenetically multifactorial disease. This conclusion does not deal with the question of whether the EEG trait of benign focal sharp waves may be transmitted by an autosomal dominant gene, as is assumed by Heijbel et al.¹⁸ The conclusion of these authors, however, was based on a comparison of the incidence of the EEG pattern in a healthy population with that in siblings of epileptic children. Because it cannot be excluded by the available data that the expressivity of the pattern can be augmented by other genetic factors in the families of epileptic children, the hypothesis of an autosomal dominant trait should be proved by studying families of probands with focal sharp waves but without seizures.

These considerations about the interactions between different genetic and exogenous lesional factors may extend our understanding of the pathogenesis of the epilepsies. However, they explain only a relatively small proportion of the tremendous variability of epileptic symptoms and syndromes as well as of the findings in families. A number of other genetic factors are yet unknown or only insufficiently investigated (Figure 5).

So-called maternal effects in the transmission of convulsibility have been observed by numerous authors but have hardly been understood until now.²⁶ Our studies in 87 families with an affected parental generation clearly demonstrated the differential significance of an affection of either parental line: if the maternal generation was affected (mothers or mothers' siblings), the siblings' risk was clearly increased as compared to paternal affection. In this context, the maternal EEG was the most valuable criterion.¹⁴

Finally, the study cited of the families with a seizure-

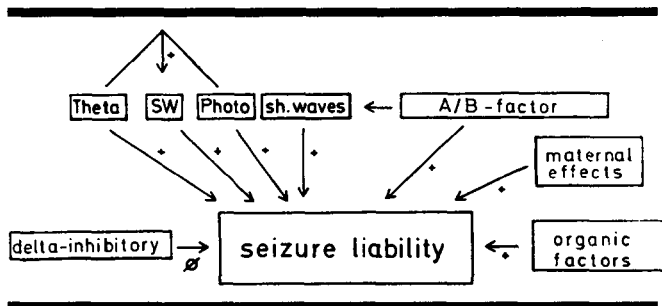


FIGURE 5. Multifactorial determination of the convulsive liability.

affected parental generation led to the assumption of another important familial trait.¹⁴ The study showed that the type and onset age of seizures in the probands are closely related to corresponding characteristics in the parental generation. For children starting with seizures before the age of 5 (A-seizures), the pertinent parental generation tended to manifest more early onset; those belonging to later onset probands (B-seizures) tended to report later-onset epilepsies as well. Moreover, patients with A-seizures and pertinent siblings experienced convulsive seizures more frequently than individuals with B-seizures with prevalently non-convulsive symptoms. As has been demonstrated elsewhere,¹⁴ the A- and B-impacts are probably the expression of qualitatively different sets of genetic factors. The findings clearly support the assumption of the genetic heterogeneity of childhood spike-wave epilepsies with minor seizures. Formal genetic analysis based on the Pointer strategy of Lalouel and Morton²⁷ clearly supported this view from a different methodological approach.²⁸ We may conclude that etiologic

heterogeneity of childhood spike-wave epilepsies with minor seizures is beyond reasonable doubt.

SUMMARY

The extensive studies pertinent to these problems cannot be elaborated here. We have restricted ourselves to a few representative concepts, which can be summarized as follows. The genetic aspects of convulsibility and epilepsy are highly complex phenomena. The level of convulsibility is determined by a number of different excitatory (and inhibitory) genetic factors. None of these factors is strictly specific to epilepsy. Each one is only a partial aspect of a complex genetic constitution which is strikingly common in perfectly healthy individuals, and which is related to a variety of psychic and somatic particularities. Almost all of these genetic factors seem to be polygenetically determined; in other words, they seem to reflect the actions of many genes. An increased liability to convulsions, and, finally, to epilepsy, is induced by an accumulation of these factorial sets, and, of course, by the effects of exogenous lesional factors. Special constellation of these polygenic sets may lead to the manifestation of different epileptic syndromes and may also explain the segregation of seizure types in the descendants of patients with seemingly uniform epileptic syndromes, as observed, for instance, in absence epilepsy and in juvenile myoclonic epilepsy.

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