Oligogenic inheritance in photosensitive juvenile myoclonic epilepsy?

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ABSTRACT – The interplay of multiple genetic factors, as opposed to monogenic inheritance, is suspected to play a role in many idiopathic generalized epilepsies. This leads to a digenic or oligogenic inheritance model, which although rather simplified, may explain at least some of the clinical observations. Here we describe a family in which the clinical phenotype in the offspring can be explained by a combination of photosensitivity and epilepsy traits that segregated independently of each other. This case history demonstrates the need to evaluate family histories in more detail in order to uncover potential clinical markers for genetic factors in complex epilepsies.

Key words: photosensitive epilepsy, juvenile myoclonic epilepsy, genetics, oligogenic, biparental inheritance

Idiopathic generalized epilepsy (IGE) is regarded as a complex disorder in which the interaction of multiple genes, external factors and age determine the penetrance and the clinical phenotype. Gene loci (Greenberg et al., 1988, Weissbecker et al., 1991, Liu et al., 1996, Elmslie et al., 1997, Durner et al., 1999, Sander et al., 2000, Durner et al., 2001, Pinto et al., 2004) and candidate genes (Escayg et al., 2000, Cossette et al., 2002, Haug et al., 2003, Pal et al., 2003, Dibbens et al., 2004, Suzuki et al., 2004) have been associated with the phenotype of juvenile myoclonic epilepsy (JME). Other potential IGE genes (Fong et al., 1998, Mikami et al., 1999, Sander et al., 2000, Kananura et al., 2002) and IGE-associated EEG traits (Waltz and Stephani, 2000, Doose et al., 2002) have been identified, but the findings in published reports are not consistent. This may be due to methodological differences (proband ascertainment, extent of family studies, models of affectedness, multiple testing), population differences, or a complex genetic etiology. The latter explanation has been suggested since for the majority of familial JME/IGE cases, a complex inheritance pattern is observed, where related cases often have a wide variation in clinical phenotype of IGE. This may reflect: (a) a number of interacting but independently segregating genetic factors with distinct phenotypic expression (b) a small number of
genetic factors with reduced penetrance and variable phenotypic expression, or (c) a mixture of the two. Finally, environmental factors may also play a role in the variable clinical expression of disease. Some evidence points to model (c) being the most likely. A few, rare, large families with a relatively homogeneous IGE phenotype have been observed that display a Mendelian inheritance pattern. Not surprisingly, most mutations identified for IGE have been found in these type of families. In contrast, the vast majority of IGE cases have weaker evidence for a familial history indicative of oligogenic inheritance reflecting model (a). The large, intrafamilial variation also suggests that such genetic factors have a rather high prevalence in the general population. Surprisingly, these families may present specific epileptic EEG abnormalities (Greenberg et al., 1992, Delgado-Escueta et al., 1999, Pinto et al., 2004) or they may present photosensitivity (Pinto et al., 2005), which seems to follow a Mendelian inheritance (Waltz and Stephani, 2000). Therefore, the assessment of these clinical traits and endophenotypes (measurable components unseen by the unaided eye) may help us to dissect oligogenic or polygenic idiopathic epilepsies.

As indicated above, photosensitivity may be one such trait. The prevalence of a photoparoxysmal response (PPR) in the general pediatric population is reported to be between 0.5 and 1.5% (Kasteleijn-Nolst Trenite et al., 2003). In children with epilepsy, a PPR can be demonstrated in about 5% of cases (Reilly and Peters 1973, Kasteleijn-Nolst Trenite, 1989), and in IGE up to 30% (Wolf and Goosses, 1986). This increased comorbidity provides evidence for a causal relation between PPR and IGE (Pinto et al., 2005). In the general population, subjects with a generalized PPR are usually not identified, probably because many of them may have only subtle symptoms such as myoclonic jerks or a short confusion on visual stimulation (Herrlin 1960, Schwartz 1962, Kasteleijn-Nolst Trenite 1989).

Here we present a family with three members with photosensitive JME, in which the PPR appeared to segregate independently from a putative epilepsy trait. Our observation underlines the argument for the oligogenic model (a) of inheritance of IGE, and shows the potential contribution that clinical traits such as photosensitivity may make to the genetic dissection of common complex epilepsies.

Methods

From the database of the Netherlands working group on Epilepsy Genetics, we have identified this family, which was large enough to evaluate the segregation of epilepsy and photosensitivity. The family has previously been included in a linkage study (Pinto et al., 2004). Neither the phenotype of JME, nor the endophenotypes of fast-background EEG or PPR have been linked to markers on chromosome 6p11-12 in this family, suggesting that other chromosome regions are involved. The extent of the pedigree is insufficient to allow for a genome-wide linkage study.

The family included three cousins with photosensitive JME. Clinical information was collected from available medical records. All patients and first-degree relatives were interviewed in accordance with a standardized protocol including questions on myoclonic jerks, provocation of seizures by sleep deprivation and visual stimuli. Subsequently, a family history was also taken from each person in the family, which included all the spouses and their families as well. EEG data were collected from all epilepsy-affected subjects and their first-degree relatives. A new EEG was requested with informed consent and was recorded using a standardized protocol for photic stimulation, unless photosensitivity had already been documented before (Kasteleijn-Nolst Trenite et al., 1999). Affected individuals were classified according to the international classification of epilepsies and epileptic syndromes (1989). The determination of generalized spike and wave discharges associated with the PPR was made according to a simple classification scheme (Waltz et al., 1992), by at least two neurophysiologists who were blind to the clinical status.

Case histories

This report describes three cousins who had JME with PPR on the EEG (figure 1). The index case (III-13) had onset of myoclonic jerks at the age of 18 years, late at night after a visit to a discotheque. Since then, she has had jerks regularly in the evening or at night, while awake. A single, unprovoked, generalized tonic-clonic seizure (GTCS) at the age of 20 resulted in a fall which resulted in a skull fracture and cerebral contusion. She became free of seizures and myoclonic jerks on 900 mg sodium valproate. Right frontal gliosis was demonstrated on her MRI at the age of 23, which was regarded as probably post-traumatic. Her EEG at the age of 23 years showed slowing over the right parietal regions. Intermittent photic stimulation (IPS) provoked a generalized PPR (Waltz IV) at flash frequencies between 20 and 23 Hz (Waltz et al., 1992).

Patient III-8 had onset of myoclonic jerks at the age of 13 years and at the age of 16 she experienced two GTCS without any known provocation. All epileptic seizures occurred on awakening. An EEG at the age of 16 years showed spontaneous generalized epileptiform activity, and a generalized PPR (Waltz IV), accompanied by symmetrical jerks in the shoulders. The diagnosis of photosensitive JME was made.

Patient III-6 had onset of myoclonic jerks on awakening at the age of 14 years. Sometimes the jerks resulted in a fall and once she dropped her child. At the age of 22 years, she had a single GTCS. Her EEG showed right temporal slow-
ing and a generalized PPR (Waltz IV). She too was diagnosed as having photosensitive JME.

The fathers of these three cousins were three brothers from a family with no known seizure history over the preceding two generations. A genealogical survey confirmed that the three mothers were unrelated to each other, but revealed that one of the mothers (II-12) had common ancestors with her husband five generations back. The EEGs of the fathers (II-4, II-6, II-11), recorded at the ages of 40, 46 and 59 years respectively, showed a normal reaction on IPS. All three fathers had an abnormal background EEG, with consisting of an excess of beta activity (14-20 Hz). None of them reported having used benzodiazepines or other medication that might have altered the background EEG. The three mothers' EEGs (II-5, II-7, II-12) were recorded at the ages of 47, 52 and 57 years, respectively. Mother II-5 had spikes and slow waves restricted to the occipital area (Waltz II) at flash frequencies between 22-30 Hz. Mothers II-7 and II-12 had occipitally-localized spike responses in their EEGs (Waltz I) at frequencies of 6-25 Hz, and 18-25 Hz, respectively.

The five siblings of the three affected cousins have been examined. None of the siblings had a seizure history. Two of the five siblings had a PPR in their EEG.

**Discussion**

The three affected cousins and their siblings were related through their three, clinically unaffected fathers (who were brothers), without any seizure history but with fast background EEG in all three of them. The three unrelated mothers of the probands were also unaffected but had an asymptomatic PPR found on subsequent evaluation of the family. We hypothesize that the epilepsy phenotype was brought to expression by the inheritance of a gene or set of genes from the unaffected fathers in combination with a gene or set of genes from their equally unaffected mothers. In previous studies, an autosomal dominant inheritance pattern for photosensitivity has been suggested with age-dependent penetrance (Waltz and Stephani, 2000), but a complex inheritance cannot be excluded (Steinlein 2004). A PPR limited to the occipital regions without clinical representation, suggests that occipital PPR belongs to the same phenotypic spectrum and represents a milder expression of the same genetic trait (Doose and Waltz, 1993).

Photosensitivity as a common epidemiological factor that increases seizure susceptibility or specifies the epilepsy phenotype may often remain undetected or unrecognized. Most photosensitive patients indicate that they consider their jerks during flashes or in sunlight as normal physiological phenomena. Only if the carrier is exposed to appropriate stimuli, or if the trait is accompanied by obvious clinical symptoms might the photosensitivity be detected. Detailed EEG-video recording is usually needed to detect these abnormalities. All three mothers of the IGE-affected subjects had a PPR that was not known about at the time the family was selected, but was only detected when they underwent an EEG examination within the framework of this study.

Photosensitivity appears to be transmitted more often via the maternal than the paternal line (Wolf and Goosses, 1986). The observations in this family are compatible with this, although obviously our family is too small to provide independent evidence for this gender-dependent transmission. A higher frequency of apparent maternal transmission has been demonstrated for a number of types of epilepsy (Ottman et al., 1988, Doose and Neubauer, 2001).

Since a large minority of JME patients is photosensitive and this study suggests a distinct mode of inheritance for photosensitive JME, it may be important to separate the JME phenotype into two subtypes. This may be relevant not only for genetic research, but also from a clinical point of view. First, photosensitive patients may benefit from advice to avoid visual stimuli. Second, the prognosis may be influenced by photosensitivity, since this trait has an age-dependent expression, with maximum expression be-
fore the age of 30 years. Studies of long-term follow up in JME are needed to address the question as to whether JME with and without PPR differ with respect to other clinical features and long term prognosis.

The family history presented here illustrates a number of difficulties faced in evaluating the genetic basis for common complex epilepsy. The JME phenotype in this family was connected through the paternal line, and the PPR was inherited through three independent maternal lineages. The absence of clinical symptoms in the extended paternal and maternal families is compatible with oligogenic inheritance. Furthermore, oligogenic inheritance is illustrated by the biparental segregation in this case: a paternal IGE or JME susceptibility and a maternal PPR susceptibility, apparently both necessary for the clinical expression of disease. Inherited seizure tendencies may not be discovered without extensive and standardized clinical evaluations of the preceding generations. Unrecognized tendencies to have seizures, such as a photosensitive response and other EEG traits, may not be uncovered without appropriate testing, and there may be technical as well as biological reasons as to why these tendencies are not identified. Therefore, we propose to explore and include such traits as endophenotypes in genetic studies of the common idiopathic epilepsies.

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