JUVENILE MYOCLONIC EPILEPSY

Characterisation of the syndrome and examination of linkage to the HLA locus in families from the Western Cape.

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I, Jonathan Ambrose Carr, hereby declare that the work on which this thesis is based on is my original work (except where acknowledgements indicate otherwise) and that neither the whole work or any part of it, is being, or is to be submitted for another degree in this or any other University. I empower the university to reproduce, for the purpose of research, either whole or any portion of the contents in any manner whatsoever.

DEDICATION

This work is dedicated to Barry Pieterse, 1972-1992.

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LIST OF ABBREVIATIONS

AD	Autosomal Dominant
AR	Autosomal Recessive
BFNC	Benign Familial Neonatal Convulsions
CAE	Childhood Absence Epilepsy
CT	Computerised Tomography
EEG	Electroencephalogram
EGMA	Epilepsy with Grand Mal on Awakening
FC	Febrile Convulsion
GABA	γ-amino butyric acid
HLA	Human leukocyte antigen
IGE	Idiopathic generalized epilepsy
IPSP	Inhibitory post-synaptic potential
JAE	Juvenile Absence Epilepsy
JME	Juvenile Myoclonic Epilepsy
MRI	Magnetic Resonance Imaging
MultiSW	Multiple Spike and Wave
NMDA	N-methyl-D-aspartate
NRT	Nucleus Reticularis Thalami
PolySW	Polyspike and wave
PCR	Photo convulsive response
SW	Spike and Wave

1. INTRODUCTION

The publication of the International Classification of Epileptic Seizures in 1969 by the International League Against Epilepsy (Gastaut, 1969) marked the onset of an improved approach to the description and characterisation of seizure types. In particular, it paved the way for a more precise definition of seizures of generalized onset.

Certainly prior to, but particularly since the explosion of clinically applied molecular genetics, the various forms of generalized seizures have attracted attention in terms of their modes of inheritance and in the perception that an underlying genetic defect exists which manifests as the seizure disorder.

The expectation exists that, as in other genetic conditions, a defective gene and its altered protein product will be identified. This has either a putative chromosomal localisation, as in juvenile myoclonic epilepsy, or a definite one, as has been shown to be the case in benign, familial neonatal convulsions.

As in other heterogeneous conditions, for example schizophrenia, a great need for accurate grouping of specific forms of the generalized epilepsies exists: splitting as opposed to lumping. In part, this is important for purely practical reasons, such as the fact that certain forms of generalized seizures have a clearer inheritance pattern or tend to have family members more frequently affected.

In the generalized epilepsies, different genetic defects may manifest as clinical conditions of similar appearance: a need for an accurate, "watertight" description of the individual clinical syndromes is of paramount importance. Gene mapping studies work best when the phenotype can be accurately determined.

2. OVERVIEW OF THE IDIOPATHIC (PRIMARY) GENERALIZED EPILEPSIES (IGE)

2.1 UNDERLYING PATHOGENESIS OF THE SPIKE AND WAVE DISCHARGE

Gloor (1979) in his William Lennox lecture of 1977 described the fundamental pathogenesis of the generalized epilepsies as an abnormal response pattern of cortical neurones to the afferent thalamocortical volleys which are normally involved in the elicitation of spindles. This aberrant response occurs under conditions of diffuse mild cortical hyperexcitability, and results in an increased number of action potentials generated as a result of the afferent input from the thalamus. These findings were based on Gloor's work with penicillin-induced seizures in the cat, in which thalamic structures were stimulated directly with the additional administration of penicillin either systemically or applied topically to the cortex.

Three levels of the central nervous system are involved in the genesis of the discharges (Gloor, 1979):

i) the cortex, which is hyperexcitable

ii) the thalamus, particularly the midline and intralaminar nuclei

iii) the brainstem reticular formation, which allows for facilitation of generalized discharges if its activity is depressed.

This work followed on initial experiments that demonstrated that stimulation of midline structures could produce bilateral spike and wave (SW) discharges.

However, in addition to the three level model described above, electrical stimulation of human frontal cortex, particularly the mesial aspect, may also produce EEG activity indistinguishable from spontaneous SW and attacks which clinically resemble either simple or complex absence. This suggests that subcortical structures are not necessary for the generation of the SW discharge (Bancaud et al., 1974).

The proposals put forward by Gloor have been supported by further animal work in rodents (Snead, 1995), and, in addition, genetic models, including the genetic absence rat, have been identified.

Oscillatory activity in the thalamus, such as that resulting in sleep spindles, is dependant on the intrinsic ability of neurons within the Nucleus Reticularis Thalami (NRT) to impose their oscillatory behaviour on thalamo-cortical circuitry: NRT cells show rhythmic burst firing during periods when the EEG activity is synchronised, whereas during wakefulness, tonic single spike firing is seen. The transition between rhythmic and tonic firing is hypothesised to be mediated by the low-threshold calcium spike (von Krosigk, 1993). This hypothesis is supported by the known effects of antiepileptic agents such as ethosuximide in decreasing low threshold calcium currents in thalamic neurones (Coulter et al., 1990.) The NRT forms a shell surrounding the dorsal thalamus, comprising γ-amino butyric acid (GABA) neurons projecting amongst each other and also to the thalamic relay nuclei. These NRT neurons are stimulated by both thalamocortical and reciprocal cortico-thalamic projections. Furthermore, there is likely to be a network of GABAergic interneurons within the thalamus and also, projection by NRT neurons to a homologous area in the contralateral thalamus. As Snead (1995) states: "The uniqueness of this situation relates to the circuitry of the GABAergic and glutamatergic neurons in the thalamus and cortex rather than the intrinsic ability of the neurons themselves to oscillate. Other neurons in the brain (e.g., those in the hippocampus) also have oscillatory properties, but do not have the same control over consciousness as those cells in the Nucleus Reticularis Thalami. It is probably this basic difference between hippocampal and thalamocortical circuitry and the neurotransmitters involved that accounts for the clinical and pharmacological differences between partial complex and generalized absence seizures".

In SW discharges recorded from thalamus and cortex there is preservation of GABAergic function, with preserved Inhibitory Post Synaptic Potentials (IPSPs) and absence of the paroxysmal depolarising shifts typically seen in focal forms of epilepsy. Preservation of GABAergic inhibition aids in synchronisation of SW discharges because these discharges are dependant on rhythmically recurring inhibition in both cortex and thalamus (Gloor and Fariello, 1988). Administration of GABA-A agonists actually results in enhancement of SW duration (Vergnes and Marescaux, 1994) as is seen in rodents with genetic forms of epilepsy.

However, the inability experimentally to demonstrate a response to GABA-A antagonists has led to consideration for the role of the GABA-B receptor in the pathogenesis of generalized seizures: This receptor is responsible for the mediation of the late, long-lasting potassium dependent IPSP, which activates a low-threshold calcium potential, leading to burst firing and oscillatory behaviour in thalamic neurons (Crunelli and Leresche, 1991).

In addition, glutamate mediated recurrent excitation between thalamus and cortex and vice-versa may be of importance and N-Methyl-D-Aspartate (NMDA) receptor antagonists have been demonstrated to reduce generalized convulsive seizures (Chapman, 1994).

The crucial postsynaptic event required for the occurrence of a generalized seizure is an NMDA-mediated Excitatory Post Synaptic Potential followed by GABA-A/GABA-B mediated inhibition which triggers a low-threshold calcium current in NRT neurons. This low threshold current leads to another depolarisation and the cycle repeats itself.

The calcium current is mediated by GABA-B receptors via slow IPSPs and indirectly by NMDA receptors, since an initial excitation is required to generate the low-threshold calcium current. The overall set point of thalamic and cortical excitability is modulated by ascending cholinergic pathways that project to the thalamus as well as noradrenergic and dopaminergic neurons projecting to the cortical end of the thalamocortical loop where they influence bursting cells in layer V of the cerebral cortex (Snead, 1995).

2.2 NOSOLOGY OF THE SYNDROMES OF IDIOPATHIC GENERALIZED EPILEPSY

There are two main groups of generalized epilepsies:

i) *idiopathic* or *primary* generalized epilepsy with an EEG expression of a generalized, bilateral and synchronous, symmetrical discharge. There is no known or suspected aetiology and it is associated with a possible hereditary predisposition and normal mental development.

ii) generalized epilepsies *secondary* to some underlying process either identified (symptomatic) or unidentified (cryptogenic) (Drury and Henry, 1993; Roger et al., 1985).

As defined by the Commission on Classification and Terminology (1989), idiopathic generalized epilepsies (IGE) are forms of generalized epilepsies in which all seizures are initially generalized, with an EEG expression that is a generalized, bilateral, synchronous and symmetrical discharge (such as is described in the seizure classification of the corresponding type). The patient has a normal interictal state, without neurologic or neuroradiologic signs. In general, interictal EEGs show normal background activity and generalized discharges, such as spikes, polyspikes, spike-waves (SWs), and polySWs $\geq$ 3 Hz. The discharges are increased by slow sleep. The various syndromes of idiopathic generalized epilepsies differ mainly in age of onset.

Many patients with epilepsy have more than one type of seizure and the expression of clinical seizures may be modified by factors such as age, menstruation, and the administration of anticonvulsant drugs (Delgado-Escueta and Greenberg, 1984). The IGEs are thus also known also as the "idiopathic age-related epilepsies" and include the following seizure types: absence, myoclonus, clonic, tonic, and tonic-clonic seizures (Dreifuss, 1989).

However, according to Roger's interpretation in 1994 of the International Classification (Commission, 1989), only three types of seizures are found in the IGEs: absences, massive myoclonias (myoclonic jerks) and generalized tonic-clonic convulsions.

2.3 DESCRIPTION OF THE INDIVIDUAL SEIZURE TYPES

Absence is the best characterised in terms of pathogenesis, clinical description and nosology and will be discussed in greatest detail.

2.3.1 ABSENCE

A generalized absence seizure is defined as a paroxysmal loss of consciousness of abrupt and sudden onset and offset which is associated with bursts of bilateral synchronous SW discharge recorded on the EEG. Absence seizures are characterised by the lack of both an aura and a postictal state (Snead, 1995).

The classic interictal EEG of absence seizures consists of a normal background activity on which are superimposed bilateral, symmetrical and synchronous 3 Hz SW discharges, usually of maximal amplitude in the frontal regions.

The generalized SW discharges begin abruptly at 3.5 Hz, gradually slowing to 2.5-3 Hz (Drury and Henry, 1993). As the burst progresses the spike discharges may become lower in amplitude. The discharges are readily provoked by hyperventilation and hypoglycaemia. Hyperventilation is the easiest way in which to evoke an absence seizure, and the diagnosis should be questioned if an untreated patient does not have an absence during hyperventilation (Roger, 1994) The distinction between ictal and interictal activity may be a measure of the duration of the discharge: discharges which last longer than 3 seconds have a readily recognised clinical accompaniment with an arrest of movement, frequently with a vacant appearance to the eyes. Of seizures lasting longer than 7 seconds, 50% will have an automatism (Penry et al., 1975). Absence seizures are frequently associated with minor motor activity with alteration in tone, clonic activity, and with autonomic phenomena, or a combination of these features.

Absence seizures may also occur with other types of discharges, such as a 4-6 Hz SW pattern, generalized atypical SW bursts, and with either slow SW activity (Gomez and Westmoreland, 1987) or with generalized paroxysmal fast activity (Drury and Henry, 1993).

Most patients with absence seizures have IGE, but absence seizures are also described in secondary generalized epilepsies, in which case there are usually associated tonic and atonic seizures or bilateral myoclonus. On examination, such patients (Merlis, 1970) may

have focal signs, cognitive impairment, and evidence for an acquired aetiology. The EEG has a slow background and the SW discharges are of a frequency of 2 Hz or less.

Absences symptomatic of other disorders are described in subacute sclerosing panencephalitis, in which they have a frequency of 2.5 Hz with periods of desynchronization (Ishikawa et al., 1981). They are also seen in lysosomal storage diseases (Andermann, 1967) and, in particular, a case of Batten's disease has been described with this pattern, indicating that a 3 Hz SW pattern may occur as a manifestation of diffuse neuronal disease. Metabolic encephalopathies such as renal failure (Berkovic et al., 1987), hypoglycaemia and metrizamide use (Pritchard and O' Neal, 1984) may cause absence seizures, although in the case of the latter, a slow 2 Hz sharp and slow wave pattern was noted.

In terms of focal cerebral lesions giving rise to absence seizures (Figure 1), diencephalic lesions have been reported to cause absence seizures and generalized SW discharges (Scherman and Abraham, 1963). However, this report was based on pneumoencephalography with no histological confirmation and there has been no further substantiation of this in the literature.

As noted previously (Bancaud et al., 1974) a particular problem is that of absences associated with frontal damage with bilateral synchronous epileptic discharges, in which case it may be impossible to ascertain the nature of the seizure type, whether focal or generalized.

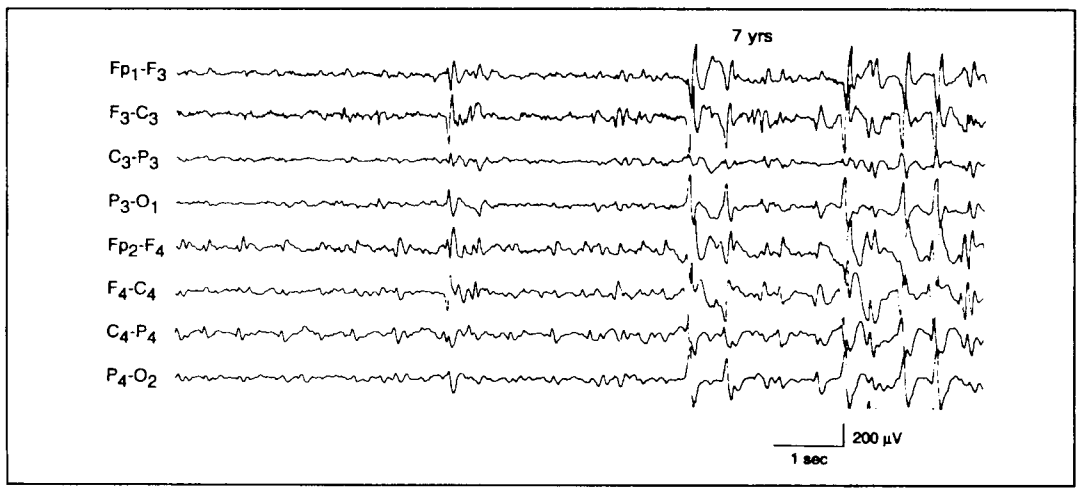

Figure 1: Right frontal-central spikes leading to bisynchronous discharges in a patient with right hemisphere pachygyria (Blume, 1994).

However, the seizures may be atypical, both clinically and electroencephalographically. As Gloor et al. (1976) state: "More frequently, the spike and wave complexes are somewhat irregular in shape, with a frequency of 2-2.5 Hz but little evidence of lateralization. The multiple spike burst pattern likewise often showed little or no hint of lateralization.... The differentiation from true generalized corticoreticular epilepsy is made more difficult in some of these patients, however, by the presence of brief attacks similar in appearance to true petit mal absences... Most patients with secondary bilateral synchrony have frontal epileptogenic lesions. Rarely, a pattern of secondary bilateral synchrony in the EEG is associated with unilateral temporal or parietooccipital epileptogenic lesions and with clinical attacks appropriate to those sites of origin".

The differential diagnosis of absence seizures includes daydreaming and brief complex partial seizures of temporal and frontal lobe origin. Complex partial seizures are usually distinguished on the basis of their longer duration, the presence of complex automatisms and postictal confusion. The interictal EEG may demonstrate a focal abnormality, but recording of the seizure itself may be required (Berkovic et al., 1987). Interestingly, the existence of unilateral central SWs does not necessarily exclude absence, since there is a link between childhood absence and benign epilepsy of childhood with centro-temporal (rolandic) focus (Loiseau, 1985) and similarly, children with petit mal absences and 3 Hz SW may develop spikes over the central areas after appropriate treatment (Niedermeyer, 1981).

2.3.2 MYOCLONUS

Myoclonic seizures may either occur alone or may precede generalized tonic-clonic seizures, typically with high amplitude, 10-15 Hz spikes with or without slow waves on EEG. More specifically, in Juvenile Myoclonic Epilepsy (JME), the EEG during myoclonic jerks may show similar discharges sometimes preceded by diffuse irregular 2-5 Hz SW complexes and followed by irregular 1-3 Hz slow waves (Delgado-Escueta and Enrile-Bacsal, 1984).

Clinically, a myoclonic seizure consists typically of a sudden or shock-like movement of the body, commonly of the upper extremities, which may be symmetrical in its distribution. Myoclonic seizures occur singly or repetitively in a bilaterally synchronous manner and correspond to a burst of generalized bilaterally synchronous, symmetrical, single- or multi-SW complexes at 3-5 Hz lasting $\leq$4 seconds with the jerks appearing rhythmically at the

same frequency, with maintained consciousness (Oguni et al., 1994). Myoclonic jerks are always associated with SW complexes, but the converse is not true. The amplitude of the SW discharge is greater in the event of being associated with myoclonic jerks.

Both real and perceived asymmetry occur, making the incorrect diagnosis of a partial epilepsy possible. Falling is likely to be due to a shift in the centre of gravity associated with immobilisation of the legs, related to the phenomenon of post-myoclonic inhibition (Oguni et al., 1994). In addition, although typically myoclonic jerks are said to involve arms and shoulders (Janz, 1985), video studies have shown that involvement of the hands and forearms was most frequent (Oguni et al., 1994).

2.3.3 GENERALIZED TONIC-CLONIC SEIZURES

In some forms of IGE with generalized tonic-clonic seizures, the resting record is normal , whereas others show bursts of generalized 3-Hz SW, irregular polySW or bursts of frontal intermittent rhythmic delta (Drury and Henry, 1993). Immediately before the tonic phase of the seizure, there may be pre-ictal bursts of generalized polySW activity associated with bilateral massive myoclonus. The seizure will usually commence with a build-up of generalized low-voltage fast activity, which develops into a high amplitude polySW discharge. The brief periods of muscular relaxation responsible for the jerking appearance of the clonic phase of the seizure are associated with generalized EEG suppression (Engel, 1989).

2.4 THE SYNDROMES OF IDIOPATHIC GENERALIZED EPILEPSY (Roger et al., 1985; Commission, 1989).

2.4.1 CHILDHOOD ABSENCE EPILEPSY (CAE) (pyknoleptic petit mal)

This typically has its onset between 4 and 8 years with greater involvement of the female sex. The absences are brief and frequent, from 10 to 200 daily. Absences may be simple, or associated with mild clonic, tonic, atonic, automatic or autonomic phenomena (Drury and Dreifuss, 1985), but myoclonic absences should not be present (Loiseau, 1985).

The EEG shows regular, bilaterally synchronous 3 Hz SW discharges during absence attacks, although regular 4 Hz and 2 Hz irregular SW may also be recorded with absence and do not differ clinically (Penry et al., 1975). Interictal paroxysmal activity, consisting of single or brief discharges of bilateral SWs are frequent (Loiseau, 1985). In some children, a posterior 3 Hz sinusoidal delta rhythm is seen posteriorly in the interictal state.

The prognosis is favourable and the attacks are suppressed in 80% of cases with ethosuximide or valproate (Drury and Dreifuss, 1985). Most patients have a remission of seizures with the onset of puberty and persistence into adulthood is uncommon. However, the longer the follow-up, the smaller is the percentage of patients who remain controlled (Loiseau, 1985), typically because of the occurrence of tonic-clonic seizures, which may occur many years after the cessation of absence seizures. Tonic-clonic seizures will ultimately develop in about 40% of patients (Loiseau, 1985), usually 5-10 years after the onset of absence. Delgado-Escueta and Greenberg (1984) report that in 14% of patients the illness commences with both petit mal and tonic-clonic seizures. The later the onset of the absence seizures, the more likely it is that generalized tonic-clonic seizures will develop (Charlton and Yahr, 1967), although in this study, about 30% of the cases had mental retardation and the age difference was slight, in that those with onset at age 5-6 did not have GTCS, whereas children of 7-8 would. The usual sex distribution is reversed, boys being more likely to develop tonic-clonic seizures. In 6% of cases absence seizures will persist into adulthood, generally infrequently and of relatively minor significance to the patient (Loiseau, 1985).

The differential diagnosis of CAE includes:

i) juvenile absence.

ii) epilepsy with myoclonic absences.

iii) absence seizures occurring in patients with focal brain injury: *generalized* epilepsies secondary to a neurological disorder.

iv) eyelid myoclonia with absences: photosensitive patients with rhythmic eyelid myoclonias and sursumvergence, of onset between 2 and 5 years and sometimes with self-induction.

v) perioral myoclonia with absences (Panayiotopoulos, 1994b).

2.4.2 JUVENILE ABSENCE EPILEPSY (JAE)

This has an equal sex distribution, starting around puberty; and the absences do not differ clinically from those of CAE, excepting that absences with retropulsive movements are less common. The frequency of absence attacks is low, it being unusual for the attacks to occur daily, and they are sporadic in character and may present predominantly on awakening (Wolf, 1985a).

The majority of patients also have generalized tonic-clonic seizures, although this may represent an ascertainment bias, in that patients who only have absence will not present since they are not bothered by the seizures (Wolf, 1985a). Approximately 10% of both childhood and juvenile absence patients are reported to have myoclonic seizures of JME type, and varying subtypes are discussed below.

The background of the EEG is normal, and the characteristic epileptic feature is a generalized symmetric SW discharge with frontal accentuation, the EEG manifestations being similar to CAE (Drury and Henry, 1993). However, the SW frequency is usually 3.5-4 Hz and the first complex of a group is usually faster with the frequency thus somewhat faster than in CAE (Janz et al., 1992). The slow wave is often preceded by two or three spikes. The SW discharge is easily precipitated by sleep withdrawal and hyperventilation.

The response to treatment is usually good, despite the presence of GTCS, which is usually a negative prognostic factor (Wolf, 1985a).

Delgado-Escueta et al. (1983) distinguish several other forms of absence, which start during later childhood and adolescence and which may represent phenocopies or a different

genetic basis. The frequency of attacks in these forms is relatively low, but parents are said "almost always" to have tonic-clonic seizures.

These forms of absence include:

i) classic absence.

ii) absence with 8 to 12 Hz rhythms, identical to classic absence as far as the clinical manifestations of the attacks are concerned, but the condition starts later in childhood and adolescence, shows 8-12 Hz rhythms during attacks, is frequently associated with tonic-clonic convulsions, and persists into adulthood.

iii) *myoclonus* absence: this is associated with 8 to 12 Hz rhythms and consists of short attacks of unconsciousness of 8-10 seconds, with stereotyped automatisms and asymmetrical myoclonus.

iv) a separate syndrome of *myoclonic* absence of childhood and adolescence has symmetrical myoclonic jerks of limbs and trunk associated with diffuse 3 to 6 Hz multi-SW complexes and myoclonic activity which is more pronounced than that seen in classic absence.

2.4.3 JUVENILE MYOCLONIC EPILEPSY

This syndrome was initially described by Janz and Christian (1994). The sex ratio is about equal and onset is between 12 and 18 years. The cardinal features are myoclonic seizures and tonic-clonic seizures, both of which are frequent in the morning. The tonic-clonic seizures may be preceded by a crescendo of myoclonic jerks, and both seizure types may be exacerbated by early wakening and sleep deprivation. Absences, although not prominent, are seen in 10 to 37% of cases (Berkovic et al., 1987).

There are reportedly two subvarieties of generalized convulsion in JME (Delgado-Escueta and Enrile-Bacsal, 1984):

i) Clonic-tonic-clonic seizures: these typically occur on awakening, and are triggered by sleep deprivation, fatigue or alcohol. The interictal EEG is that of diffuse 4 to 6 Hz multi-SW complexes. Diffuse 4 to 6 Hz multi-SW complexes also appear during the initial clonic phase and precede the rhythmic 16 to 18 Hz fast spikes and the tonic contractions. Multi-SW complexes appear again during the last clonic phase. The EEG trait persists and most relapse on withdrawal of treatment. This entity

corresponds to a period of increasing myoclonic jerks ending in a GTCS (Reutens and Berkovic, 1995).

ii) Tonic-clonic seizures, whose interictal EEG traits are the well formed diffuse 3 Hz SW and multi-SW complexes. During the ictus, epileptic recruiting patterns of 9-12 Hz diffuse rhythms herald the tonic phase. Infrequently, these seizures appear only as nocturnal tonic-clonic seizures, characteristically triggered by stage 1 sleep. The remission rate is better than the previous group, since only 8-20% will relapse after drug withdrawal.

The background of the EEG in JME is usually normal and the pathognomonic type of discharge is the polySW complex. The number of spikes varies between 5 and 20, and is reported to correlate with the intensity of the clinical seizures (Janz and Christian, 1994). PolySW discharges noted interictally typically have a slow wave preceded by no more that two or three spikes.

Discharges of 3 Hz are typical in the absences which form part of the syndrome of JME (Janz, 1985; Asconape and Penry, 1984; Delgado-Escueta and Enrile-Bacsal, 1984).

The syndrome is, in general, responsive to valproate (VPA), whereas breakthrough seizures are common with phenytoin, carbamazepine and the barbiturates. In addition, the EEG trait and the tendency to have seizures if untreated, are probably life-long (Delgado-Escueta and Enrile-Bacsal, 1984).

2.4.4 OTHER IDIOPATHIC GENERALISED EPILEPSIES

In addition to these three syndromes, the following are described (Wolf, 1985c):

Epilepsy with Grand Mal on Awakening (EGMA)

This condition manifests with generalized tonic-clonic seizures, predominantly (over 90%) shortly after awakening. The onset is mostly in the second decade. Other seizure types may occur, mostly absences or myoclonic seizures. The seizures may be precipitated by sleep withdrawal. However, recently the syndrome is becoming discounted, since pure manifestations of this disorder without absences or myoclonic jerks are very rare and many of the patients will go on to develop JME (Janz et al., 1992).

These patients have generalized 3 Hz or more rapid SW discharges on EEG but no evidence of absence seizures or myoclonic jerks (Drury and Henry, 1993).

Grand Mal epilepsies/ Generalized Tonic Clonic Seizures (GTCS)

Grand mal epilepsies are considered pure when they are not associated with absence, myoclonus or other forms of epilepsy. Four to ten percent of all epileptic patients have pure grand mal as the only type of attack (Delgado-Escueta et al., 1983). Roger et al. (1994), referring to GTCS, comment that the international classification does not explicitly cite this as a category of the epilepsies, although GTCS does fulfil the criteria of the IGEs. In their experience, a large number of patients experience only infrequent GTCS, sometimes after a febrile convulsion, of variable onset ranging from early childhood to adulthood. There is no clear relationship between the timing of the seizures and the sleep wake cycle, and interictal changes are represented by generalized SW discharges.

2.4.5 PHOTOSENSITIVE EPILEPSIES (Jeavons, 1985)

Photosensitivity is genetically determined, commoner in females and usually manifests around puberty, with a median age of onset of 14 years. Approximately 5% of epileptic patients are found to be photosensitive. The diagnosis depends on the evocation by intermittent photic stimulation of a photoconvulsive response (PCR), which is typically a generalized SW or polySW pattern and is stable and repeatable. If myoclonic jerking is associated with the PCR it is highly probable that the patient has epilepsy. Seizures are usually GTCS, less commonly absence or myoclonic jerks.

Jeavons (1985) defines 6 groups:

i) Pure photosensitive epilepsy (TV or reflex epilepsy). In this group, patients only have seizures induced by flickering light. Seizures are mostly GTCS (84%), with absence in 6% and myoclonus in 1.5%.

ii) Epilepsy with photosensitivity: Spontaneous seizures may occur, either with or without photic stimulation.

iii) Eyelid myoclonia with absences: marked jerking of the eyelids with sursumvergence is noted (mentioned above in discussion of CAE).

iv) Self-induced epilepsy.

v) Pattern sensitive epilepsy.

vi) Laboratory induced seizures only.

Photosensitivity could be considered to be a syndrome on its own, and certainly, the prevalence is greater in families with this phenomenon than in the general population, but there is also a prominent overlap between it and other syndromes, particularly JME (Kasteleijn-Nolst Trenite et al., 1994). There is a general decline in photosensitivity after the age of 25 years.

2.5 OVERVIEW OF THE IDIOPATHIC GENERALISED EPILEPSY SYNDROMES

Janz (1985) comments that there is considerable overlap between JME and the other two syndromes of generalized epilepsy which manifest at adolescence, JAE and EGMA. The former is similar to JME, both in the high percentage of major seizures on awakening (82%) and in that myoclonic jerks may occur in 15% of patients with EGMA. Furthermore, it is not possible to differentiate JME and JAE on the basis of the EEG alone, although photosensitivity is somewhat less common in the latter.

Wolf (1985a), in discussing the nosology of the syndromes of the IGEs, points out that the various syndromes have

2.6 BORDERLINE SYNDROMES WITH ABSENCE

In this group, Berkovic et al. (1987) include the conditions of:

i) Intermediate petit mal and idiopathic myoclonic astatic epilepsy of childhood (syndrome of Doose). Intermediate petit mal is a condition of absence seizures which is clinically similar to childhood absence, but is associated with atypical SWs: these are irregular, with a frequency of less than 2.5 Hz and are asymmetrical. The condition is seen mostly in males with a history of brain damage and drug resistance, commencing at an early age.

   Doose syndrome is characterised by an interictal EEG with a theta background and frontal bursts of polySW activity. Myoclonic jerks may be prominent or may be a minor symptom amongst daily convulsive seizures, and some patients are mentally retarded. The disorder begins usually between the age of 2 and 5 years and, although classified as a generalized cryptogenic or symptomatic epilepsy, there may be a large subgroup with an idiopathic epilepsy or IGE (Guerrini et al., 1994).

ii) Epilepsy with myoclonic absences: this rare condition usually has its onset at the age of 7 years, has a male preponderance, and is noteworthy for the feature of mental deterioration. The seizures consist of absences with prominent myoclonus or clonic jerks, frequently associated with tonic contractions. The ictal EEG displays a typical 3 Hz pattern which may be precipitated by hyperventilation.

Drury and Henry (1993) comment that both epilepsy with myoclonic absences and the syndrome of Doose represent forms of symptomatic generalized epilepsy beginning in the latter half of the first decade in children who evolve to look like patients with Lennox-Gastaut syndrome.

Berkovic (1987), commenting on the above syndromes, notes that some patients with absences have features of both primary and secondary generalized epilepsy. Moreover, he feels that the entity of the borderline syndromes is an indication of the weakness of the syndromic approach, "as a heterogeneous group of unclassifiable cases are coerced into a nosological category with little diagnostic, therapeutic, or prognostic relevance."

The concept of "normal brain with good prognosis", which serves as a standard model for the IGEs, as has been discussed above, is not a perfect model:

i) The examination of brains in patients with IGE have revealed changes, known as microdysgenesis, which include an increase in cell density in the stratum moleculare, protrusion of nerve cells beneath the pia, an abnormal columnar arrangement of cortical neurons, and an increase in white matter neurons (Meenke and Janz, 1984). These findings, however, are disputed (Lyon and Gastaut, 1985) and may represent normality.

ii) The prognosis of CAE, as noted above, is unclear, and JME may well be a life-long condition, requiring life-long treatment.

The generalized epilepsies may represent a spectrum: one extreme may be that of a pure IGE, with the aetiology being a genetic disturbance, expressed in a specific EEG discharge. The other end of the spectrum is secondarily generalized epilepsy, where there is diffuse grey matter disease, usually due to acquired factors. A large group may lie between these two extremes, with features of both types. Thus, the self-evident problem with the syndromic classification is that not all patients are classifiable.

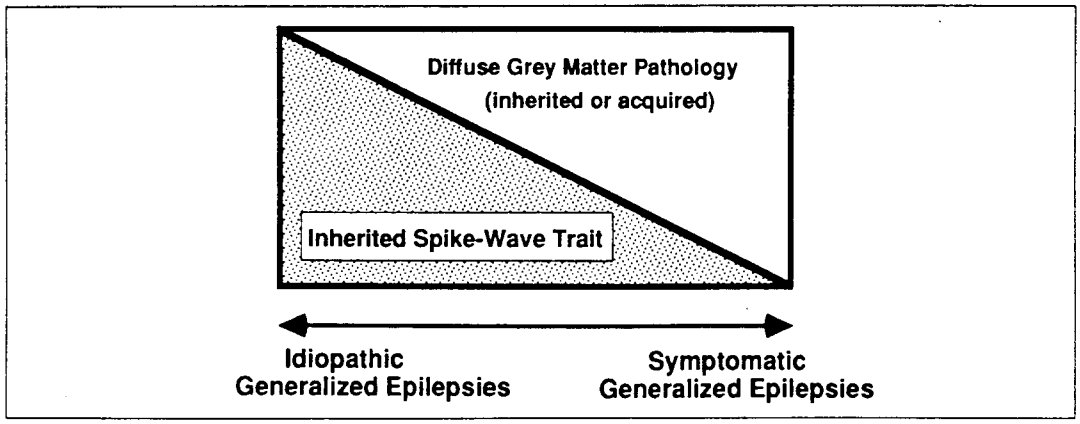

Figure 2. Spectrum of the idiopathic and symptomatic generalized epilepsies (Berkovic et al., 1987).

3 THE STUDY

3.1 AIMS

The primary purpose of this study was the identification of patients with JME, in order to identify suitable families for studying the nature of the linkage of the syndrome of JME to the HLA (Human Leukocyte Antigen) locus. This search for suitable candidate families necessitated examination of a large number of individuals with a range of IGE syndromes, and patients were classified into these various syndromes. Patients with JME were thereafter investigated further.

The study could thus be broken up into three sections:

i) Determination of the various syndromes of IGE.

ii) Characterisation of JME.

iii) Linkage Studies on JME patients.

3.2 METHODS

3.2.1 DETERMINATION OF THE VARIOUS SYNDROMES OF IGE

The initial aim of the study was to identify patients with IGE syndromes. Once identified as such, the patients were classified as to the particular syndrome.

EEGs and their request forms from 1986 to 1991 were reviewed for all studies performed at Groote Schuur Hospital. This is a large teaching hospital in the Western Cape Province of South Africa. The hospital serves a wide population base and is a referral centre for patients from the adjoining Northern and Eastern Cape provinces. Patients who were referred from outlying hospitals exclusively for the EEG service and who were not seen in consultation subsequently were not included in the study. The hospital does serve a paediatric population, but is not the major children's hospital in the region.

The EEG records are standard 20 minute 16 channel recordings incorporating hyperventilation and photic stimulation. From 1988 the Mayo clinic system of classification has been utilised to classify the EEG abnormalities (Mayo Clinic and Mayo Foundation, 1981).

3.2.1.1 Inclusion Criteria

Seizure Manifestations

Patients were included in the study if their seizure manifestations included generalized tonic-clonic convulsions, absence seizures or myoclonus.

Age

Patients were included in the study if subsequent review of the patient record or information derived at interview indicated that seizure onset fell between the age of 9 and 30 years. These age cut-offs were used based on the descriptions of the individual syndromes by Wolf, (1985a, b, c, d) who reports the age of onset for the various syndromes as follows:

i) JAE from 10 to 17 years.

ii) JME from 8 to 26 years.

iii) EGMA from 9 to 24 years.

It should be noted that these age criteria were applied to all the various seizure manifestations of JME, namely absence, myoclonic jerks and tonic-clonic seizures. Specifically, patients were rejected from the study if their absence seizures occurred prior to the age of 9 years.

EEG criteria

Patients were included if the following EEG patterns were found:

i) 3 Hz spike and wave.

ii) Atypical spike and wave.

iii) Polyspike and wave.

iv) Photoparoxysmal responses.

These records were reported as dysrhythmia grade 3 generalised, 3 Hz SW, atypical SW or polySW and as dysrhythmia grade 3 photoparoxysmal response, under the Mayo clinic system of classification. Typically, the background was normal, but records with a mild excess of theta transients or sporadic delta transients were included. Patients reported as having fragmentary frontally predominant SW bursts or isolated bilateral SW bursts were included, provided there was not persistent asymmetry.

The photoparoxysmal response is defined as a SW or multiple SW response to intermittent photic stimulation, which is bilaterally synchronous, symmetrical and generalized and which may outlast the stimulus by a few seconds (Takahashi T, 1993).

All medical records of the patients who had an IGE type EEG pattern and initially complied with the age requirements were then studied further.

Review of the medical record provided the following information:

i) Confirmation that the age and EEG inclusion criteria were met and that the patient had an IGE syndrome.

ii) Ascertainment of the particular syndrome type.

iii) Investigation of the characteristics of those patients with JME.

iv) Assessment of suitable candidate families for a genetic linkage study of JME.

3.2.1.2 Exclusion Criteria

The following groups were excluded following initial review:

i) Patients with mental retardation or clinically relevant evidence of structural brain disorder.

ii) Degenerative disease.

iii) Clinically relevant abnormality on CT scan (if performed).

These exclusion criteria were used since the syndromes of IGE occur in the setting of normal mental and physical development. Degenerative disease may manifest with a SW or polySW pattern, but in association with progressive neurological degeneration.

3.2.2 ASSIGNMENT OF PATIENTS TO A PARTICULAR SYNDROME

3.2.2.1 Guidelines for assignment

The patients were placed into syndromes according to Wolf (1985a, b, c and d: Table 1). The following guidelines were used in ascertaining and classifying the seizure type:

i) All patients with childhood absence were excluded. JAE, with which childhood absence may be confused, has a low seizure frequency and a later age of onset, childhood absence occurring typically between the age of 4 and 8 years. In addition, childhood absence predominantly has absence seizures as its only manifestation (Drury and Dreifuss, 1985).

ii) All patients who had myoclonus were grouped under the category of JME. This has bearing on the overlap between JME, JAE and EGMA, since the latter two categories may have other seizure types, including absences and myoclonic seizures. Patients who had myoclonus as their *sole* seizure type were included in the JME group, provided progressive forms of myoclonic epilepsy had been excluded.

iii) A large group of patients with generalized tonic-clonic seizures without reported absence, myoclonic seizures or a predominantly awakening onset of seizures was found and this is referred to as the pure generalized tonic-clonic seizure group (GTCS). This is not listed in the Classification of Epilepsies and Epileptic

Syndromes (1989), but is included amongst the syndromes of IGE by Drury and Henry (1993), and has been described by Delgado-Escueta et al. (1990).

iv) Other groups included patients with photic types of epilepsy, either on the basis of a pure GTCS type with a photoparoxysmal response or because of a GTCS type which on history was exclusively induced by photic stimulation.

Table 1. Assignment of patients to syndromes according to Wolf (1985a, b, c and d). A plus (+) denotes presence of the seizure type. A minus (-) denotes that the seizure type is not present.

Syndrome	Absence	Tonic-Clonic	Myoclonic	Awakening GM	Age of Onset (years)	Photic response
JAE	+	+	-	-	9-30	+
JME	+	+	+	+	9-30	+
EGMA	-	+	-	+	9-30	+
GTCS	-	+	-	-	9-30	-
PHOTIC	+	+	-	-	9-30	+

3.2.2.2 Mode of assignment

The medical record and prior EEGs were examined in all cases.

Personal interview was possible or was required to establish the type of syndrome in 45% of cases. In 33% of cases a telephonic interview was sufficient; the usual reason for telephonic interview being that the patient no longer attended the hospital and was no longer living in the local area. In the other 22% of cases, the medical record only was used: of this group, 35 patients (15% of the total number of cases) were excluded for further classification on the basis of insufficient data, predominantly because they were lost to follow-up. In the remainder, the information obtained from the medical record was judged adequate by itself to classify the IGE syndrome, this group representing 7% of the patients.

3.2.3 CHARACTERISATION OF JME

For the purpose of examining the specific characteristics of JME, new patients presenting with JME after 1991 were included, as were JME patients referred from sources other than the Groote Schuur EEG laboratory. These sources included the Neurology Outpatient Department and neurologists working outside the hospital setting.

Patients were interviewed and the record reviewed regarding:

i) Demographics

ii) Presence of specific seizure types

iii) Mode of onset (myoclonus, absence or GTCS)

iv) Precipitants: awakening, sleep deprivation, menses

v) Family history

vi) Drug profile

vii) Follow-up

viii) Nature of the EEG disturbance

ix) Radiology

3.2.4 LINKAGE STUDIES

The families of patients who were found to have JME from the 1986-1991 EEG source and patients referred with JME from other sources were reviewed as to their suitability for genetic studies. Families were considered suitable for inclusion if a first degree relative was affected with an IGE.

Informed consent was obtained from families participating in the linkage analysis and the project was approved by the Ethics and Research Committee of the University of Cape Town.

Family members were considered affected if they had any of the syndromes described in the section on syndromes of IGE: JAE, JME, EGMA and GTCS. In the families used for linkage analysis the only seizure types found were JME and GTCS.

EEGs from non-affected family members were only examined to a limited degree and clinically non-affected family members were assumed not to have the condition. Specifically, attention was not paid to the existence of sub-clinical "electrical traits" in non-affected family members.

If a family member had a seizure disorder with either myoclonic jerks, absence or tonic-clonic seizures, they were considered to be affected, even if the EEG was normal.

Blood samples were taken for HLA typing at the Western Province Laboratory for Tissue Immunology. The results were subsequently analysed using the LIPED program of J Ott (1974) and expressed as the log of the odds (lod score) at various recombination fractions.

4 RESULTS

4.1 EXCLUSION OF PATIENTS

A total of 14 119 EEGs were reviewed from January 1986 to December 1991. From the six year period, 221 patients had records which fell into the category of a IGE type of record, as defined above and occurring in patients over the age of 9 years at the time of the recording.

On review of the criteria for age, the EEG criteria and the criteria for making a diagnosis of IGE (see methods), certain groups of patients were excluded:

i) After initial review of the medical record, 41 cases were not included on the basis of their seizures commencing before the age of 9 or after the age of 30 years. This information was not available from the initial EEG request form. Four patients were rejected for being too old: they were 37, 44, 47 and 50 years of age at the time of onset of their seizure disorder. For the group whose seizures had started prior to 9 years of age, an average time of 18.25 years had elapsed, from the onset of seizures, at the time of the EEG recording.

ii) In total, 20 patients with appropriate EEG criteria were excluded because of the presence of a documented neurological deficit, some with onset prior to the age of 9 years. These patients represent a group of secondarily generalized epilepsies, and included the following conditions:

Mental retardation (4 patients), meningitis, microcephaly and kernicterus

Neurocysticercosis(2 patients) and non specified granulomas (2 patients)

Neurofibromatosis

Noonan's syndrome

Holt-oram syndrome

Hydrocephalus

Alexander's Disease

Mitochondrial cytopathy

Hypothalamic tumour

Gluconeogenesis defect

Cerebral Anoxia.

iii) Three patients were identified who had a progressive myoclonic epilepsy (PME) syndrome, presenting in adolescence with tonic-clonic seizures and myoclonic jerks, and initially considered to be JME. These patients all belonged to a single family and the condition is considered to be of autosomal dominant inheritance. It is likely that this represents a form of idiopathic generalized epileptic myoclonus as described by Hallett (1985).

iv) 35 patients were lost to follow-up or had insufficient data to make a diagnosis.

v) 6 patients were felt to be unclassifiable despite having the same degree of information available as the cases in which a syndromic diagnosis could usually be made. These cases included predominantly mixed seizure types and in addition to having an EEG or EEGs with a typical IGE pattern, also had seizures of partial type on history or focal EEG abnormalities.

4.2 SYNDROMES OF IDIOPATHIC GENERALISED EPILEPSY IN THE STUDY GROUP

A total of 113 patients could be identified as having an IGE syndrome or seizure type (Table 2). The mean age of onset for JAE was 13.7 years (range of 9 to 20 years), whilst that for GTCS was 16.1 years (range of 10 to 26 years). The mean age of onset for JME was 14.1 years.

Table 2. The occurrence of various IGE syndromes in the 113 patients.

SYNDROME	Number of patients	Percentage occurrence
Juvenile Absence Epilepsy	28	25%
Juvenile Myoclonic Epilepsy	43	38%
Generalized Tonic-Clonic Seizure	34	30%
EGMA	0	0%
Photic Epilepsy	8	7%

Nine patients with GTCS were known to be in remission for an average of 4.4 years (a range of 1 to 9 years). Three patients with JAE were known to be in remission, for an average of 2.3 years and 3 had a photo convulsive response on EEG.

4.3 CHARACTERISATION OF JME

In addition to the 43 patients identified in the initial EEG record review, a further 13 patients with JME were identified. Thirty-eight of the patients had the diagnosis made by the author or by Dr J R Reid, Senior Neurology Registrar, Groote Schuur Hospital.

The mean time to diagnosis was 6.5 years, with a range from 2 months to 25 years.

4.3.1 DEMOGRAPHICS

Of the total of 56 patients, 42 were of mixed ancestry, 7 were South African Negroes and 7 were of Caucasian origin. The ratio of affected males to females was 0.65. The mean age of onset was 14.1 years for the first seizure type

Table 3. Demographics of JME patients in the study group

Race	Male	Female
Mixed Ancestry	14	27
SA Negro	5	3
Caucasian	3	4
Total	22	34

4.3.2 PRESENCE OF SPECIFIC SEIZURE TYPES

All patients had myoclonus, 34% had absence seizures and 93% had tonic-clonic seizures. Twenty-two of the patients had myoclonic jerks immediately preceding a GTCS. The percentage occurrence of a combination of different seizure types was as follows:

GTCS combined with Myoclonus:	34 (60.7 %)
GTCS combined with Myoclonus and Absence:	18 (32.1 %)
Myoclonus and Absence combined:	2 (3.6%)
Myoclonus only	2 (3.6%)

4.3.3 MODE OF ONSET OF THE SEIZURE MANIFESTATIONS

Ten patients displayed myoclonic jerks followed by GTCS, whilst seven had GTCS followed by myoclonic jerks. The onset of seizures in eight patients was characterised by the simultaneous occurrence of myoclonic jerks and GTCS.

One of the patients had only a single GTCS up to the time of interview and one had suffered only two GTCS convulsions. GTCS did not occur in four patients, and in an additional patient GTCS occurred rarely.

In two patients initial absence seizures were followed by GTCS and subsequently by myoclonic jerks; one patient had absence followed by myoclonic jerks, and two had only myoclonus and no other manifestations.

4.3.4 PRECIPITANTS OF SEIZURE ACTIVITY

In the majority of patients, myoclonic jerks were noted on waking or shortly afterwards, and both GTCS and myoclonic jerks were worsened by sleep deprivation.

Table 4. Precipitants of seizure activity.

Precipitant	Patients (percentage)	Information unavailable
Arousal	40 (75%)	3 patients
Sleep deprivation	33 (67%)	7 patients
Menses	12 (41%)	5 patients

4.3.5 FAMILY HISTORY

There was a family history of an affected relative having seizures in 46% of the patients. Fifteen patients (26% of the total) had an affected sibling or parent, whilst 11 patients (20% of the total) had either aunt or uncle or cousin affected.

4.3.6 DRUG PROFILE

Information was available in 44 of the 56 patients, of whom 42 had improved control with sodium valproate or valproic acid, with or without combination therapy and 2 did not.

Forty-one patients were treated with valproate at a mean dose of 1060 mg daily, varying from 400 to 2200 mg daily in divided doses (sodium valproate and valproic acid were treated as equivalent for this purpose). Fourteen patients were controlled on these medications (sodium valproate or valproic acid) from the onset of therapy.

Ten patients had been on three anti-epileptic drugs, five had been on four drugs, two patients on five drugs, and one on six drugs. Medications included phenytoin, phenobarbital, carbamazepine, combinations of phenobarbital and phenytoin, sodium valproate and valproic acid, clonazepam and acetazolamide.

4.3.7 FOLLOW-UP

Follow up assessment of patients was conducted over a mean of 2.6 years, ranging from 6 months to 6 years:

15 patients were seizure free.

2 had persistent myoclonic jerks.

7 had occasional myoclonic jerks.

21 continued to have intermittent seizure manifestations; 2 of whom were poorly controlled.

Eleven patients were not followed up (lost, referred back to primary centre or transferred to private care)

4.3.8 NATURE OF EEG DISTURBANCE

108 EEGs were performed in 56 patients. 24 of the total number of EEGs were normal. Only one patient was not documented as having epileptogenic activity (SW, polySW, atypical SW, photoparoxysmal response).

The types of EEG patterns are shown in Table 5.

The frequency of SW discharge varied as follows: 2-4 Hz, 2.5 Hz (three cases), 2.5-3 Hz (two cases), 3 Hz (two cases), 3-3.5 Hz, 3.5 Hz, 3.5 -4 Hz, 3-4 Hz (two cases), 4 Hz (two cases), 4-5 Hz (two cases), 5 Hz (three cases). (Frequency was reported in twenty of the records.)

The frequency of polySW discharge varied as follows: 2-2.5 Hz, 2.5 Hz, 2.5-3 Hz, 2-3 Hz, 3 Hz, 3.5-5 Hz, 4-5 Hz. (Frequency was reported in seven of the records.)

Table 5. EEG Patterns.

Pattern	Number of patients with abnormal EEGs	Percentage of total number of patients
SW	26	46
PolySW	22	39
Atypical SW	20	36
SW and polySW	11	20
Photic sensitivity	9	16
Exclusively photic sensitive	4	7
Hyperventilation induced increase in SW or polySW	35	63

Asymmetry of the spike activity was noted in 10 records, in 7 of which the amplitude was greater over the left hemisphere. Bilateral fragments of SW activity or SW occurring independently at times in either hemisphere were noted in 5 patients.

Recorded ictal events

Seven absence seizures were recorded during the performance of the EEG.

One generalized tonic-clonic seizure was recorded during the EEG.

Myoclonic jerks were recorded in 3 patients with multispikes noted on one occasion, and in association with an absence on one occasion.

Other EEG changes

Nine patients were noted to have areas of focal slowing during the recording, consisting of focal theta transients.

Four patients had mild intermittent slowing of background activity, classified as a Dysrhythmia Grade 1 on the Mayo classification.

One patient had bifrontal slowing and one had rhythmic 2-3 Hz delta activity and one had generalized intermittent delta transients.

EEGs performed on other family members

Thirteen EEGs were performed on other members of the JME patient's families. All were normal, excepting for one which showed focal unilateral temporal slow activity.

4.3.9 RADIOLOGY

Twenty-five patients had CT scans of the brain, with all scans being normal.

Two patients had MRI scans , both of which were normal.

Twenty-five patients had skull X Rays, all being normal.

4.4 LINKAGE STUDIES

Five families were used for linkage analysis. The family trees of the patients who underwent linkage analysis are depicted in Figures 3 to 7. All of the families were both multiplex and multigenerational. Linkage studies were performed using the LIPED program of J. Ott (1974).

Only two syndromes, JME and GTCS, were identified among members of all five families. One sibling had onset of seizures at the age of 4 years and had a history of meningitis and was not considered as affected. Fourteen individuals in the five families had JME (two are deceased) and five had GTCS, making a total of 19 affected individuals at an average of 3.9 individuals per family.

One individual, proband of family F was included, although the age of onset of his seizures was 34 years.

4.4.1 CHARACTERISTICS OF FAMILIES

FAMILY A

The proband and her sister had been followed up since their teens when a diagnosis of JME had been made. They had exacerbations following sleep deprivation and responded well to VPA, but did not have predominantly morning myoclonus. Their father, interviewed at home, had suffered a severe cervical myeloradiculopathy following a seizure. In addition, he reported occasional myoclonic jerks and was classified as a case of JME (EEG not obtained). A cousin of the proband had intermittent generalized tonic-clonic seizures from the age of 12.

EEG performed on the proband demonstrated intermittent 5-7 Hz theta slowing and a 4 second burst of 2.5-3 Hz polySW activity. EEG on the proband's cousin was normal: she was classified as GTCS. This family was of mixed ancestry, belonging to the Cape Malay ethnic group.

FAMILY B

The proband had JME, with rare nocturnal seizures, awakening myoclonus and improvement with VPA. The proband's mother and maternal aunt both had generalized

seizures, exacerbated by lack of sleep since adolescence. No history of myoclonic jerks or absence seizures was obtained and both were classified as GTCS. The EEG of the proband showed a 5 Hz polySW pattern; the EEG of the proband's mother was normal. This family was of mixed ancestry, belonging to the Cape Malay ethnic group.

FAMILY C

The proband and his brother had JME, with predominantly morning myoclonus, exacerbated by sleep deprivation, and a good response to VPA. The proband's younger brother had several generalized tonic-clonic seizures at the age of 12 years, which had decreased in frequency when interviewed at the age of 17. The proband's mother had one generalized tonic-clonic seizure at the age of 10 years and a single seizure during two of her pregnancies. No history of eclampsia was obtained. In addition, the proband's mother had a history of TB meningitis in adulthood. The proband's younger brother and his mother were classified as GTCS. This family was of mixed ancestry.

FAMILY D

The proband, her half-sister and mother had JME. The proband's uncle had a seizure disorder commencing at the age of 4 years probably related to childhood meningitis and his status was classified as unaffected. The EEG of the proband showed a single burst of generalized spike and slow wave. This family was of mixed ancestry.

FAMILY E

The proband presented at the age of 34 years with the picture of JME. The proband's father (deceased) was affected by a similar condition and was classified as JME. In addition, 3 of the proband's brothers had JME, one of whom was deceased. The proband's EEG was normal other than a mild excess of theta transients, as was the EEG of one brother. The other two brothers had SW activity on at least one EEG. The proband and one brother had occasional myoclonic jerks, and one brother had predominantly morning myoclonus, exacerbated by sleep deprivation and alcohol. This family was of mixed ancestry.

FAMILY A

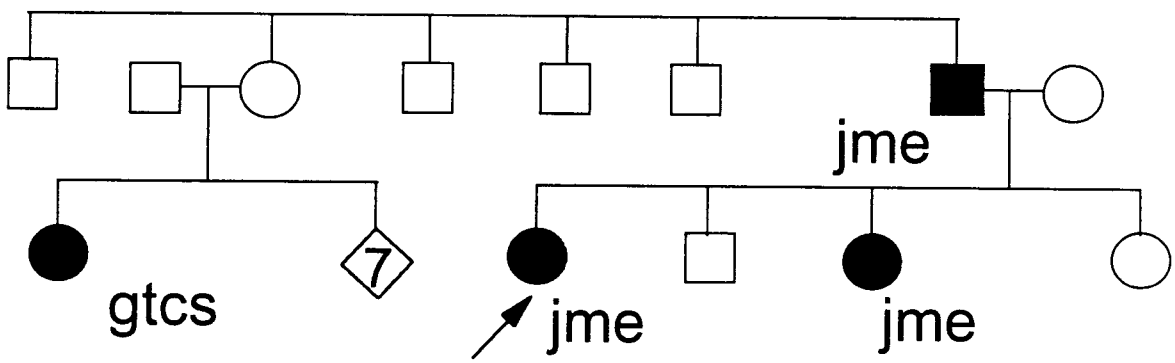

Figure 3. Family tree of family A

FAMILY B

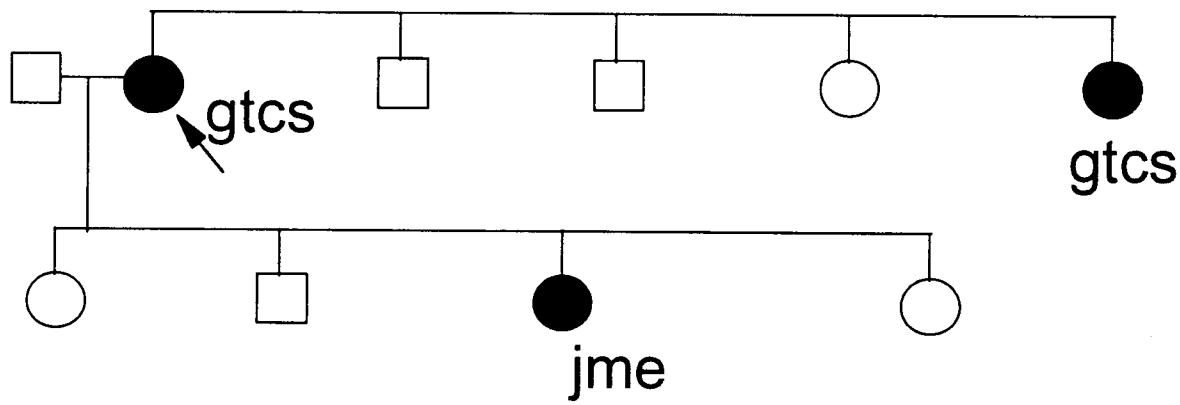

Figure 4. Family tree of family B

FAMILY C

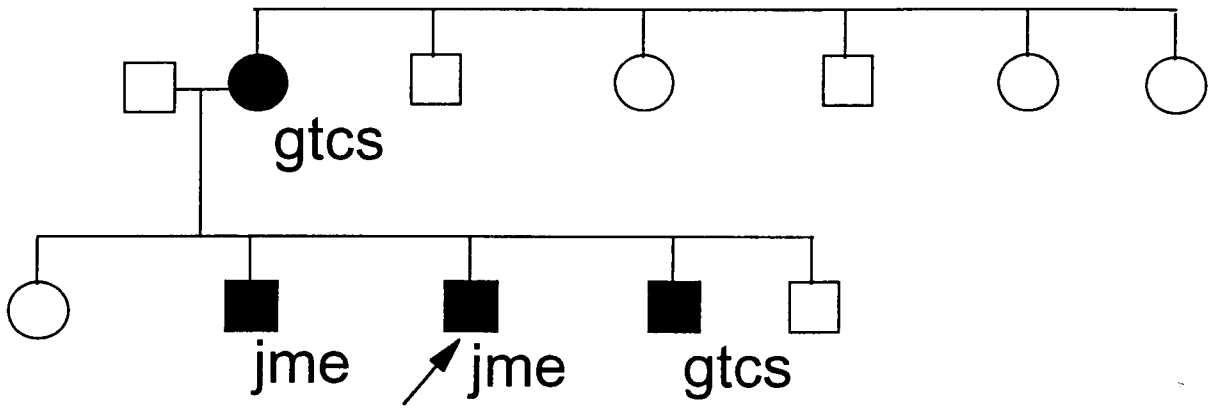

Figure 5. Family tree of family C

FAMILY D

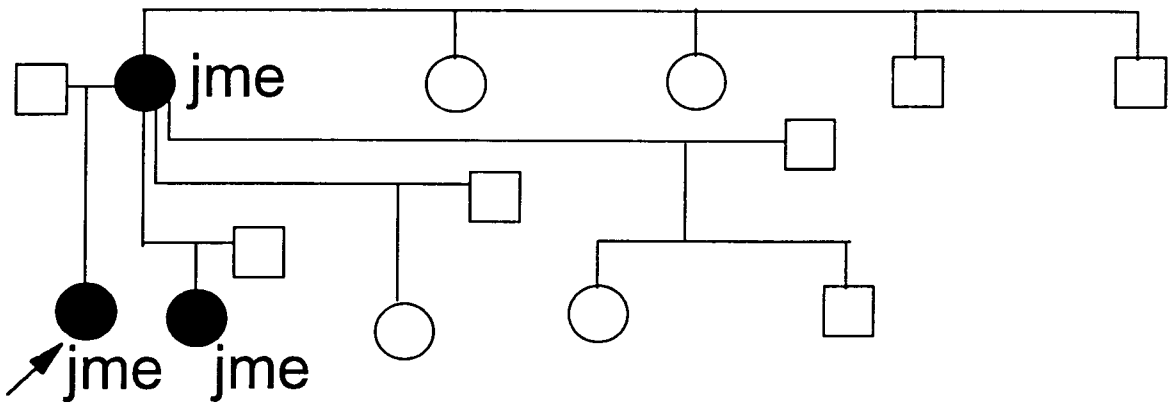

Figure 6. Family tree of family D

FAMILY E

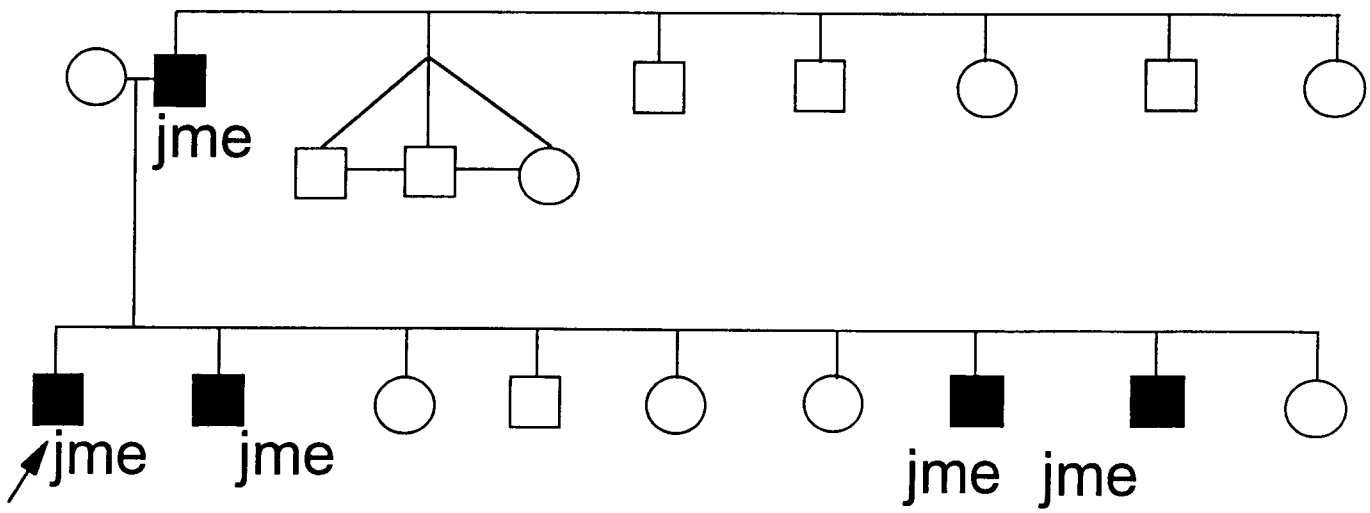

Figure 7. Family tree of family E

4.4.2 LINKAGE ANALYSIS

The linkage analysis in this study assumed an AD (Autosomal Dominant) inheritance, and the results are summarised in Table 5 for the various recombination fractions, θ, at penetrance values of 0.7 and 1. The lod scores for the individual families are given in Appendix 1.

Table 6. Summary of results of linkage analysis.

Recombinant fraction: θ at penetrance values of 1.0 and 0.7	Lod Score	
	1.0	0.7
0.0	-499.45	-499.45
0.01	-11.44	-11.46
0.1	-3.07	-3.07
0.2	-1.10	-1.11
0.3	-0.33	-0.34
0.4	0.02	-0.05

Thus, at a θ value of 0.1 odds are greater than a 100 to 1 against linkage, and the lod scores remain negative for all other values of θ, other than 0.4. The lod scores of < -2 are against linkage of the HLA locus to JME in the families examined.

5 DISCUSSION

5.1 CHARACTERISATION OF JME

JME was first described by Herpin in 1862 and by Rabot in 1899, but the Janz school in Berlin (Janz and Christian, 1994) has been mainly responsible for its identification as a clinical syndrome, along with Delgado-Escueta and Enrile-Bacsal (1984) . Since becoming recognised, the incidence amongst all epilepsies has grown from 2.7% in 1957 to 11.9% in 1984 (Delgado-Escueta et al., 1989).

The precise criteria for JME are somewhat unclear. This is of manifest importance in attempting to derive a "pure" syndrome for purposes of genetic studies. Various clinical subgroups which present difficulties with diagnosis and affectedness state include:

i) isolated myoclonus.

ii) myoclonus and absence without GTCS (possibly an overlap with JAE).

iii) JME patients with a history of febrile seizures.

iv) acceptable age of onset for absence to be included in the syndrome.

v) various EEG patterns: 3 Hz SW, 3-4 Hz SW, 4-5 Hz SW, >5 Hz SW and MultiSW.

vi) photosensitivity as a discrete syndrome or common phenomenon.

vii) typical patients presenting at extremes of usual age range.

There is debate as to whether or not the condition is a homogenous disorder or a spectrum of various disorders. One striking example of this is that rare cases occur in which there is no response to anti epileptic drugs, suggesting a variable genotype. Delgado-Escueta et al. (1994b) have drawn up 8 subgroups, depending on the various forms of seizures found in relatives of the proband, the nature of the EEG in relatives and the frequency of myoclonus. Currently, it appears unlikely that there is a shared locus between other syndromes of IGE and JME, and that JME itself is, certainly genetically, a heterogeneous syndrome in that subgroups of JME exist which do not map to chromosome 6p.

Regarding the core of the syndrome, that of an IGE with myoclonus, GTCS and relatively low frequency absences, certain notable nosological difficulties are occasionally reported:

i) Janz (1985) reports that 8.2% of patients with pyknoleptic absence (CAE) have myoclonic jerks and that 15.9% of patients with JAE have myoclonus.

ii) As reported in Wolf (1985b), Tsuboi (1977) reported the association of psychomotor seizures with JME in 3.7% of cases.

In general, however, to quote Genton et al. (1994), 'In clinical practice, juvenile myoclonic epilepsy can be easily and firmly diagnosed by careful interviews...and by EEG'. The typical onset is in adolescence with myoclonic jerks and GTCS, frequently with absence as a less prominent symptom and an EEG with a polySW pattern. In the experience afforded by this study there was usually little difficulty with the clear pattern recognition of the core JME syndrome.

The core syndrome is as reported by Dreifuss (1989): in addition to myoclonus, 80% of patients have GTCS, both of which are more frequent in the morning. Absence is found in 25%. The typical onset is that of myoclonic jerks followed by GTCS months to years later. The condition is exacerbated by lack of sleep and alcohol, and there are frequent relapses after discontinuation of therapy: the condition is *persistent*. The condition is very responsive to VPA, approximately 80% responding to the drug. The syndrome most often starts about the age of 15 years (Delgado-Escueta et al., 1989).

Data from Marseilles (Genton et al., 1994) indicates that the commonest first seizure is myoclonus (54%), followed by GTCS (35%) and absence (11%).

Review of Table 7 (Characteristics of JME in various studies) shows that the features of the 56 patients in this study are identical to those discussed in other reports from the United States, Germany and Saudi Arabia, although certain features require specific comment:

5.1.1 MYOCLONUS

The presence of myoclonus is indispensable to the diagnosis of the syndrome and one would thus take issue with the inclusion by Panayiotopoulos et al. (1994a) of 2 cases who did not have myoclonus. In addition, in this Saudi Arabian study, largely of families with a high degree of consanguinity, the myoclonic jerks were described as mild (Panayiotopoulos 1989a, 1994a) and confined to the fingers, and an essential tremor not related to use of VPA was found in 35%. This is atypical, both in the experience of the patients involved in this study and elsewhere (Janz 1985; Oguni et al., 1994), where the myoclonus is reported

typically to consist of large movements (myoclonias) of proximal muscles and the forearms: this raises the concern that the movements seen in the Saudi Arabian population were those of polyminimyoclonus, and were related to some other disorder of AR inheritance pattern, possibly a progressive form of myoclonic epilepsy. As noted above, during this study, 3 patients with a form of PME were identified, part of a large family with at least 10 affected members who had myoclonus, convulsions and a p patients were characterised by having persistent fine tremulous movements at fingers, wrist and elbow and clearly did not have JME.

The inclusion of two patients in this study with myoclonus alone appears to be the rule rather than the exception in comparison with other studies. The frequency of myoclonus in JME is variable, and since certain patients are included with rare or single convulsions, it appears to follow logically that others, who have only myoclonus, but in other respects share the typical characteristics of the syndrome, should be included. It should be noted that one patient had only 1 convulsion, one had only 2 and one had rare convulsions, in addition to the 4 who had no convulsions.

5.1.2 SEIZURE TYPES

The precise onset of each of the seizure types (myoclonus, absence and GTCS) could not be determined, but a relatively common phenomenon was that of myoclonus followed by, or occurring synchronously with, GTCS. When myoclonic jerks alone herald the disease, major convulsions generally appear 2-3 years later (Delgado-Escueta et al., 1989; Janz 1985). The commonest combination of seizure types was that of myoclonus and GTCS (60.7%), followed by myoclonus combined with GTCS and absence (32.1%) with the combination of myoclonus and absence being rare (3.6%). These figures reflect the fact that GTCS is a common component of the syndrome (93% of cases), whereas absence is relatively uncommon (35.7%). Patients with a combination of absence and myoclonus may be less likely to present to a physician. Of note, all absences started in the teenage years of the patients and childhood onset of absence would have been viewed as an exclusionary criterion. In a Saudi Arabian study, in 4 cases a diagnosis of pyknolepsy was made and the age of onset for absence was between 5 and 14 years (Panayiotopoulos et al., 1989b).

Table 7. Characteristics of JME described in various studies.

	Asconape	D-Escueta	Janz	Obeid	Pan*	D-Escueta	Penry	Pan	Genton	Carr	Aliberti
Year	1984	1984	1985/1969	1988	1989	1989	1989	1994	1994	1995	1994
n	12	43		50	47	68	50	66	82	56	22
Myoclonus only	17%	2%	10%	2%					11%	3.6%	
MJ present	100%	100%		100%	100%		100%	97%	100%	100%	
GTCS	83%	95%		80%				78.8%	89%	93%	
GTCS + MJ	58%	63%					50%	57.6%	62%	60.7%	
Absence		40%	10%	12%	38%	37%		33%	27%		
GTCS+ ABs + MJ	25%	37%					36%	21.2%	24%	32.1%	
Onset (years)		13.6(8-24)	12-18	15.5(6-28)	0	15	12.5		14.5(7-33)	14.3(9-23)	
Onset abs	4.3				9.7(5-14)	11.5		10.5(5-16)	11.7(7-16)		
Onset MJ	14.75				14.1			15.0(8-26)	15.3(10-20)		
Onset GTCS	16.4				14.5			16.0(9-28)	15.1(7-33)		
% onset MJ/abs		26%						9.1%			
% onset GTCS		51%						78.8%			
Time to Diagnosis	6.5	2-54 years					10.5 years			6.5 years	
Awakening MJ	100%							87.5%		75%	
Awakening GTCS			95%					69%(16pts)			
Exacerbations											
Sleep Deprivation							42%	89.5%		67%	
Menses							15%	24.1%		41%	
Family History	50%	40%		48.7%			36%	66%	30%	46%	
History: Sib/Parent		26%						27%incl FS	16%	32.6%	
Complete/Good Control	73%	93%		84%	83%		86%	88%			
Poor control (VPA)	8%	8%		10%	8%			9%		5%	
Male/Female	0.33	1.15			0.9	o	0.23	1.1	0.71	0.65	0.29
Normal EEG	50%			26%	5%			15.2%		22%	22.7%
Gen PolySW pattern	58%	100%3.5-6Hz	39%	sw,polySW 4	100%			51.5%	45%	39%	72.7%
Sharp theta with spikes								27%			
3-4 Hz Sw	17%	26%(2.5-3)		Present		17%			16%	46%	
4-5 HZ									82%		31.8%
Focal Slowing	8%							15%			36.4%
Asymm/Focal Spike				34%				15%	15%		40.9%
PCR	33%		30.5%	30%	21%		16%	27.3%	33%	16%	
Hyperventilation								100%		63%	

* abbreviation for Panayiotopoulos

5.1.3 IMPAIRED DIAGNOSIS

Many factors contribute to failure of diagnosis, the paramount one being ignorance of the condition, in part because it has only been generally known since the reports of Delgado-Escueta and Enrile-Bacsal and of Asconape and Penry in 1984. If convulsions are not present, the condition frequently remains undiagnosed as minor irregular jerks of the arms and shoulders (Delgado-Escueta et al., 1989) and patients themselves may not be aware of myoclonus if it occurs prior to a convulsion.

In one recent study, 31% of patients had asymmetries, either clinical or on EEG. Clinical asymmetries were initially unilateral myoclonus, or unilateral GTCS. Asymmetries lead to incorrect diagnoses of partial seizures. Delay in diagnosis was 7.5 to 9.5 years for the groups of symmetrical and asymmetrical seizures (Lancman et al., 1994). As has been noted in other studies, occasional individuals respond poorly to VPA, which is atypical.

5.1.4 SUCCESSIVE MYOCLONIC JERKS

A series of successive myoclonic jerks that evolves into a tonic-clonic convulsion can usually be elicited in the history (Delgado-Escueta et al., 1989, Janz 1985), and a history of this phenomenon was obtained in 36% of the patients.

Myoclonus status was present in 5 of Asconape and Penry's (1984) 12 patients, characterised by a state lasting from several minutes to several hours, during which the myoclonus recurs every few seconds, either isolated or coming in salvos of 3-5 jerks, consciousness being maintained throughout (Janz, 1985). This seems a rare occurrence, recorded in only one patient in this study.

5.1.5 PRECIPITANTS

Penry et al. (1989) report that stress was a factor in 100%, emotion in 96% and chronic anxiety in 70%, but no attempt was made to elicit the role of these virtually universal precipitants in this study. The majority of the patients had exacerbations as a result of sleep deprivation, and this feature should perhaps be considered to be essential to the diagnosis or creation of a "pure" syndrome.

5.2.6 EEG

This study showed, as have most others, that a polySW pattern is neither pathognomonic nor the predominant EEG abnormality. According to the data of Tsuboi (1977, in Wolf, 1985b) there were epileptic discharges in 93% of his patients, but in only 70% was it a SW type, with polySW found in 37% of patients, rapid SW in 21.5%, 3 Hz SW in 11% and irregular SW in 12%. Thus also, Janz et al. (1992) have observed that, "despite our expectations", polySW and more rapid patterns do not predominate in JME, but are found approximately as often as the classic pattern.

Twenty-two percent of the EEGs recorded were normal, as is well accepted to occur (Delgado-Escueta et al., 1989; Roger et al., 1994), particularly if the patient is taking VPA (Greenberg et al., 1988a). One patient had 6 studies, and a specific epileptogenic discharge could only be demonstrated with a sleep study, as has been recommended by some authors (Asconape and Penry, 1984; Roger et al., 1994).

Bilateral fragments of SW activity or SW occurring independently were noted in 5 patients, and 9 were observed to have focal slowing. This is currently entirely compatible with the diagnosis, one study reporting focal abnormalities in 30%, half of whom had focal single spikes and SW, and the remainder had unilateral preponderance of theta and delta (Panayiotopoulos et al., 94). In the study of Aliberti et al. (1994), 27% had a focal onset of either the spike or slow wave of a generalized discharge, and 9% had focal spikes or SW; 13.6% had unilateral slow waves and 18.2% had independent right or left slow activity. 45.4% of patients had generalized abnormalities consisting of transient bursts or runs of generalized theta or delta wave.

Greenberg et al. (1988b) reported a similar pattern of diffuse paroxysmal rhythms and mixtures of diffuse spikes and sharp waves mixed with theta rhythms in asymptomatic patients: they are said "to occur frequently in a one-hour EEG record" and it is further noted that "there was seldom any ambiguity about their presence." Delgado-Escueta et al. (1989) report the presence of EEG traits in asymptomatic parents and siblings consisting of diffuse paroxysmal 3-6 Hz slow waves mixed with spike and sharp waves and/or diffuse paroxysmal 4-7 Hz waves (the paroxysmal theta waves of Doose). For purposes of linkage, these authors included the following:

i) paroxysmal, generalized theta (4-7 Hz) rhythms or

ii) mixtures of generalized spikes, sharp-waves and theta rhythms.

It is perhaps worth noting that Doose et al. (1968) investigated a centrencephalic EEG pattern of abnormal theta rhythms of 4-7 Hz with parietal accentuation, taking the place of the non-rhythmic age-appropriate background, similar to hypnagogic activity of infancy. This was seen only in children aged 2-7 years and was particularly marked in the 2-4 year age group, 54% being affected in comparison with 12% of controls. The waves are seen in early childhood absence, myoclonic and astatic fits and centrencephalic grand mal. It would appear to be inaccurate to link paroxysmal bursts of slowing occurring in asymptomatic relatives of JME patients, who were predominantly not in the 2-7 year age group, with the abnormalities described by Doose.

5.2 DETERMINATION OF THE VARIOUS SYNDROMES OF IGE

5.2.1 ASCERTAINMENT OF PATIENTS WITH IGE

Regarding the figures for the various IGE syndromes reported in this study, based on identification of patients through abnormal EEGs, one concern is that not all patients with IGE will have abnormal EEGs, and if particular subtypes/syndromes are less prone to have abnormal EEGs, they will be underrepresented by this method of ascertainment: for example, whereas patients with absence are highly likely to have abnormalities on hyperventilation (Roger et al., 1994), patients with pure myoclonus or GTCS may be more likely to have a normal record. Despite this, the figures reported in this study resemble those previously reported:

5.2.2 COMPARATIVE REVIEW OF THE BREAKDOWN OF IGE INTO SUBTYPES

In a study of 1486 prospectively studied patients by Roger et al. (1994), 17% were considered to have IGE, and 11.4% could not be classified. JME was found in 23%, JAE in 11.1%, EGMA in 11.9%, isolated GTCS in 15.4% and photogenic epilepsies in 3.2%. Childhood and infantile syndromes made up the remainder (30.9%) and 4.3% were not further classified. If the childhood/infantile onset group is excluded, the corrected percentages for the other types are approximately 35% (JME), 17% (JAE), 18% (EGMA), 24% (GTCS) and 5% (Photic).

In an Italian study of 74 families (Canger et al., 1992) the seizure types could be broken down as follows:

Febrile Convulsions (FC)	34.5%
Childhood absence	16.6%
JME	6.7%
Epilepsy with tonic-clonic seizures	7.8%

Other idiopathic epilepsies reported in this study were one each of JAE, childhood epilepsy with occipital paroxysms, benign myoclonic epilepsy in infancy, idiopathic West syndrome and epilepsy with myoclonic-astatic seizures.

In 25% of the families there was only *one* clinical form of epilepsy among the affected members, 9 families with FC, 3 with CAE, 2 with JME and 4 with GTCS. There was a high representation of GTCS in affected parents of probands with CAE and JME of 35% and 39% respectively, but a rare association between CAE and JME, as opposed to other findings in the literature (Delgado-Escueta et al., 1990; Panayiotopolous et al., 1994). The authors hypothesise that there are genetically transmitted clinically homogeneous subforms and other subforms that may be associated with different epileptic syndromes.

Berkovic et al. (1994) report that in 101 cases with IGE, 21 patients had JME, 26 had myoclonus +/- absence +/- GTCS and 37 had JAE. 17 had GTCS alone, 10 having this only on awakening (EGMA). The group of 26 with myoclonus and absence are stated to represent a major overlap group between JME and JAE, although the triad of myoclonus, absence and GTCS is entirely compatible with JME.

The results reported in this study of South African patients mirror those of the study of Roger et al. (1994), if EGMA is included under GTCS, and also resemble those reported by Berkovic. Essentially JME and GTCS are common conditions, and JAE is less common, although it is an overlap syndrome, and may be interpreted in different ways by independent workers.

5.2.3 EGMA:A DISTINCTIVE SYNDROME?

The lack of any patient with EGMA is likely to be related to the fact that the majority of patients, if not all, with awakening forms of GTCS, in fact have JME, many of them having myoclonic jerks (Janz et al., 1992; Delgado-Escueta et al., 1994a) and further, that EGMA itself is an over-diagnosed syndrome. As noted by Roger et al. (1994), a prominent sub-category is formed by patients with a pure form of GTCS, who do not fit in the other absence related syndromes of JME and JAE. In addition, as Genton et al. (1994) observe, "the major problem encountered when dealing with this syndrome (EGMA) is that most cases with infrequent generalized tonic-clonic seizures will be ascribed to this category, whether or not the seizures show a clear circadian dependency."

Typical cases with GTCS on awakening, and other IGEs with infrequent GTCS share the EEG markers of JME and may occur relatively frequently in families of patients with a JME proband and may be a form of the latter (Genton et al., 1994): this was the experience in the six families examined for evidence of linkage in this study, where all relatives with syndromes of IGE other than JME, were classified as having GTCS. An alternative

explanation for failing to find cases of EGMA may be that it represents a discrete genetic syndrome not found in South Africa: this seems unlikely in view of the fact that all other syndromes are detected.

5.2.4 JAE: AN INTERMEDIATE SYNDROME?

As currently defined, the syndromes of JAE and JME are clearly overlapping: both manifest around puberty and in JAE, "not infrequently, the patients also have myoclonic seizures" (Commission, 1989). As will be reviewed, absence is present in a third of patients with JME in most series. The EEG is unhelpful in distinguishing these conditions: for the purpose of this study, all patient with myoclonus were included in the category of JME, and certainly the majority of these could be said to have the characteristic syndrome, 75% of them having myoclonic jerks predominantly in the morning, and 67% having their condition exacerbated by sleep deprivation. As stated by Wolf (1985a), JAE may be an intermediate syndrome between CAE and JME. The existence of the syndrome may be necessary, but there are bound to be cases which overlap with the two other syndromes associated with absence which flank the typical age of presentation of JAE. As regards CAE, recent data (Genton et al., 1994) points to a lack of a relationship between JME and CAE, which is of particular importance in that some genetic studies of JME have included patients with a childhood onset of absence: patients with CAE were excluded from this study, and none of the six families used for linkage analysis had family members with a history of CAE. The mean age of onset (13.7 years for JAE; 16.1 years for GTCS; and 14.3 years for JME) resemble the figures given by Janz (1994; Figure 9), supportive of the proposition that the syndromes described in this study resemble those seen elsewhere.

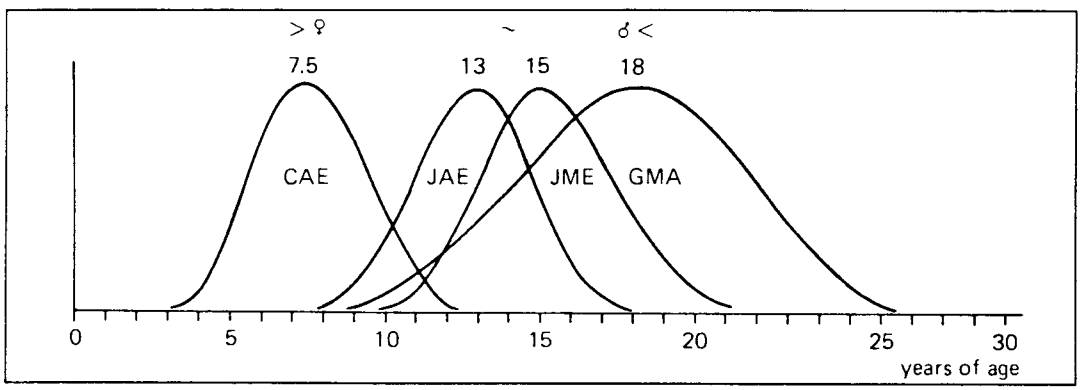

Figure 8. Onset of the IGE syndromes (Janz, 1994)

5.3 LINKAGE STUDIES

5.3.1 INHERITANCE IN EPILEPSY

Epilepsies best suited for genetic linkage analysis are those most likely to be caused by a single mutant gene showing a Mendelian pattern of inheritance: autosomal dominant (AD) or autosomal recessive (AR).

Autosomal Dominant

Several AD conditions are associated with epilepsy, such as the neurocutaneous disorders, tuberose sclerosis and neurofibromatosis., with a seizure frequency of 88% and 12% respectively (Bird, 1987) Thus, using polymorphic markers, 15 families were mapped to a gene determining tuberous sclerosis on chromosome 11q14-11q23, without evidence of genetic heterogeneity in their families (Smith et al., 1990). Another AD condition, Huntington's disease, is associated with a 50% frequency of convulsions in the juvenile form, and is now known to be a disorder of triplet codon repeats located to chromosome 4. In addition, Schiffer et al (1995) have reported that the condition of nocturnal paroxysmal dystonia is a form of nocturnal epilepsy, with AD inheritance, the partial seizures being of frontal lobe origin.

Of more direct relevance than the above are those patients presenting with benign neonatal convulsions (BFNC) with an AD type of inheritance, although genetic heterogeneity is present (Ryan et al., 1991). BFNC has been assigned to chromosome 20q by tight linkage to the genetic markers D20S19 and D20S20 (Leppert et al., 1989).

Autosomal Recessive conditions

These conditions, classically associated with an enzyme defect, may also present with seizures. An example is phenylketonuria in which phenylalanine hydroxylase is deficient. The gene for this condition is localised to the long arm of chromosome 12. Similarly, a number of lipid storage diseases may result in epilepsy in infancy and childhood. Thus, clearly defined genetic biochemical pathway disorders have a tendency for seizures to be part of the phenotype.

AR inheritance is also well known in certain of the groups of PME, such as Baltic myoclonus or Lafora body disease. Of these, the gene for PME of Unverricht-Lundborg type has been

assigned to chromosome 21 band q22.3 by linkage analysis in 12 Finnish families using polymorphic DNA markers (Lehesjoki et al., 1991).

X-linked conditions

Diseases such as the Lesch-Nyhan syndrome are also associated with seizures. Another disorder associated with excessive triplet codon repeats is the fragile X syndrome, which is associated with epilepsy in between 5% to 30% of males.

Multifactorial and Polygenic Influences in Epilepsy

These terms are used when a disorder is documented to have an increased familial incidence, but does not fit a single gene inheritance pattern, nor is it the result of a gross chromosomal abnormality. Multifactorial refers to the influence of environmental factors on genetic factors, whereas polygenic inheritance refers to the state of having several different genes each contributing additive effects.

These concepts may be applied to the idiopathic generalized seizures.

In general, there is a small but reproducible genetic influence in patients with epilepsy. 2-10% of siblings or children of index patients with epilepsy are likely to develop a seizure disorder (Bird, 1987). In patients with IGE, Annegers and Hauser (in Bird, 1987) have demonstrated that the cumulative risks for epilepsy for siblings, children, and the control population up to age 20 years were 2.7%, 10.6%, and 1.1% respectively.

Other factors are important (Bird, 1987): the risk to relatives increases with an increasing number of affected persons in the family. The risk also seems to increase when the proband has a generalized SW EEG pattern or when such a pattern is found in another first-degree relative. The risk decreases with increasing genetic distance from the index case, and with the presence of an acquired lesion or of partial seizures.

Twin studies

Studies have shown a concordance for epilepsy in monozygotic twins that varies between 60% and 95% for various groups, the range largely depending on the manner of seizure classification (mixed, febrile convulsions, with or without aetiology etc.) (Newmark and

Penry, 1980). EEGs in unaffected twins were not considered in the production of these figures.

In contrast, the average concordance rate for epilepsy in dizygotic twins is about 11%, with a range of 3-35%. The high rate of concordance in monozygous twins suggests that genetic factors may be decisive in the aetiology of IGE (Janz et al., 1992).

In a study by Berkovic et al. (1990), all concordant monozygous twins shared the same epileptic syndrome, which is further support for a genetic determination of the IGE syndromes. Of 131 twin pairs, 32 had generalized forms of epilepsy. 9 of the 13 monozygotes were clinically concordant, whereas only 2/8 dizygotes were concordant.

5.3.2 APPROACHES TO GENETIC LINKAGE

If a single alteration in a gene, an allele, is responsible for the production of the epilepsy trait, then that allele should be present in the DNA of all carriers of the condition. A marker is a gene of sufficiently high prevalence that it is likely to be found in the family under study, and if two affected members of that family should have the *same* allele at the marker locus more often than would be expected, this finding increases the probability that there is linkage between that marker allele and the trait being investigated, for example, epilepsy.

Genes may be said to be closely or loosely linked, depending on their distance apart from one another. A frequent occurrence during meiosis is the process known as crossing over, which consists of the exchange of parts between the chromatids of homologous chromosomes. Crossing over of chromosomes between two linked genes results in a new combination, known as a *recombination*, between the two loci. The frequency with which these recombinations occur increases with increasing distance between two genes. The genetic map distance between two genes is defined as the expected number of crossovers occurring between them, observable as regions of contact known as chiasmata. In male meioses an average number of 53 chiasmata occur and the total male map length is thus 26.5 Morgans (Ott , 1991) with the average length of the human genome (male and female) being about 33 Morgans (3300 centimorgans). At any given meiosis, there is a 1% chance that recombination will occur between two genetic markers that are separated in the DNA by 1 centimorgan, representing approximately 10 million base pairs of DNA. Two genes

located 1 centimorgan apart will be passed on together from parent to offspring 99% of the time (Delgado-Escueta and Greenberg, 1984).

Linkage describes a distance relationship between two genetic loci and quantifies the location of a polymorphic marker relative to a gene for a disease (Delgado-Escueta and Greenberg, 1984). The process of meiosis is associated with the separation of alleles so that each gamete ends up with only one of an allele-pair. Linkage analysis is a test to determine whether in this process, known as segregation, a trait or disease associates with some known genetic marker within families more frequently than would be predicted by Mendel's law of independent segregation. The probabilities that the observed associations are caused by linkage or arose by chance (no linkage) are calculated. The ratio of these two possibilities is expressed as a logarithm (base 10) and is termed the odds ratio for linkage (lod) (Treiman, 1993). Usually the lod in each family is calculated and the "lod scores" are added together.

The lod scores either support or reject the hypothesis that the disease locus is near the marker locus. Support for linkage is suggested by positive lod scores, where a result of more than 3 is a threshold value for accepting the existence of linkage, representing odds of 1000 to 1 in favour of linkage (Greenberg et al., 1988b), whereas scores of less than -2 are indicative of odds of 10 to 1 against linkage (Durner, 1994). Since recombination between two loci becomes more likely the further apart they are on a chromosome, the genetic distance between the disease locus and a given marker locus can be estimated by the recombination frequency (θ) which is the rate of recombination between them. The recombination frequency has an upper limit of 0.5, which is equivalent to no linkage (random assortment). For a given data set at a particular recombination fraction tight linkage may be excluded, but this does not exclude linkage at a greater distance (Anderson and Rich, 1994).

Linkage analysis requires the identification of an unequivocal epilepsy phenotype, a familial clustering of this epilepsy phenotype, and the availability of a sufficient number of adequate informative pedigrees. Genetic linkage should be performed under various modes of transmission, including dominant, recessive and co-dominant alleles.

Genetic analysis becomes more difficult when the penetrance of the disease phenotype is low or when the penetrance is an unknown function of age. Errors in the assessment of the phenotype can obscure linkage findings because they may lead to the mis-scoring of

recombinant events (Leppert, 1990). Genetic or locus heterogeneity may also obscure linkage findings, if a similar phenotype is caused by separate genes in unrelated families, since one family may give a positive lod score with a given close marker whereas another family may give a strongly negative lod score with the same marker (Leppert, 1990)

Genetic heterogeneity causes problems in linkage analysis, since for each meiosis in which the disease trait does not segregate with the marker, one has to differentiate between a crossing over (between the disease gene and the marker) and non-linkage (Lindhout et al., 1992).

Segregation analysis is a technique used to determine how diseases and traits are inherited: it consists of the computation of the ratio of affected to unaffected offspring from at-risk matings and the comparison of that ratio to the ratio expected for some known mode of inheritance. This may be affected by non random ascertainment of families and a bias towards obtaining families with several generations affected: this may suggest a stronger genetic contribution than exists, or even the wrong mode of inheritance. In addition, family members who have not reached the usual age of onset of the disease cannot be classified (Greenberg et al., 1992a). Thus, segregation analysis in, for example, the JME families in Los Angeles "can no longer provide accurate results on the mode of inheritance of JME" (Greenberg and Delgado-Escueta, 1993).

In general, samples for the establishment of genetic linkage should be obtained from a minimum of 10 to 12 affected individuals, within a family, for evidence of linkage to be demonstrable. A single large family of a given size provides more potential linkage information than does a combination of several smaller families with the same total number of individuals (Ott, 1991), large families being better suited for linkage analysis because they contain potentially fewer unrelated individuals than do smaller families. Pedigrees with larger sibship sizes are more efficient than those with smaller sibships because the proportion of meioses scored per genotype is higher when many offspring are available for inclusion in the analysis (Leppert, 1990).

5.3.3 DEFINITION OF THE JME SYNDROME IN LINKAGE ANALYSIS

Despite the clinical recognition of a core syndrome of JME (as discussed in section 5.1), as noted by Janz et al. (1994b), the syndrome of JME is not uniform enough: there is consistency in the presence of occasional bilateral jerks of the shoulders and arms mainly

after awakening, but "all other signs are variable". Accurate definition of a phenotype and ascertainment of families with multiplex and multigenerational involvement are necessary prerequisites for studying linkage. Unanswered questions remain as to whether the following characteristics should be considered as indicative of an affected state of JME:

i) GTCS alone

ii) absence alone

iii) JME syndrome with onset of absence in childhood

iv) clinically unaffected state with either specific or non-specific EEG change

v) age of onset of typical syndrome outside of usual age limit

vi) patients with JME and prominent photosensitivity

Work on the genetics of JME has been reported mainly by four main groups:

i) Delgado-Escueta and Greenberg from Los Angeles

ii) Weissbecker and Janz from Berlin.

iii) Greenberg from New York.

iv) Whitehouse and Gardiner from London.

Regarding classification of the JME syndrome and designation of affectedness, the following is noteworthy concerning the different groups:

i) Los Angeles (Delgado-Escueta et al., 1989): in the initial studies, patients were excluded if the only EEG abnormality was that of 2.5 to 3.5 Hz SW complexes (unless these were present in addition to 3.5-6 Hz multiSW complexes), when myoclonic jerks or myoclonus occurred during absence attacks (myoclonic or myoclonus absence), and when history revealed myoclonic and tonic-clonic convulsions to be clinically sensitive to light. On the other hand, subjects *were* classified as affected, provided that their EEGs showed specific or non-specific paroxysmal EEG abnormalities, even if clinically asymptomatic.

   In addition to the 35 probands, 10 family members had clinical epilepsy and there were 17 with abnormal EEG traits (Greenberg and Delgado-Escueta, 1993). This study therefore tested a combination of EEG findings and epilepsy traits.

   However, in 1994, following contradictory reports raising the possibility of genetic heterogeneity, Delgado-Escueta et al. (1994b) reported that of the initial 11 families,

2 were multiplex on the basis of specific 3.5 to 6 Hz multiSW paroxysms, 2 others were multiplex because of non-specific epileptiform patterns and 3 families were multigenerational by virtue of a parent with non-specific epileptiform paroxysms. "Thus, in 6 of 11 informative families, affectedness of a family member was determined by the EEG." In addition, one patient had adolescent drop attacks, and would now be excluded (Delgado-Escueta et al. 1994a).

Work reported in 1993 (Delgado-Escueta et al., 1994a) using DNA markers, gave results which were significantly negative for linkage, in contradistinction to previous reports from this group.

ii) Berlin: In the study of Weissbecker (1991): patients were included as affected if they had absence, GTCS or an EEG trait.

The following definitions for affectedness were used:

A: JME only (Relatives with abnormal EEGs not counted).

B: JME, GTCS, Absence (Relatives with abnormal EEGs not counted).

C: JME, GTCS, Absence, EEG abnormality counted as affected. (This definition corresponds to that of the Los Angeles group)

D Any history of seizure, including febrile seizures. Relatives with abnormal EEGs included.

Use of the EEG to confer affected status in asymptomatics (Definition C) gave lower lod scores than if they were counted as unaffected (Definition B).

iii) London (Whitehouse et al., 1993): individuals were classified as affected if they has a diagnosis of JME, JAE, CAE or EGMA. and any other epilepsies meeting the criteria for IGE. IGE was diagnosed in the event of generalized seizures starting between 2 and 30 years. EEGs were either normal or indicative of IGE with generalized bursts of SW or polySW between 2.5-6 Hz, the latter being either regular or irregular. JME was diagnosed with onset of seizures between the age of 8 and 26 years. Other groups include Sleep Grand Mal, in which nocturnal seizures occurred without an IGE record. The term unclassified generalized epilepsy (UGE) was a description used for those with GTCS without an IGE record

5.3.4 PROPOSED MODES OF INHERITANCE IN JME

Polygenic Inheritance

Tsuboi and Christian (1973) suggested that inheritance of JME was polygenic, with a differential sex effect, females being more affected than males. They investigated relatives of 319 patients with JME and discovered that 27% of patients had a parent, child or sibling whose history included epilepsy and this figure increased to 33.5% if female patients alone were considered. These authors state also, however, that is "very difficult to exclude AD inheritance with low penetrance from polygenic inheritance". Hodge et al. (1989) could not reject polygenic inheritance in an examination of 78 families from Berlin and 27 families from Los Angeles, and more recently, considering the IGEs in general, Berkovic et al.'s (1990) twin study data suggest a complex or complexes of polygenes underlies the inheritance of the IGEs.

Doose et al. (1973) concluded that absence seizures with the 3 Hz SW pattern were likely to be inherited in a multifactorial manner. Relatives of female probands had a higher frequency of paroxysmal (non-specific) EEG abnormalities than males, and siblings of female probands were more frequently affected than male probands, which is possibly suggestive of mitochondrial forms of transmission (Delgado-Escueta, 1994a).

Two-Locus Models

Greenberg et al. (1988a) performed segregation analysis on Los Angeles pedigrees and showed that the data fitted a two locus model best, where one locus was inherited in a recessive manner and the other was either dominantly or recessively inherited. Segregation ratios in 28 families were examined, and after including aysmptomatic members with abnormal EEGs as either affected or unaffected, the authors rejected the fully penetrant recessive model in both cases, but could not exclude a simple recessive with random reduced penetrance. However, if only family members were examined who had epilepsy without inclusion of those asymptomatics with the EEG trait, the two-locus postulate was rejected.

Under a two locus model, dominant and recessive, high concordance rates in twin studies could be explained along with the low rate for dizygotic twins (Greenberg et al., 1992a).

The Berlin Prospective Study, directed by Janz (in Greenberg et al., 1992a) reported that 3-7% of offspring were affected in families in which one parent had epilepsy. In offspring of parents with generalized epilepsy, 9% had generalized SW paroxysms and if abnormal EEG patterns were considered to convey an affected status, the percentage of affected offspring would be approximately 15%. As Greenberg et al. (1992a) point out, if the inheritance is dominant, then about 50% of offspring should be affected, and if recessive with an assumed high gene frequency of 5%, then about 4% of offspring would be affected (as a result of matings between an affected individual and a gene carrier). A figure corresponding to that of 15% is obtained from a two-locus dominant-recessive model.

Autosomal Recessive vs. Autosomal Dominant

In a study of 17 families, Panayiotopolous and Obeid (1989) have suggested that the inheritance is autosomal recessive: the segregation ratio in their patients was 0.123, but increased to 0.18 for correction of age of onset, the ideal ratio for AR disease being 0.25. The conclusion of AR inheritance is based on the high incidence of parental consanguinity (45% of the sibships had parental consanguinity), and the approximation of the segregation ratio to 0.25 in 7 sibships. In reply, Greenberg et al. (1990) have criticised the low segregation ratio, the methodology used to obtain it, and the applicability of simple segregation analysis in highly consanguineous families.

The data of Metrakos and Metrakos (1961) are compatible with IGE being an autosomal dominant trait, but with a low seizure frequency amongst those inheriting the gene.

Greenberg has plotted lod scores under a range of assumed penetrances (Delgado-Escueta et al., 1990) assuming either dominant or recessive inheritance: lod scores showed linkage under either mode, but were higher under dominant than recessive inheritance. However, the mode of transmission is not conclusively clarified, and subsequently, Greenberg et al. (1992b) have stated that the gene locus for JME designated EJM-1 is probably inherited in an autosomal dominant fashion.

The fact that twin studies (Berkovic et al., 1990) have shown a concordance rate of almost 100% in IGE suggest that the disease is fully penetrant (Durner, 1994)

As noted previously, Delgado-Escueta (1994b) has observed 8 possible phenotypes of JME, based on the presence of other IGE seizure types and of an EEG trait in family

members. A total of 55 families were subjected to segregation analysis, which gave rise to figures of 0.252 and 0.151, with or without family EEG data respectively. The former figure fits an autosomal recessive inheritance pattern, whereas the latter figure is similar to that seen in Saudi Arabia (Panayiotopolous and Obeid, 1989). When multiple families only were examined in order to reduce the possible interference of sporadic cases, a value of 0.265 was found, suggesting AR inheritance. However, when 6 sibships were examined, with siblings who had a multi SW EEG trait, the segregation ratio was suggestive of an AD inheritance. Thus, in the most recent studies, both AR and AD patterns of inheritance, intermixed with sporadic cases, are present.

Alternatively , the genes may express their gene products in a codominant manner giving rise to an intermediate phenotype such as that of asymptomatic family members with abnormal EEGs. Different mutations in the JME locus can cause a phenotype that is dominant in some families and recessive in others. If there is one JME mutation, the variability of clinical seizure phenotypes, EEG abnormalities, and age of onset of symptoms in family members may reflect the expressivity of the JME mutation and not the function of penetrance. Expressivity of clinical expression describes the range of phenotypic effects in individuals with a mutant genotype. Thus, patients in the same JME family may have the same JME phenotype, or epilepsy with grand mal seizures only, CAE, or the EEG SW complex only (Delgado-Escueta et al., 1990).

5.3.5 DIFFICULTIES ENCOUNTERED IN GENETIC STUDIES IN JME

JME, childhood absence and epilepsy with generalized tonic-clonic seizures account for at least 30% of all epilepsies and according to Delgado-Escueta et al. (1990) are the most common genetic epilepsies. JME has an estimated frequency of 1 in 2000 (Anderson and Rich, 1994).

Initially (Delgado-Escueta and Greenberg, 1984), JME was felt to be the most available and practical form of epilepsy for study, since the absence epilepsies are heterogeneous, and the most common form of absence studied was that of JME, since it was commoner than classic absence, or any of the other forms of absence (myoclonic absence with 3 Hz multi-SW complexes, JAE with 8 to 12 Hz rhythms and myoclonus absence with 12 Hz rhythms (Delgado-Escueta and Greenberg, 1984)). In addition, JME was more common than pure tonic-clonic seizures and pure clonic-tonic-clonic seizures. Furthermore, JME and other forms of generalized epilepsy are commoner in family members of JME probands. For

example, in the study of Tsuboi and Christian (1973), 27% of the probands were reported to have a near relative with epilepsy and a similar figure of 26% was obtained in Los Angeles (Delgado-Escueta and Enrile-Bacsal, 1984). In the investigation of JME, since the EEG trait may start in childhood, and clinical seizures become evident at adolescence, and because both persist to adulthood, it is theoretically possible to identify three to four generations of afflicted persons within a pedigree (Greenberg et al., 1988a).

As noted above, for the purpose of linkage studies, families would need to be identified through an index case with a clearly defined epilepsy syndrome, and of the various IGE syndromes, JME was an obvious candidate for study. However, despite over four decades of study, the mode of inheritance, degree of penetrance and precise definition of the syndrome of JME are neither clearly defined nor known.

Problems with genetic mapping of the epilepsies arise from the following areas (Delgado-Escueta et al., 1990):

5.3.5.1 Asymptomatic family members with abnormal EEGs

Metrakos and Metrakos (1961, 1966) in their studies on patients with centrencephalic EEGs emphasised two points:

i) An individual carrying a gene for epilepsy may never have clinical seizures, but may have an abnormal EEG.

ii) Penetrance of the gene may vary with age: being very low at birth and rising to complete penetrance for ages 4.5 to 16.5 years, and declining to almost no penetrance after the age of 40.5 years.

In the studies of Metrakos and Metrakos, 37% percent of the siblings of patients with centrencephalic type epilepsy (petit mal or grand mal) had similar specific EEGs, compared to 9% in the control group. In the twin study of Berkovic et al. (1990), of the 4 discordant monozygotes, each of the clinically unaffected siblings had EEG evidence of the condition.

However, Doose et al., (1973) found that only 8% of siblings of patients with the 3 Hz SW pattern shared the pattern. Of controls, 2% had the EEG abnormality.

In an investigation of JME, Tsuboi and Christian (1973) found that 4.1% of near relatives had epilepsy and 15% of relatives examined had a specific epileptiform EEG abnormality,

whereas 40% had non-specific paroxysmal EEG abnormalities. The specific abnormalities are reported as SW complexes and/or spikes and the non-specific disturbances are not described, other than as being paroxysmal. The incidence is age-dependent, showing a marked fall-off by the fourth decade (Figure 9). Offspring had the highest frequency of paroxysmal as well as specific EEG abnormalities, siblings an intermediate frequency and parents the lowest.

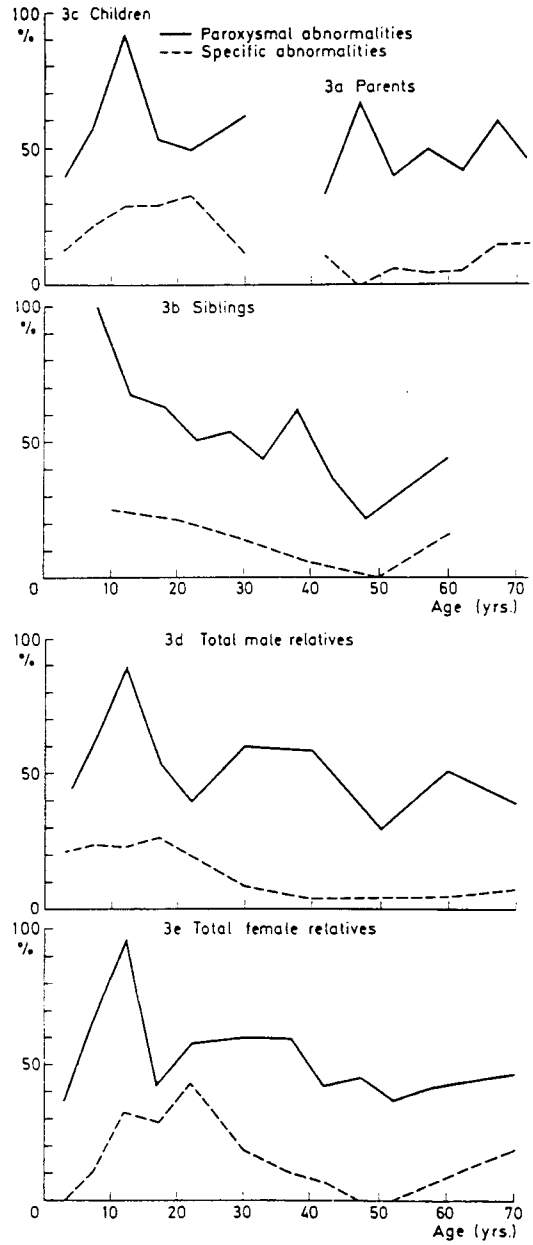

Figure 9. Graphs showing falling incidence of age related EEG abnormalities in relatives of JME patients (Tsuboi and Christian, 1973).

The existence of an EEG trait raises the problem of incomplete penetrance vs. expressivity of the condition. Initial reports regarding linkage of JME (Greenberg et al., 1988a) suggested that the EEG trait found subclinically may represent a marker for at least part of the disease genotype. For the purpose of linkage analysis, Delgado-Escueta et al. (1990) classified as affected not only patients with JME and generalized tonic-clonic seizures, but also asymptomatic family members who had EEGs with diffuse 4 to 5 Hz multiSW complexes or generalized spikes and sharp waves mixed with paroxysmal theta and delta rhythms. This group recommended ascertainment of EEGs in nuclear and extended families in the case of large pedigrees.

Whitehouse et al. (1993) did not see fit to investigate asymptomatic family members in the UK-Swedish study, commenting that "the availability of some EEG data on family members does not necessarily provide a valid, reliable or specific biological marker". Similarly, Panayiotopoulos and Obeid (1989) stated that "we wish to express our reservations about this practice of classifying clinically healthy relatives of JME patients as affected on the basis of non-specific EEG abnormalities". There are several potential methodological problems with the performance of EEGs on family members:

- EEGs may be normal in clinically affected cases, and presumably also at times in family members who at other times may well demonstrate the EEG trait.
- The syndrome is largely age-dependent and it is logical to assume that young children and adults of advanced age may not display an EEG abnormality, whatever their clinical state. Certainly, specific abnormalities show an age related decline in siblings and other relatives of patients with JME (Tsuboi and Christian, 1973). In the study of Metrakos and Metrakos (1961), they state that "the centrencephalic type of electroencephalogram is age-specific and tends to "burn itself out" by the time the patient reaches his late teens". The EEG traits that disappear after childhood are probably not related to JME and considering them as related to the JME phenotype would only introduce heterogeneity in the JME data set (Greenberg et al., 1988a).
- In particular, the decision to consider "diffuse paroxysmal theta rhythms, occasionally with spikes and/or sharp waves" (Greenberg 1988a), as indicating an affected status, is difficult to justify. The duration, distribution and precise characteristics of these rhythms have not been described, and their existence appears to be too non-specific to be given the same weighting as a polySW or 3-4 Hz SW discharge.

Nevertheless, the detection of the latter, specific discharges in asymptomatic family members is an important finding and cannot be entirely discounted. The practical problem is whether to consider such a finding as being indicative of affectedness. One may argue that if a patient is considered affected, for example, with a diagnosis of GTCS on the basis of only two convulsions with or without an abnormal EEG, the existence of a specific EEG disturbance in a clinically unaffected relative has ultimately a similar significance.

5.3.5.2 Aetiological and phenotypic heterogeneity

Heterogeneity may take place on several levels:

- genetic vs. non-genetic forms of epilepsy,
- the variety of forms of the idiopathic generalized syndromes,
- within a syndrome, the presence of different types of seizures.

This may represent the variable expressivity of a single gene defect or the expression of variable and possibly unlinked disease alleles with clinically overlapping phenotypes. "Genetic" and non-genetic forms of epilepsy can appear clinically identical, as can a variety of genetic forms: such genetic diversity can be the result of different genetic loci (e.g. different locations in the human genome) or different alleles at the same locus. It is likely that in epilepsy, with its many different syndromes, "genetic heterogeneity is the rule rather than the exception" (Lindhout et al., 1992).

Durner reports (1994), that after pooling her data of 1991 with that of Greenberg (1993) and the New York group (unreferenced), she was unable to prove heterogeneity, although it was not excluded.

5.3.5.3 Different modes of inheritance for the same epilepsy phenotype

This is reviewed in section 5.3.4. A classic example of this problem is that of childhood absence, which has been considered to be either AD with variable penetrance, or polygenic and multifactorial. Similarly, as noted previously, JME has been considered to be polygenic and multifactorial or either AR with consanguinity or AD with high penetrance.

5.3.5.4 Non-JME subtypes in JME families

Delgado-Escueta et al. reported in 1990 that they examined 412 nonproband family members in 60 families with an index case of JME, and the following were observed:

- JME was present in 45% of all affected members, 55% of affected siblings, 44% of affected parents, 9% of all siblings and 4% of all parents.
- CAE was present in 18% of affected siblings and not in affected parents.
- CAE plus GTCS was present in 22% of affected parents.
- GTCS only was present in 23% of all affected family members.

In the same report, the epilepsy phenotypes in 14 families with CAE probands were examined: 12 of the families had CAE plus GTCS, 2 had only CAE. Of 23 affected family members, 17% had CAE only, 39% had GTCS only and 26% had both syndromes, but only 4% had JME (Serratosa et al., 1990). In the study of Tsuboi and Christian, (1973) of 116 epileptic relatives, 15% had JME, and EGMA was present in 17%. Absence was present in 14%, although age criteria would not be currently considered appropriate, 37 of the patients having their onset of "impulsiv petit mal" before the age of 9 or over the age of 30.

According to Janz et al. (1992) of the three types of IGEs, CAE, JAE and JME, there is not a significant difference in terms of the incidence of first degree relatives affected, this varying from 4.5 to 5.8%. Although based on the incidence in the general population of the generalized epilepsies, he reports that this figure is about ten times more common in families of patients with IGE.

In studies of family members of patients presenting with either childhood or adolescent epileptic syndromes, only idiopathic generalized epilepsies are present as phenotypes. The fact that all concordant monozygous twins in Berkovic's study (1990) shared the same epileptic syndrome gives greater credence to the suggestion that the IGE subtype is genetically determined. The fidelity of the subsyndromes in monozygous pairs may indicate that the syndromes are genetically distinct. Similarly, Janz et al. (1994a) have reported in 21 families with absence epilepsy that 16 families shared the same form of absence, further supporting Berkovic's postulate.

Furthermore, pure absence not associated with tonic-clonic seizures, in contrast with other phenotypes, has an excellent prognosis, with a low remission rate after withdrawal from

medication, (Delgado-Escueta and Greenberg, 1984) as opposed to absence associated with tonic-clonic seizures and with JME. Thus, absence associated with tonic-clonic seizures and with JME probably represent genetically different disorders with separate modes of transmission.

5.3.6 LINKAGE STUDIES IN JME

The results of the linkage analysis studies are discussed below and a summary of the various reports is given in Table 8 (Linkage analysis in JME).

i) LOS ANGELES

Using clinical and EEG characteristics, Greenberg et al. (1987) reported in 11 families that maximum lod scores of 3.03 were obtained in a 60% penetrant AR model at a recombination fraction (θ) of 0.05 for HLA and Bf (properdin factor). The score for Bf alone was 1.68 at a θ of 0.1. This provisionally localised the JME locus to the 6p21.3 area. Of these 11 families, six had affectedness of family members determined by the EEG.

In the following year, the Los Angeles group (Greenberg et al., 1988b) reported the examination of 24 families with a proband with JME, with age of onset between 8 and 20 years. They assumed the same 60% penetrant AR model with a gene frequency of 0.1, and also did the analysis assuming fully penetrant AR and AD models. Of the 24 families, 11 were informative for Bf and the lod scores summed to 1.66 with an assumed AR inheritance and a penetrance of 60%. Bf is located in the middle of the HLA region, and by HLA typing in 3 families and substituting the HLA lod scores for the Bf scores a lod score of greater than 3 was obtained. Changing gene frequency and assumed penetrance made little difference.

If asymptomatic individuals with abnormal EEGs were not counted as affected, the Bf Lod score became negative and with HLA substitution remained negative at -3.6. Under AD inheritance, the lod score for Bf was 1.14 and for HLA, it was 1.24 at a penetrance of 30%, the latter figure being appropriate for the calculated segregation ratio.

Since the condition of whether or not asymptomatic individuals with abnormal EEGs were declared affected made a crucial difference as to the linkage of JME to the HLA locus, Greenberg et al. (1988b) concluded that "that the EEG paroxysms are related genetically to

the epilepsy, whether they fit the generally accepted definition of epileptiform or not". They stated that it is highly unlikely that if one were to assume that the EEG paroxysms were a *random* trait, and then subsequently to define them as related to the disease under study, this would lead to a positive linkage result. However, the presence of the characteristic EEG as a defining criterion was not used in *clinically* affected patients (Greenberg et al., 1988a). Patients were counted as affected when they had more than one seizure and/or were taking anti-seizure medication.

In the report of Delgado-Escueta et al. (1989) the same figures are again quoted, and, in addition, when AD inheritance was assumed, the combined lod score for HLA and BF was 2.6, and with a penetrance of 90%, the lod score was 3.9.

Subsequently, in 1990, 22 families were reported as being informative for HLA or Bf (Delgado-Escueta et al., 1990) and a maximum lod score of 3.78 was obtained ($\theta m=f=0.01$), with an AD/90% penetrant model. The maximum lod score for AR inheritance was 3.05 ($\theta m=f=0.05$). The family trees shown in this report indicate that 29% of those classified affected were done so on the basis of EEG abnormality alone.

A highest lod score of 4.2 at a θ of 0.01 under the assumption of dominant inheritance with penetrance of 70% was reported by Greenberg et al. in 1993.

A maximum total lod score of 5.5 for HLA-Bf in 24 informative families, with an assumed AD inheritance and 90% penetrance has been reported by Liu et al. (1992).

No evidence was obtained for linkage in these families by using the centromeric markers GLO1, D6S41 and a DNA marker, D6Z1 (Liu et al., 1991; 1992). These authors examined 11 families with a model-free sibling pair analysis and 15 families with the likelihood method. Probands were affected if they had JME, absence or grand mal or abnormal EEGs. Sibling pair analysis showed strong support for linkage between HLA and JME, but there was no evidence for linkage of JME to GLO or the centromeric DNA markers.

Table 8. Linkage analysis in JME.

	Greenberg 1988	Greenberg 1988	Greenberg 1988	Greenberg 1988	Delgado-E 1989	Delgado-E 1990	Delgado-E 1990	Delgado-E 1990	Weissbecker 1991	Weissbecker 1991	Durner 1991
n	24	24			?	33	33	33	23	23	21
age range	8-20										
'AFFECTED'	4-6Hz SW Parox Gen 0	Trait included	4-6Hz SW Trait excluded	Trait excluded	Trait excluded	Trait included	Trait included	Trait included	Trait included	Trait excluded +ABS/GTCS	Trait excluded +ABS/GTCS
n: Informative Bf	11					18					
n: HLA	3					4					
Marker	Bf	HLA sub Bf	Bf	HLA sub Bf		HLA+Bf	Bf	HLA	HLA	HLA	HLA-DQ RFLP
Lod score: AD	1.14	1.24				3.78	2.12	1.86	2.74	3.11	3.9
0 = m; f						0.01; 0.01	0.01; 0.01	0.01; 0.4	0.001; 0.50	0.001; 0.20	0.01; 0.01
Penetrance	0.3	0.3				0.9	0.9	0.9	0.9	0.9	0.7
Lod Score: AR	1.66	3.04	<-2.0	-3.6	>4.0	3.05	1.93	2.67	0.23	2.73	1.5
0 = m; f	.01; .01	.01; .10			?	0.05; 0.05	0.2; 0.01	0.01; 0.1	0.20; 0.50	0.001; 0.50	
Penetrance	0.6	1			?	1	1	1	1	1	
Method	LIPED	LIPED	LIPED	LIPED					LIPED	LIPED	LIPED
Seg Ratio	0.15-0.14		0.04-0.03								

Explanation of abbreviations

n	number of families
'AFFECTED'	criteria used to determine affectedness status, including or excluding the EEG trait in asymptomatics
Trait	presence of abnormal EEG pattern in asymptomatics
ABS	absence seizure
GTCS	generalized tonic-clonic seizure
AD	autosomal dominant
AR	autosomal recessive
sub	substituted for
Method	technique of linkage analysis
Seg Ratio	segregation ratio

Table 8 (continued). Linkage analysis in JME.

Durner 1991	**Whitehouse 1993**	**Whitehouse 1993**	**Panay 1988**	**Delgado-E 1994**	**Liu 1992**	**Janz 1994**	**Greenberg 1993**	**Greenberg 1993**	**Greenberg 1993**	**Carr 1995**
21	25	25	17		12	16	35			6
	2-30	2-30	5-18		Reported DE 9					9-34
Trait included	Trait excluded +ABS/GTCS	Trait excluded +ABS/GTCS	Trait excluded +ABS/GTCS			Trait included +CAE/GTCS/JA	Trait included		Trait excluded	Trait excluded +GTCS
							either Bf			
					6p reference		or HLA(24)			
HLA-DQ RFLP	HLA-DQA1/A2	HLA-DQA1/A2				HLA				HLA-DR
4.1	073-0.76	<-2.0			Neg	4.87	4.2	>3.0	<1	-3.07
0.01; 0.3	0.20						0.01; 0.01			0.1
0.9	High-Low	Low			0.7	0.7	0.7	0.1		1.0
0.9	1.4	<-2.0					3.1			
	0.20						0.05; 0.2			
	0.9						0.8			
LIPED	LINKAGE	LINKAGE			Pair-wise					LIPED
	Two point	Mulitpoint	0.12-0.18	0.15-0.28						

This results suggest that there is heterogeneity within the IGEs and in JME, since Liu et al. (1992) have demonstrated that there are families with JME which do not map to chromosome 6p.

Subsequently, Delgado-Escueta et al. (1994a) reported screening 12 families with eight chromosome 6p reference markers above and below HLA, with consistently negative lod scores. No apparent phenotypic or EEG differences exist between JME patients who do or do not map to 6p. Further review of this data shows that only half of the 12 families are informative both for DNA markers and for HLA/Bf, so that the comparison between the HLA/Bf typing and Bf markers is not based on identical family samples.

In a report from 1993 (Greenberg and Delgado-Escueta), of 35 families, 24 were informative for either Bf or HLA and lod scores of 4.2 were obtained if the EEG trait in unaffecteds was accepted, based on an AD model with a penetrance of 70% and θ of 0.01. If the unaffecteds with EEG trait were excluded, the lod score varied between 0.5 and 0. When the family members with other seizure types were excluded, under the initial parameters, the lod score dropped, although a score obtained under AR inheritance was higher. As the lod score was not significantly different whether the non-JME cases were classified as affected or unaffected, the different phenotypic forms of epilepsy seen in JME families may represent a single genetic disturbance.

In the most recent report of Serratosa et al. (1996), a three generation pedigree from Honduras was examined and maximum lod scores of 3.43 at $\theta m=f=0.00$ were obtained for DNA markers centromeric to the HLA locus, this study classifying asymptomatic cases with fast polySW complexes as affected.

ii) BERLIN

In a study by Weissbecker et al. (1991) the provisional linkage of JME with the HLA region of chromosome 6 was reportedly confirmed.

The Berlin group used HLA serological markers in 23 families ascertained through JME probands, and the study was thus independent of the Los Angeles group, although contributed to by some of the same authors. The affected status of relatives of the probands was assigned by 4 definitions of the disease phenotype:

A: JME only(Relatives with abnormal EEGs not counted).

B: JME, GTCS, Absence(Relatives with abnormal EEGs not counted).

C: JME, GTCS, Absence, EEG abnormality counted as affected.(This definition corresponds to that of the Los Angeles group).

D: Any history of seizure, including febrile seizures. Relatives with abnormal EEGs included.

The data were analysed for linkage under 2 genetic models:

AD with 90% penetrance and 70% penetrance.

AR with full penetrance and 90% penetrance.

Lod scores were calculated at recombination frequencies ranging from 0.01 to 0.50.

Evidence for linkage of JME to the HLA region was found with the AD/90% penetrant model, using definition B and resulting in a lod score of 3.11 at $\theta m=0.001$, $\theta f=0.20$.

Using definition B, and $\theta m=0.001$ and $\theta f=0.50$, suggestion of linkage could be obtained with an AR/fully penetrant model, the lod score being 2.73.

When EEG data of non-affected relatives was included, tight linkage was excluded. The findings with regard to the effect of including unaffected members with abnormal EEGs as positive are therefore contradictory to the LA group: the results of linkage were highest under both genetic models when the phenotypes classified as affected included all forms of IGE, and excluded EEG data of unaffected family members. The findings were also against *tight* linkage, and further, that θf was much higher than θm at the highest lod score.

A subset of 21 of these families were studied using restriction fragment length polymorphism markers in the HLA-DQ region on chromosome 6, patients being classified under one definition as affected when they had JME, absence and/or GTCS, and in a second definition, asymptomatic family members with generalized SW patterns were included, giving rise to lod scores of 3.9 ($\theta m=0.01$, f=0.01) and 4.1 ($\theta m=0.01$, f=0.3) respectively (Durner et al., 1991).

Maximising the lod score with respect to penetrance gave a lod score of 3.9 at a penetrance of 70%, with AD inheritance assumed. Data was analysed using the LIPED program and assumed a range of penetrance values from 0.1 to 0.9, and various recombinant fractions.

All 21 families were fully informative for the HLA-DQ locus. Analysis of data under a recessive mode of inheritance gave much lower lod scores: 1.5 and only 0.9 if EEG data was included.

These authors suggest that the gene on chromosome 6 may be a general susceptibility gene for IGE, "or a triplet of JME, absence and grand mal epilepsy".

However, in a genetic linkage study in 10 CAE families, linkage was excluded between DNA markers in the 6p chromosome (Short tandem repeat polymorphism at TNF locus) with use of the LINKAGE package and varying modes of inheritance and penetrance, with asymptomatics with abnormal EEGs considered as being affected. Total lod scores were strongly negative. This is against the concept that a 6p gene locus is shared by JME, CAE and EGMA (Serratosa et al., 1993).

Subsequently, Janz (1994b) has examined 25 pedigrees and used 16 for linkage analysis, categorising as affected patients with CAE, JAE, single seizures and SW on EEG in addition to patients with JME. Positive lod scores with an autosomal dominant model were obtained, and reducing penetrance from 0.7 to 0.5 made individual families who were initially negative generate a positive lod score. Larger families and those with more affected members generated more positive scores and curiously, those with affected members with absence epilepsies generated the highest scores. Similarly, a history of febrile convulsions and subclinical SW favoured linkage. They concluded that the EJM1 locus is located near to the HLA region.

iii) NEW YORK

Greenberg has also looked at families in the New York area: 13 families with JME and 5 families with non-JME forms of IGE (adolescent onset of Tonic-Clonic seizures). Linkage to the JME families for HLA gave rise to a lod score of 1.8, (penetrance of 0.8) and for non-JME families was negative at all values of θ and less than -2 for low values of θ. They conclude that a proportion of IGE has a genetic basis different to that of JME, but that this does not rule out that another non-6p locus is common to both JME and IGEs.(Greenberg et al., 1992b)

iv) LONDON

In a study from the United Kingdom and Sweden (Whitehouse et al., 1993) linkage analysis was performed in 25 families with a proband with JME and at least one first-degree relative with IGE. Family members were typed for eight polymorphic loci on chromosome 6p. Pairwise and multipoint linkage analysis was carried out assuming autosomal dominant and autosomal recessive inheritance and age-dependant high or low penetrance. The definitions used are those of the first definition of Durner et al. (1991) and that of category B used by Weissbecker et al. (1991). However, patients were included with GTCS of onset at the age of 2.

Thus, in this study EEG traits in normal family members were not used, for reasons reviewed previously. As Whitehouse et al. note: "In the absence of Mendelian inheritance, the specifications concerning mechanism of inheritance, the dominance of disease-causing alleles, and penetrance, which are used for linkage analysis, are bound to be arbitrary. Assumption of a falsely high penetrance may generate spurious exclusion data, as individuals with the disease genotype who lack the disease phenotype may appear as recombinants. A more stringent approach might be to assume low penetrance, but this involves loss of power, as information from unaffected individuals tends to be disregarded...Whether the mode of inheritance can be inferred from comparison of lod scores remains controversial and computer simulation methods indicate that maximisation of the lod score over model parameter values - as done by Greenberg et al. (1988b) - leads to substantial inflation."

The data of Whitehouse et al. provides evidence against the existence of a locus predisposing to IGE in families of patients with JME. One explanation may be that there is locus heterogeneity within this particular epilepsy phenotype, with the present group of families not including a significant proportion of linked families. However, these authors raise concern as to the possibility of spurious linkage results in other studies, commenting that the significance of linkage in these studies is reduced by the maximisation of the lod scores over different parameters.

6 CONCLUSION

Two main conclusions may be drawn from this study:

1) Linkage to the HLA locus was not found.

2) In South Africa, JME and the other IGE syndromes are similar to those previously described in other countries.

1) The aim of this study was to assess whether linkage to the HLA locus could be established in a South African population of patients with JME. The results of the analysis are against such linkage being present. Similar findings have been reported from patients in the United Kingdom and Sweden (Whitehouse et al., 1993) and Delgado-Escueta et al. (1994a) found negative lod scores when they searched for linkage using markers above and below the HLA locus.

The negative lod scores may be attributed to genetic heterogeneity, but this must remain an open question. Despite an apparently uniform clinical picture, various groups have not used the same criteria to determine the status of family members in JME studies. It is not surprising that varied results have been obtained from the genetic studies of JME. A prominent example of this is the role of the EEG trait, which was initially (Greenberg et al. 1988b) given an important role in the linkage analysis, since its presence or absence made the difference between a positive or a negative lod score. Subsequently, Weissbecker et al. (1991) demonstrated that the inclusion of the trait *lowered* the lod scores.

The inconsistent findings emphasise the need for agreement on the definition of the phenotype. JME is widely accepted to be a clinical entity, but it does not seem to be a precise genetic entity. From the presently available evidence it is likely that a locus on 6p is part of the story, but it is not well enough defined to permit a direct search for the gene. Despite claims that the odds in favour of linkage are now 25 million to one (Durner, 1994) , manipulation of recombinant fractions, penetrance and modes of inheritance have been the rule in the history of the search for the gene causing JME.

Whether or not genetic heterogeneity exists, this study suggests that in the population studied, the gene for JME is not located near the HLA locus. The findings may be criticised

on the grounds that, in comparison with other studies, only five families were examined. In part, the large number of families required for linkage studies reflects the fact that single families with large numbers of affected individuals do not exist if one accepts only 'pure" JME as the criterion for affectedness. The *maximal* number of affected patients with JME in a particular family varied from three in the United Kingdom and Sweden (Whitehouse et al., 1993) to two in Berlin (Durner et al., 1991) and six in Los Angeles (Delgado-Escueta et al., 1990). The number of affecteds with any form of IGE (including absence) was four in the study of Whitehouse et al., four in the Berlin study, and six in Los Angeles. In this South African study the maximal number of affected individuals with JME was 5, and the total number of affecteds was 19, an average of 3.9 per family, with relatively larger sibships than in other studies. The families represent a well-defined group of uniform phenotype, appropriate to the purpose of assessing linkage to the HLA locus. Although the study examined patients of mixed ancestry, Caucasians and the South African Negro population, the families used for linkage analysis were drawn exclusively from the mixed-ancestry group. A problem which may arise in studying JME is that, perhaps owing to the paucity of families with multiply affected members, age inclusion criteria may vary. All the patients in this study had seizures disorders beginning only after the age of 9 years. Similarly, inclusion of seizure types, such as pure absence (CAE), which are unlikely to form part of the spectrum of the clinical presentation of JME, may be included amongst families subjected to linkage analysis, although in this study the seizure type were restricted entirely to JME or GTCS. Furthermore, in some studies, families may only become multiplex or multigenerational on the basis of the EEG trait, as illustrated by Delgado-Escueta et al. (1994b) who reported that following contradictory reports of genetic heterogeneity, they reviewed the families they studied initially, and concluded that in more than half affectedness of a family member was determined by the EEG.

2) JME and the other IGE syndromes have been observed in Europe, the United States, Japan and Saudi Arabia. The EEGs used to identify patients in this study were obtained from a population comprising Caucasians, the South African Negro population and a group of mixed ancestry. The syndromes of JAE, JME and GTCS are well represented in the population studied, and the absence of the syndrome of EGMA is likely to represent the fact that such patients tend to have JME. In particular, the syndrome of JME shares the same characteristics as described in other countries. The characterisation of the IGE syndromes in population groups other than those which gave rise to the original description lends credence to their identity as separate entities. This may lead to more accurate definition of the subtypes with potential for improved genetic studies.

Of practical importance, regarding the local experience of JME this study confirmed the experience of other centres, in that the syndrome was underdiagnosed. As a result, most patients had not received appropriate drug therapy until the time that JME was actually diagnosed.

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APPENDIX 1

LOD SCORES OF INDIVIDUAL FAMILIES (A - E)

(penetrance values of $\theta = 1.0$)

FAMILY A

R MALE	R FEMALE	LOD SCORE
0	0	-99.99
0.01	0.01	-1.11
0.05	0.05	-0.464
0.1	0.1	-0.229
0.2	0.2	-0.06
0.3	0.3	-0.011
0.4	0.4	-0.001

FAMILY B

R MALE	R FEMALE	LOD SCORE
0	0	-99.99
0.01	0.01	-4.207
0.05	0.05	-2.164
0.1	0.1	-1.331
0.2	0.2	-0.581
0.3	0.3	-0.227
0.4	0.4	-0.053

FAMILY C

R MALE	R FEMALE	LOD SCORE
0	0	-99.99
0.01	0.01	-2.508
0.05	0.05	-1.165
0.1	0.1	-0.637
0.2	0.2	-0.2
0.3	0.3	-0.038
0.4	0.4	0.003

FAMILY D

R MALE	R FEMALE	LOD SCORE
0	0	-99.99
0.01	0.01	-0.813
0.05	0.05	-0.186
0.1	0.1	0.022
0.2	0.2	0.124
0.3	0.3	0.095
0.4	0.4	0.031

FAMILY E

R MALE	R FEMALE	LOD SCORE
0	0	-99.99
0.01	0.01	-2.805
0.05	0.05	-1.442
0.1	0.1	-0.887
0.2	0.2	-0.388
0.3	0.3	-0.151
0.4	0.4	-0.035

TOTAL	LOD SCORE
0	**-499.45**
0.01	**-11.45**
0.1	**-3.07**
0.2	**-1.10**
0.3	**-0.33**
0.4	**0.02**