Juvenile myoclonic epilepsy

Epilepsy with impulsive petit mal

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HISTORY

LIKE the first patient known to have infantile spasms,[1] the first patient with juvenile myoclonic epilepsy (JME) whose history was well known was a doctor's son. Herpin,[2] author of the classical report on this condition, attempted to circumscribe the principal symptom with various terms, such as "impulsions," "sécousses," "commotions épileptiques," without attaching any labels to it (*Table 1*).

Rabot[3] later introduced the neutral yet expressive description "myoclonia" into the terminology of epilepsy. In order to prevent confusion with the rare, progressively degenerative myoclonus epilepsy, Lundborg[4] in his terminology emphasized the intermittent nature of the jerks. In 1957, Christian and the writer[5] described this type of idiopathic epilepsy, characterized by intermittent morning jerks, on the basis of 47 cases as a clinically and clearly definable epileptic syndrome. Almost thirty years later, this syndrome has been rediscovered in the United States and brought to the notice of the English-speaking world by Asconapé and Penry[6] and by Delgado-Escueta and Enrile-Bacsal.[7] Delgado-Escueta, and before him, Matthes[8] honored the writer by naming the syndrome after him.

CLINICAL MANIFESTATIONS

Myoclonic jerks

The cardinal symptom of JME—myoclonic jerks—is a pattern of very short, bilateral, symmetrical and synchronous muscle contractions, affecting mainly the shoulders and arms. They may occur singly or in close succession in clusters of a few jerks at irregular intervals, and they may vary in frequency and intensity. Sometimes they are only perceived inwardly like mild electric shocks, but they may with equal frequency lead to movements so violent that the patient may throw down objects he is holding. As the jerks occur predominantly after waking, irrespective of whether the patient has gotten up or is still lying in bed, the objects thrown and sometimes broken are usually those connected with the patient's toilet in the morning or his breakfast. If the jerks are violent, the patient may drop to his knees, or in rare cases may even fall down completely, but will get back on his feet again immediately. In exceptional cases the jerks occur in only one arm;[9–11] in rare cases, the jerks are both monolateral and bilateral.[11] Occasionally, especially if the patient continues what he is doing and does not lie down immediately, the jerks may occur in a protracted series or may lead to a true myoclonic status,[9,12,13] which Gastaut[14] classified as "myoclonic status epilepticus in generalized epilepsy." An "impulsive petit mal status" of this sort is reminiscent of a chorea-like presentation with more or less violent jerks at irregular intervals.

Unlike absences, which may also be accompanied by jerks of eyelids, eyeballs, and arms (although these are usually of less violent intensity and are of a regular and rhythmic nature), the jerks in JME occur while the patient is fully conscious. Such a stimulus as a sharp knock may cause the patient to appear momentarily "in a fog" or briefly "miles away." However, even jerks occurring in series or in status do not give rise to any impairment of consciousness. For this reason, the possibility of confusion with what are known as myo-

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TABLE 1
SYNONYMS

Disease name	Investigator	Date
Impulsions, sécousses, commotions épileptiques	Herpin[2]	1867
Myoclonie épileptique	Rabot[3]	1899
Intermittierende myoklonische Epilepsie	Lundborg[4]	1903
Myoclonic epilepsy	Lennox[54]	1945
Epilepsie myoclonique benigne ou fonctionelle	Solé-Sagarra[55]	1952
Myoclonic petit mal	Penfield & Jasper[56]	1954
Impulsiv-Petit mal	Janz[28]	1955
Epilepsia mioclónica bilateral y consciente	Castells & Mendilaharsu[57]	1958
Epilepsie generalisée a myoclonies intermittentes ou sporadiques	Lécasble[58]	1958
Jerk epilepsy	Lennox[59]	1960
Janz-Syndrom	Matthes[8]	1969
Juvenil myoclon epilepsi	Lund[60]	1975
Myoclonic epilepsy of adolescence	Jeavons[61]	1982
Juvenile myoclonic epilepsy of Janz	Delgado-Escueta[7]	1984

clonic absences can be ruled out.

Cases of pure impulsive petit mal, i.e., patients who have hitherto experienced only morning jerks, are rarely seen in clinical practice. The reason for this lies in the fact that patients (and doctors, too, when they are consulted about them) are happy to dismiss such disorders as "nervous reactions" or "stress reactions." This is not entirely unjustified, because the jerks, and incidentally major seizures as well, generally manifest themselves initially following events which are associated with a lack of orderliness in the patient's way of life, with a lack of sleep, frequently with excessive consumption of alcohol, and with being waked prematurely.

Generalized tonic-clonic seizures (GTCS)

The syndrome usually starts with jerks, which are followed by GTCS after an average period of between 1.3 years[11] and 3.3 years.[9] The seizures are often similar to those described by Delgado-Escueta et al[15] as clonic-tonic-clonic, because they are often preceded by generalized jerks which advertise their coming just minutes in advance with a series of regional jerks of increasing intensity. In most cases, the major seizures, like the myoclonic jerks, occur after waking. As patients with JME tend to have a less than orderly way of life and are inclined to go to bed late and to rise late, the reported time of day at which the seizures occur may be misleading. They follow the pattern of so-called awakening epilepsy, in that jerks and seizures occasionally may occur also in the evening when the patient is in a relaxing situation.[9,16–18] Also like pure awakening epilepsy, the seizures are very sensitive to external precipitating factors, among which lack of sleep, often combined with alcohol and premature awakening, plays a crucial role.

Neurologic findings

Pathologic findings are not part of the clinical picture. In 280 cases, the writer has only once seen a patient with residual hemiplegia following perinatal injury.[9] Simonsen et al[19] mention "neurological findings" in six out of 35 cases and Tsuboi[20] in 24 out of 399 cases. In our latest series of 181 cases, we did not have a single patient with pathologic findings.[11] We also failed to find anything of etiologic relevance in either computed tomograms of the cranium[21] or in magnetic resonance tomograms.[22] We noticed, however, remarkably frequent signs of diffuse cortical brain atrophy.

Psychological findings

Mental behavior appeared to us to be less normal. Admittedly, all the researchers point out that impaired intelligence has been observed only in exceptional cases[19,20] or not at all[6,7]; Tsuboi[20] and Simonsen et al[19] recorded psychiatric symptoms or "disorders of character" relatively often, although without giving more details. They are very probably alluding to the personality traits we describe as typical—an engaging, but emotionally unstable, fairly immature personality, wavering between camaraderie and mistrust, which may lead to difficulties in social adaptation.[5,9] These traits which point to a degree of disturbed maturation are consistent with the habit observed in almost all patients with JME of going to bed late, with the associated consequences in terms of precipitating seizures. This is also consistent with a tendency to conceal the illness and the problems this consequently presents for treatment. Controlled psychological and sociological studies have confirmed the observation in practice that patients with JME frequently display neurotic character traits,[5] and a tendency, albeit not significant, to inadequate social adjustment.[23–25]

Neuropathologic findings

From the clinical standpoint, JME is a generalized idiopathic form of epilepsy. There has not been a single reported case in which the clinical manifestations were associated with cerebral trauma, encephalitis or brain tumor. From the neurologic point of view, there are reasons for believing that an undisclosed early disturbance of brain development underlies JME, as it does other forms of generalized idiopathic epilepsy. In our examination of the brains of 15 patients with primary generalized epilepsy, three of whom had JME, we found a number of changes in the form of microdysgenesis in all but one case.[26,27] These changes consist of an increase in partially dystopic neurons in the stratum moleculare, the white matter, the hippocampus and the cortex, an indistinct boundary between cortex and subcortical white matter and between lamina 1 and 2, as well as a columnar arrangement of cortical neurons. We hypothesize that microdysgenesis is the morphologic expression of the conditions responsible for generalized epilepsy. It could originate early in fetal life or could be the result of a genetic defect altering cerebral development between the seventh gestational month and birth.

Nosologic position

The nosologic relationship of JME to the other forms of generalized idiopathic epilepsy can best be demonstrated by means of a diagram (*Figure 1*).

For the sake of clarity we will leave generalized epilepsy of early childhood on one side and will confine ourselves to a comparison of those forms of generalized epilepsy which begin in children of school age and during adolescence. Overlapping circles represent the following subtypes of generalized epilepsy which are attended by minor seizures: pyknolepsy or epilepsy with childhood absences, so-called juvenile absence epilepsy, and so-called JME attended by impulsive petit mal. The oval above the circles represents so-called awakening epilepsy associated with GTCS predominantly after waking.

The position of the circles and the oval corresponds to the age at which the respective subtypes first appear.

Age of onset

In the majority of cases, epilepsy with pyknoleptic absences begins between the ages of 5 and 10 with a peak between 6 and 8.[9,28,29] Epilepsy with nonpyknoleptic juvenile absences begins between 10 and 15;[9,30–32] and JME usually (79%) begins between the ages of 12 and 18.[9] The onset of awakening epilepsy

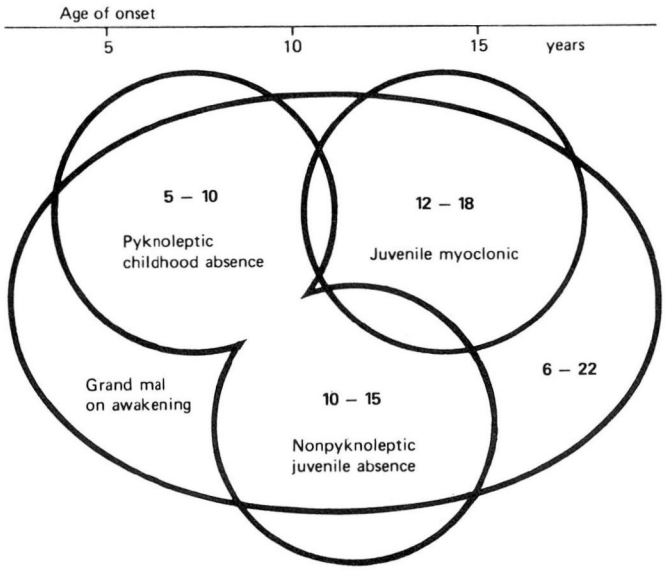

FIGURE 1. Subtypes of idiopathic generalized epilepsy: clinical overlapping and age of onset.

ranges over the entire period.[9,18] According to Tsuboi and Christian,[33] 78% of cases begin between the ages of 6 and 22.

In our group of 181 cases in Berlin, the mean age of onset of JME was 14.6 years (median 14.3). Half of the patients developed the condition between the ages of 13 and 16; a quarter of them before that time, and a quarter of them later. As onset is usually heralded by jerks, to be followed after an average of 3.3 years,[9] (or in individual cases not until decades later) by major seizures, the mean age of onset for jerks is earlier than for GTCS. At the earliest, jerks began at the age of 8 and at the latest at the age of 36. The highest frequency by far (124/152 = 81.6%) was between 12 and 19.[11]

Incidence

The frequency with which one encounters patients with JME depends on the type of hospital or practice in which one works. While Bamberger and Matthes[34] in the Heidelberg Paediatric Hospital made the diagnosis in only 3.1% of patients with epilepsy, Tsuboi and Christian[33] in the Epilepsy Outpatients' Department of the Heidelberg Neurological Hospital found the condition in as many as 7.5%. In our Neurological Hospital in Berlin, caring mainly for adults, we found 11.3%,[35] and approximately the same prevalence as Obeid and Panayitopoulos[36] (10.7%), in Saudi Arabia. Generalized epilepsy of early childhood (West's syndrome and

TABLE 2
SUBTYPES OF GENERALIZED EPILEPSY—INCIDENCE (%)

	Bamberger and Matthes 1959	Janz 1969		Tsuboi and Christian 1976	Wolf and Goosses 1986	
N =	466	6500		466	1069	
Infantile spasms	13.4	1.8	2.9	2.7	3.9	
Myoclonic astatic		1.1				
Childhood absence	12.9	7.8	10.8	15.0	9.0	17.0
Juvenile absence		3.0			8.0	
Juvenile myoclonic	3.1	4.3		7.5	11.3	

Lennox-Gastaut syndrome) presents a diametrically opposite picture, accounting for 13.4% of the epileptic population in pediatric practice, and only 2.7% to 3.9% in neurologic clinics (*Table 2*).

Remarkably, the two forms of absence epilepsy appear to be encountered by pediatricians and neurologists with approximately the same incidence of 13% to 17%. One will therefore not go far wrong in assuming that the percentage of JME in an unselected patient population comprising children, juveniles and adults in equal measure will be about 7% to 9%, that it will be found to occur in about the same numbers as the percentage of each of the two subtypes of absence epilepsy, and only a little higher than the percentage of each of the two subtypes of generalized epilepsy of early childhood. The incidence of epilepsy with awakening grand mal, with or without minor seizures, amounts to between 27%[9] and 31.5%[33] in a population comprising both juveniles and adults. The assumption that awakening epilepsy occurs in about 25% to 30% of cases in an epileptic population consisting of all age groups is therefore probably no exaggeration.

Combinations

In a few patients—7% (13/188) in our latest case studies,[11] or 8% to 17% in others[37]—jerks are the only manifestation. GTCS also develop in by far the greater number of cases. About a third (35.7%) of these have only a few seizures. Of those who had more than six major seizures, the overwhelming majority (89.8%) behaved as in awakening epilepsy.[38] Combination with absences is reported in 10% to 37% of cases.[37] In our patients in Berlin, we recorded this combination in 28% (51/181).[11] In a minority, namely 6%, the absences occurred daily, i.e., in a pyknoleptic manner; but a larger percentage (22%) did not have them every day, i.e., a nonpyknoleptic pattern. Only one patient had previously had epilepsy in childhood with myoclonic-astatic petit mal, but this had disappeared years before the onset of JME. The incidence of febrile seizures in JME was lower than in Lennox-Gastaut syndrome and lower than in both forms of absence epilepsy; but its incidence of 4.4% was equivalent to that in the general population.

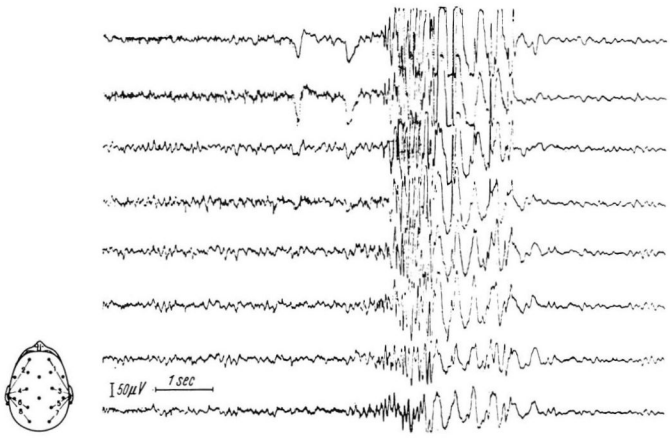

FIGURE 2. Ictal EEG in JME: generalized multispike wave pattern.

ELECTROENCEPHALOGRAPHIC (EEG) MANIFESTATIONS

Ictal

While a generalized 3 Hz spike-and-wave pattern is regarded as characteristic of absences in pyknolepsy, and the same pattern, but with a rather higher frequency of 3.5 to 4 Hz, is typical of juvenile absences, the characteristic EEG for jerks in JME is a bilaterally symmetrical, fronto-centrally accentuated polyspike-and-wave complex (PSW) (*Figure 2*).

A burst of spikes suddenly occurs simultaneously with the jerks and is followed by slow waves of varying frequency and amplitude. The spikes usually have a frequency of 10 to 16 Hz, and the slow waves preceded by or superimposed on the spikes have a frequency of 2 to 5 Hz. The number of spikes ranges from 5 to 20, and is evidently more closely related to the intensity rather than to the duration of the jerks. The EEG pattern may last longer than the clinical seizure. The PSW complex lasts for 2 to 10 seconds, even though the jerking may have ceased after only 1 to 1.5 seconds. Spikes have negative polarity and may reach amplitudes of 150 to 300 mV. The slow waves have a mean amplitude of 200 to 350 mV, rarely more than 400 mV. The PSW

TABLE 3
DIFFERENT SPIKE-WAVE PATTERNS IN 181 PATIENTS WITH JME*

	N	%
Polyspike-wave	89	49
Bispike-wave	56	31
4–6 Hz spike-wave	94	52
2.5–3.5 Hz spike-wave	99	55
2–2.5 Hz spike-wave	5	3
Irregular spike-wave	13	7

* Adapted from ref 11.

pattern does not display such strict synchronism as the 3 Hz spike-and-wave complex characteristic of pyknoleptic absences.[39] The pattern described is the characteristic equivalent of jerks. We recorded ictal PSW patterns in 14 out of 38 patients (39%) (63 leads).[5] Delgado-Escueta and Enrile-Bacsal[7] found them in 16 out of 43 patients (37%).

Interictal

Interictal PSW patterns usually display fewer spikes and are also often restricted to the frontal leads. If 3 Hz spike-and-wave complexes occur, the patient usually has absences as well. If there is a combination of absences with myoclonic jerks, one can occasionally record the EEG patterns characteristic of both forms of seizure.[5]

PSW patterns are admittedly not the most commonly occurring patterns but are the most specific patterns in JME. We found them in 49% of cases, taking into account all the EEGs from 181 patients. We found rapid spike-and-wave patterns of 4 to 6 Hz in 52% and "classical" patterns of 2.5 to 3 Hz in 55% (*Table 3*).[11]

Nevertheless, "rapid" and "classical" spike-and-wave patterns without PSWs occur only in 9% and 5.5%, respectively, of all patients with JME. In an analysis of the EEGs containing the most specific patterns, Tsuboi[20] found that PSW is the most common of all variations of spike-and-wave pattern occurring in JME, and that it occurs most frequently in JME as compared with the other forms of generalized epilepsy.

PRECIPITATING FACTORS

Hyperventilation, sleep deprivation

Our impression that hyperventilation may frequently provoke both ictal and interictal discharges in the EEG (although less frequently than in cases of pyknoleptic absences) has not been statistically tested. Similarly, the experience reported by several investigators suggesting that sleep deprivation is the most provocative factor has not been proven in comparison with other forms of epilepsy. However, after analyzing polygraphic recordings of the sleep of 18 patients (11 with and seven without grand mal), Touchon et al[40] reported that sleep deprivation is an effective method of provoking seizures in cases of JME. They were able to ascertain that the condition of the central nervous system during the transfer from the sleeping to the waking state—and conversely, although to a lesser extent—is favorable to the production and spread of epileptic activity. PSW discharges occurred more frequently after nighttime awakening than after morning awakening, less frequently during the relaxation period before sleep and during Phase 1 sleep, seldom during rapid eye movement (REM) sleep, hardly ever during Phase 2 sleep, and never in deep nonREM sleep.

The clinical observation that seizures are often brought on by sudden awakening is echoed by the finding that provoked awakening results in a higher rate of discharge than spontaneous awakening. The effect was more noticeable when sleep was interrupted during the unstable phases (such as REM sleep during the early part of the night or in Phase 2 at the end of the night).

TABLE 4
PHOTOSENSITIVITY AND EPILEPTIC SYNDROMES*

	Total N	Photosensitive n	Photosensitive %
Whole cohort			
Generalized epilepsies	598	91	15.2
Localization-related epilepsies	434	12	2.7
Syndromes of generalized epilepsy			
West and Lennox syndromes	41	7	17.1
Childhood absence epilepsy	94	17	18.0
Juvenile absence epilepsy	80	6	7.5
Juvenile myoclonic epilepsy	121	37	30.5

* Adapted from ref 35.

TABLE 5
PHOTOSENSITIVITY AND SEX RATIO IN DIFFERENT SUBTYPES OF JME*

	Total cohort N	Photosensitivity					
		Total		Males		Females	
		n	%	n	%	n	%
JME without absences	130	54	41.5	14	27	40	51.3
JME with absences	51	15	29.4	6	24	9	34.6
JME without grand mal	12	9	75.0	3	50	6	100.0
Total	181	69	38.0	20	26	49	47.1

* Adapted from ref 11.

TABLE 6
PROPORTION OF JME PATIENTS WITH SEIZURES IN RELATIVES

	N	n	%
1957 Janz & Christian	47	8	17
1958 Castells & Mendilaharsu	70	26	37
1969 Janz	280	70	25
1973 Tsuboi & Christian	319	87	27
1984 Delgado-Escueta & Enrile-Bacsal	43	17	39
1988 Obeid & Panayiotopoulos	39	19	49
1988 Durner et al	100	32	32

Induction of seizures by awakening is thus favored by an unstable initial state or by a sudden transition from one state to the other.

The fact that the rate of discharges occurring on spontaneous awakening was found to be higher after the second phase of sleep than after the first can be convincingly interpreted as a result of lack of sleep, since the total duration of sleep was shortened by repeated awakenings only during the second half of the night.

Photosensitivity

Photosensitivity, i.e., the precipitation of bilaterally synchronous spike-and-wave patterns by flickering lights, can frequently be found in patients with JME. This genetically determined bioelectric reaction occurs significantly more frequently in JME than in other subtypes of generalized idiopathic epilepsy[35] (*Table 4*).

Photosensitivity was found in 30.5% of all JME patients, compared with only 18% of patients with childhood absence epilepsy, 13% of patients with awakening epilepsy, and only 7.5% of patients with juvenile absences. The true figures are probably even higher, because photosensitivity is a variable correlated with age. Patients with JME were examined on average 7 to 8 years later than patients with childhood absences and with juvenile absences, and were still more frequently photosensitive.[35] Jeavons and Covanis[41] found photosensitivity in 22 out of 45 of their younger patients with "myoclonic epilepsy of adolescence." A particularly remarkable feature, however, is that the high percentage of photosensitivity is attributable to the proportion of girls in the group. In comparison with other forms of generalized idiopathic epilepsy, the phenomenon of photosensitivity can be detected with greater frequency only in girls with JME.[35]

Evidently the simultaneous occurrence of absence and of grand mal reduces the sex-related difference in photosensitivity. According to our own investigations, 51.3% of girls with JME but without absences are photosensitive, and actually 100% of girls with myoclonic jerks but without grand mal are photosensitive (*Table 5*).

Asconapé and Penry[6] observed one case where eye closure after waking appeared to initiate PSW with jerks. The phenomenon does not appear to be rare in this type of epilepsy. Christian[39] and Janz[9] had already provided several examples. Goosses[42] found interictal PSW complexes initiated by closing of the eyes in 26 of his 121 JME patients (21%), together with photosensitivity in 20 patients. Closing of the eyes again appears to be a more frequent initiating factor with JME than with other forms of generalized epilepsy (10.5% in GTCS on awakening, 15% in juvenile absence epilepsy, and 18% in childhood absence epilepsy).

GENETICS

Recurrence rate

The lack of exogenous factors in the etiology of JME is compensated for by the weight of genetic factors. Of patients with JME, 17% to 49% have close and distant

TABLE 7
PROPORTION OF PATIENTS WITH SEIZURES IN RELATIVES—GROUPED BY TYPES OF EPILEPSY

	N	%
Generalized epilepsies		
Doose (1964)[62]		
Propulsive petit mal	71	25
Kruse (1968)[63]		
Myoclonic astatic petit mal	80	29
Doose (1985)[64]		
Myoclonic astatic epilepsy of early childhood	100	37
Matthes and Weber (1968)[65]		
Pyknoleptic absences	129	32
Doose et al (1973)[66]		
3 Hz absences	239	30
Symptomatic and focal epilepsies		
Evans (1962)[67]		
Posttraumatic epilepsy	80	7.5
Lund (1952)[68]		
Tumor epilepsy	966	6.0
Janz (1969)[9]		
Psychomotor seizures	1990	6.5
Gibbs and Gibbs (1952)[69]		
Neocortical seizures	978	6.0
Nonselected epilepsies		
Tsuboi and Christian (1973)[33]	466	9.9

relatives with epileptic seizures (*Table* 6), but in this respect there is no apparent difference between the subtypes of generalized epilepsy.

There is, however, a difference between generalized epilepsy on the one hand and symptomatic and focal epilepsy on the other hand (*Table* 7).

Nevertheless, these figures reveal nothing about the nature of the seizures, the sex of the relatives, and the closeness of the relationship with the relative affected.

The prevalence of close relatives (i.e., parents, siblings and children) with afebrile epileptic seizures was 5.5% among our JME patients, and 4.1% among those of Tsuboi and Christian[33] (*Table* 8).

In the large-scale study of the relatives of 319 patients carried out by Tsuboi and Christian,[33] the findings agree with our experience that relatives of women are more frequently affected. The fact that febrile seizures occur in close relatives of patients with JME in only 1.7% (i.e., less commonly than in the general population) seems worthy of note, because febrile seizures are also found considerably less frequently in the history of patients with JME than in other forms of epilepsy, particularly absence epilepsy.[43]

As far as the risk to various generations is concerned, Tsuboi and Christian[33] state that parents of patients with JME are rather less frequently affected (3.7%) than siblings (4.4.%), and the latter in turn somewhat less frequently than children (5.1%). We found approximately the same situation, although the risk of the disease was rather higher among siblings (7.0%) and children (7.1%), as is shown in *Table* 9.

Our studies also show that the parents and siblings of female patients are more frequently affected, although we have as yet been unable to confirm any increased risk for the children of female patients, probably because of the fairly small numbers of patients studied.[44] Tsuboi and Christian[33] in studying the incidence of specific and nonspecific EEG changes, found the same ranking of parents, then siblings, then children, and the same emphasis on the relatives of female subjects. The predominance of females both in the frequency of manifest seizures and in the frequency of specific EEG abnormalities is worthy of note. Seizures

TABLE 8
INCIDENCE OF AFEBRILE SEIZURES IN FIRST-DEGREE RELATIVES OF JME PATIENTS*

	Men N = 51			Women N = 67			Total N = 118		
Probands	n	N	%	n	N	%	n	N	%
Male	3	319	2.2	12	163	7.4	15	302	5.0
Female	7	115	6.1	11	183	6.0	18	298	6.0
Total	10	254	3.9	23	346	6.7	33	600	5.5

* Adapted from ref 43.

TABLE 9
INCIDENCE OF AFEBRILE SEIZURES IN PARENTS, SIBLINGS AND OFFSPRING OF JME PATIENTS

	Men N = 51			Women N = 67			Total N = 118		
Probands	n	N	%	n	N	%	n	N	%
Fathers	0	51	0	4	67	6.0	4	118	3.4
Mothers	2	51	3.9	2	67	3.0	4	118	3.4
Parents	2	102	2.0	6	134	4.5	8	236	3.4
Brothers	2	65	3.1	7	67	10.4	9	132	6.8
Sisters	3	55	5.4	7	86	8.1	10	141	7.1
Siblings	5	120	4.2	14	153	9.2	19	273	7.0
Sons	1	23	4.3	1	29	3.5	2	52	3.8
Daughters	2	9	22.2	2	30	6.7	4	39	10.3
Offspring	3	31	9.7	3	59	5.1	6	84	7.1

* Adapted from ref 43.

and EEG changes are approximately equally shared only by brothers and sisters. Female subjects more frequently have relatives affected by both seizures and by EEG changes than do male subjects; and the female relatives of subjects of both sexes also proved to be affected more frequently both by seizures and by EEG changes. There is no conclusive explanation for this. The phenomenon of a certain "maternal relationship," i.e., a greater risk to children of epileptic mothers of suffering a recurrence of the disease, has been known for quite a long time. The fact that there might be a certain "daughter relationship" in JME was first mentioned by Tsuboi and Christian.[33] Tsuboi[20] postulates that the hereditary transmission of JME could probably be polygenic. He attempts to explain the predominance of female patients by suggesting a lower epilepsy threshold for the female sex.

Type of recurrence

The question of the nosologic position of JME in the system of generalized forms of epilepsy may perhaps be answered if one considers the clinical forms in which recurrence of the disease manifests itself. It is also of interest from a genetic aspect to examine whether the phenotypes occurring in relatives resemble each other or differ. According to Tsuboi and Christian,[33] the percentage of JME among other forms of epilepsy is about twice as high (14.7%) in close and distant relatives as in an unselected population of epileptic patients (7.1%). The percentage of pyknoleptic and nonpyknoleptic absences (14.6%) was near the expected 15.1%. In our patients,[44] as in those of Delgado-Escueta and Enrile Bacsal,[7] JME occurs just as frequently among first-level relatives as the two types of absence epilepsy together. On the basis of the calculations discussed earlier, it can be assumed that in a general population of epileptic patients, JME will occur in 8% of cases and the two forms of absence epilepsy will occur in about 16%. On the basis of this assumption, our study shows that JME occurs about 3 1/2 times, and epilepsy with absences occurs almost twice as frequently as expected in first-level relatives of patients with JME. Except for awakening grand mal, statistics on occurrence of other forms of generalized epilepsy and focal epilepsy among relatives are of no significance. The fact that of familial types of epilepsy with JME (excepting grand mal) only absence epilepsy and JME occur with more than chance frequency, suggests a close genetic link between the two. However, the fact that JME is more in evidence may be a sign that, in genetic and nosologic terms, JME may be a distinct, unique form of generalized idiopathic epilepsy.

Still ongoing studies in Los Angeles and in Berlin have shown some evidence that JME may be linked to the BF and HLA loci, indicating that the gene or the genes responsible for JME are located at the short arm of chromosome 6.[45,46] It would be premature to go into more detail, but this would be the first form of epilepsy where a genetic linkage has been proven.

MANAGEMENT

Changes in life patterns

As it is proven that sleep deprivation and untimely awakening adversely affect the condition, management of JME must first insure that the sleeping/waking cycle is regularized and that circumstances are avoided which

would disturb natural sleep and gradual awakening. Coffee and tea should be avoided in the evening. Alcoholic drinks appear to have a precipitating effect, not directly but indirectly via sleep deprivation, by inducing the patient to conceal his natural fatigue and stay up late. Abstinence from alcohol is therefore helpful. If the situations which put photosensitive patients at risk are sufficiently described to them, they may be able to avoid such risks. It might be supposed that at the start of the disease when only a few jerks or seizures have occurred, the physician's serious advice on how to effect a consistent change of lifestyle would in itself be sufficient to prevent further seizures. Unfortunately, I cannot think of a single case of this kind; but I can recall some patients who, after a period of managing their condition independently without drugs, requested drug therapy because they felt that the constant avoidance of circumstances which would disturb their sleep was a greater constraint in the long term than taking drugs regularly.

Drug treatment

JME is responsive to control with epileptic drugs. The drug of choice is sodium valproate.[6,7,41,47–52] Primidone and phenobarbital have also proved successful, while phenytoin appears to be less effective.[9] We have no experience with carbamazepine and ethosuximide, but we have found that out of 30 patients with JME treated with a monotherapy of sodium valproate, all were free of attacks in the form of jerks and absences, and 21 out of 22 patients (95.4%) were also free of grand mal.[51] The mean dosage was 26.3 mg/kg body weight. The mean serum concentration after reaching steady state was 88.9 mg/L. Other investigators also emphasize that to achieve freedom from seizures, patients generally require a relatively high dosage, averaging over 20 mg/kg body weight and leading to plasma concentrations of 60 to 120 mg/L.

Primidone was administered as monotherapy to 28 patients. This achieved freedom from jerks in 18 out of 27 patients, and freedom from grand mal in 11 out of 18.

PROGNOSIS

The prognosis of JME is very favorable if the condition is treated early and consistently, if the patient succeeds in modifying his way of life, and if an appropriate type and dosage of medication are used. In our experience, those patients who did not achieve freedom from seizures had had their condition for 9 years longer than those who responded well to the medication.[51] This underscores the need for early treatment, which should begin as soon as possible before any major seizures have occurred. It is therefore important to be acquainted with this epileptic syndrome in order to be able to identify it early.

However well JME attacks may be controlled with drugs, the likelihood of their being cured with drugs is slight. On the basis of experience to date, a relapse may be expected in 75% to 100% of cases, even after many years of freedom from seizures, if the dosage is reduced or the drug discontinued.[7,23,53] JME thus appears to be the only form of epilepsy in which one cannot recommend discontinuing drug therapy even after many years of freedom from attacks.

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