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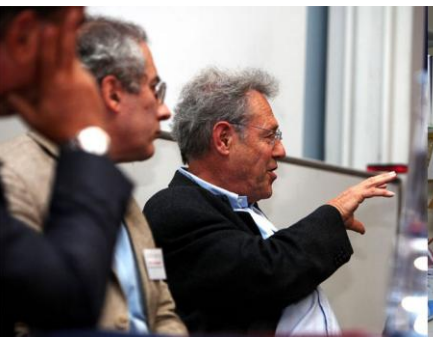
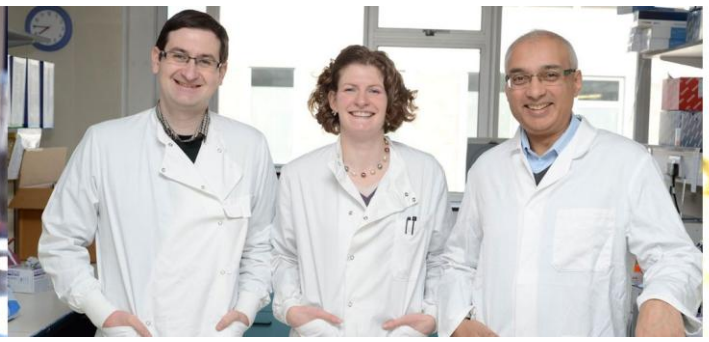


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CRITICAL REVIEW AND INVITED COMMENTARY

Dissecting the genetic basis of myoclonic-astatic epilepsy

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Summary

Herman Doose first described the generalized childhood epilepsy syndrome of myoclonic astatic epilepsy (MAE) in 1970, attributing a genetic cause from this first description. However, although the International League Against Epilepsy (ILAE) defined criteria for MAE in 1989, the diagnostic boundaries of the syndrome continue to be debated. Moreover, 40 years since Doose's first description of MAE, although a genetic predisposition is acknowledged and many studies have demonstrated familial aggregation of seizures within MAE families, the actual genetic determinants of MAE still remain unknown. Although initially thought to be within the same spectrum as severe myoclonic epilepsy of infancy, the exclusion of *SCN1A* mutations in non-generalized epilepsy with febrile seizures plus (GEFS+) MAE cases has confirmed the genetic distinction of MAE. In this critical review, we shall trace the historical evolution of concepts around MAE and its distinction from Lennox-Gastaut syndrome, review the described phenotypic features of MAE from updated studies that will allow its distinction from other overlap epilepsy syndromes, review the evidence of genetic influences and clues for genetic heterogeneity, and discuss strategies that may be helpful in elucidating the etiology of MAE in light of current genetic techniques.

KEY WORDS: Doose, Classification, Endophenotype.

Myoclonic-astatic epilepsy (MAE) is a rare, severe childhood epilepsy syndrome regarded as having a genetic etiology. However, its phenotypic manifestations and nosologic boundaries continue to evolve and be debated, and the genetic determinants of MAE are still largely unknown (Roger et al., 1992; Kaminska et al., 1999; Arzimanoglou et al., 2004; Stephani et al., 2006). For example, consensus in seizure diagnosis is complicated by criterion definition: ''drop attacks'' may be a result of myoclonic, atonic or tonic components—difficult to distinguish without combined electroencephalography (EEG)/electromyography (EMG) recordings. In addition, the clinical phenotype of MAE may at some stage in its clinical course resemble benign myoclonic epilepsy of infancy (BMEI) or Lennox-Gastaut syndrome (LGS), and early descriptions may not have distinguished these syndromes. Through this critical review we first trace the historical evolution of concepts around MAE, describe the phenotypic features of MAE, review the evidence for genetic influences and propose some etiologic hypotheses, and then discuss strategies that may be helpful in dissecting out major genetic components in its etiology.

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Historical Perspective

Description and refinement of MAE

Before the description of MAE, all such cases were probably categorized as LGS, a syndrome that was described in 1950 by Lennox & Davis. These authors described the slow spike and wave EEG pattern and correlated it with clinical manifestations including mental retardation, myoclonic jerks, atypical absences, and astatic seizures. In 1966, Henri Gastaut also described 100 patients with diffuse slow spike wave, mental retardation, frequent tonic seizures, absences with or without myoclonic seizures and called this ''Lennox syndrome or childhood epileptic encephalopathy with diffuse slow spike and waves'' (Gastaut et al., 1966). Niedermeyer (1969) subsequently recognized the contribution of both groups and coined the term Lennox-Gastaut syndrome at the American Electroencephalographic Society proceedings in 1969.

The concept of separating epilepsy with myoclonic seizures from LGS emerged around the same time when Harper (1968) described 14 children with myoclonic epilepsy distinct from LGS and infantile spasms. In 1968, Kruse described a kind of epilepsy characterized by myoclonic and astatic seizures under the heading of ''myoclonic-astatic petit mal'' among other petit mal epilepsies. Doose differentiated this further and in 1970 published 51 cases of ''centrencephalic myoclonic astatic petit mal'' characterized by onset of primarily generalized seizures in the form of myoclonic and astatic seizures, often

combined with absences, tonic–clonic, and tonic seizures in previously normal children between 1 and 5 years old. The EEG usually showed bilateral synchronous spike and wave activity with abnormal background theta rhythm. He recognized that in some instances mental retardation developed and also noticed a high frequency of seizures in family members (Doose et al., 1970). Although recently attributed to Hermann Doose, he never originally described MAE as an epilepsy syndrome per se, but instead sought to describe uniting features in a heterogeneous group of children.

Within this original group of patients reported by Doose et al. (1970), discrete epilepsy syndromes can now be recognized. Five of his 51 cases had isolated myoclonic seizures that might now fit the definition of BMEI. Ten cases had seizure onset before the age of 1 year, and 11 cases had febrile convulsions. Although specific details were not differentiated in each patient, these cases could fit a severe myoclonic epilepsy of infancy (SMEI) phenotype. Another subgroup of six cases had evidence of cerebral damage with neurologic symptoms or mental retardation, and one case exhibited frequent tonic seizures; these might better fit the label of LGS. Twenty-two years later, Doose refined his criteria for MAE, adding that tonic seizures were an uncommon feature, and acknowledging the overlap with other epilepsy syndromes (Roger et al., 1992). In 1989, the International League Against Epilepsy (ILAE) (Commission, 1989) recognized MAE to have the following features: (1) normal development before onset of epilepsy; (2) onset of myoclonic, myoclonic-astatic, or astatic seizures between 7 months and 6 years of age; and (3) presence of generalized spike or polyspike wave EEG discharges. The ILAE also recognized a ''hereditary predisposition'' with a variable outcome. These criteria are largely based on Doose's original description on a cohort that is now recognized to be phenotypically heterogenous. Tables 1 and 2 summarize the main clinical features of reported cases in MAE series. We will from this point on refer to the 1989 ILAE definitions of MAE and LGS, unless otherwise specified (Commission, 1989).

Classification

The concept of an epilepsy syndrome has evolved with the recent ILAE classification. The 1989 ILAE report adopted a broad understanding of the term ''syndrome'' as an epileptic disorder characterized by a cluster of signs and symptoms customarily occurring together and placed MAE within the category of generalized cryptogenic or symptomatic epilepsies (Commission, 1989). The 2010 ILAE classification specified that an electroclinical syndrome is a complex of clinical features, signs, and symptoms that together define a distinctive, recognizable clinical disorder. The report avoids the cryptogenic or symptomatic etiologic distinction by placing MAE (now termed epilepsy with ''myoclonic–atonic'' seizures, instead of the previously called ''myoclonic-astatic'' seizures) as a distinct electroclinical syndrome (Berg et al., 2010). Although the classification has changed, the diagnostic definitions have not altered with the new classification. Most reports about MAE in the literature use the 1989 ILAE definition. However, a recent genetic study invented operational definitions of MAE as ''narrow'' or ''broad.'' The narrow group was defined as onset between 1 and 5 years, with at least one of myoclonic or myoclonic-atonic seizures, whereas the broad group allowed a wider onset age from 7 months to 6 years and required any one of myoclonic, atonic, or myoclonic atonic seizures (Mullen et al., 2011).

Phenotypic Features

Clinical epidemiology

MAE accounted for 1–2% of childhood onset epilepsies up to the age of 9 years in the German city of Kiel in 1983 (Doose & Sitepu, 1983). Onset age ranged from 7 months to

Table 1. Summary of main clinical characteristics of MAE cases in published series

	Boys (%)	Previous febrile convulsion (%)	FH (Ep, Feb) (%)	Age of onset (mean)	Seizure cessation	IQ initial (mean)	IQ after (mean)
Doose et al. (1970) n = 51	71	22	40[a]	36–48 m	58% > 36 m	34% MR	26% N < 17 year
Kilaru & Bergqvist (2007) n = 23	83	17	39[b]	36 m	67% > 21 m	–	43% N > 21 m
Oguni et al. (2002) n = 81	75	–	35[a] (14, 18)	32 m	68% > 66 m	–	59% N > 36 m
Nabbout et al. (2003) n = 22	–	–	31[a] (13, 18)	40 m	32% > 12 m	–	–
MAE favorable							
Kaminska et al. (1999) n = 37	73	22	19[c]	35.2 m	97% > 18 m	91	57% N > 36 m
Oguni et al. (2002) n = 55	74	–	27[a] (7, 20)	33 m	100% > 66 m	–	
MAE unfavorable							
Kaminska et al. (1999) n = 18	83	11	5.5[c]	36 m	0% > 36 m	84	6% N > 36m
Oguni et al. (2002) n = 15	67	–	53[a] (40, 13)	30 m	0% > 66 m	–	–

FH, family history; Ep, epilepsy; Feb, febrile seizures; m, months; MR, mental retardation; N = IQ > 75, –: no information.
[a]Up to third-degree relatives.
[b]Up to second-degree relatives.
[c]Unknown.

Table 2. Summary of the frequency of the main seizure types reported in MAE series

	Atonic (%)	Myoclonic (%)	Myoclonic atonic (%)	Tonic (%)	Absences (%)	GTCS (%)	Partial (%)	Minor epileptic status (%)
Doose et al. (1970) n = 51	4[a]	10[a]	59	2	59	71	6	45
Doose (1992)		100[b]	100[b]		62	75		30
Kilaru & Bergqvist (2007) n = 23	57	61	61	0	52	70	–	1
Oguni et al. (2002) n = 81	64	43	100[b]		54	93		21
Oguni et al. (2001) n = 30	37	53	10					
Nabbout et al. (2003) n = 22	–	87	100	27	44	77	8	12[c]
MAE favorable								
Kaminska et al. (1999) n = 37	–	97	84[d]	38	63	79	0	14[c]
Oguni et al. (2002) n = 55	–		64[d]		49			16
MAE unfavorable								
Kaminska et al. (1999) n = 18	–	100	89[d]	55	89	95	0	94.5[c]
Oguni et al. (2002) n = 15	–		67[d]		67			47

Astatic seizures are treated as atonic seizures where reported. GTCS, generalized tonic–clonic seizures; –, no information.
[a]Reported in isolation.
[b]100% of the cohort had either myoclonic or myoclonic atonic seizures.
Minor epileptic status includes myoclonic status[c], absence status, and nonconvulsive status.
[d]Reported as drop attacks.

6 years, and peaked between 3 and 4 years. Boys were affected twice as frequently as girls with onset after the first year (Kaminska et al., 1999; Oguni et al., 2001, 2002; Kilaru & Bergqvist, 2007), but when onset was during the first year of life there was an equal sex ratio (Doose et al., 1970). MAE begins in previously normal children or children with mild speech delay (Doose et al., 1970). This normal antecedent history is similar to ''cryptogenic'' LGS, where the development of the child may seem normal before the appearance of the first seizures (Arzimanoglou et al., 2009), although in LGS subsequent cognitive decline is invariable (Arzimanoglou et al., 2009).

Pathology

Generalized subcortical atrophy on cranial computerized tomography had been reported in groups of patients with symptoms similar to MAE prior to the 1989 classification (Gastaut et al., 1966; Lagenstein et al., 1979). However, the pathologic significance of generalized subcortical atrophy is difficult to determine as it may result from repeated seizures, episodes of status epilepticus, or from hormonal treatment. Subsequent MAE series have indicated no evidence of brain lesions on magnetic resonance imaging (Kaminska et al., 1999; Oguni et al., 2001, 2002; Kilaru & Bergqvist, 2007). There are no published postmortem brain studies in MAE.

Seizures

Myoclonic–atonic/astatic seizures

The presence of myoclonic–astatic/atonic seizure is a characteristic and distinguishing seizure in MAE and an essential component in its phenotypic manifestation (Doose et al., 1970; Roger et al., 1992; Kelley & Kossoff, 2010). Doose et al. (1970) defined these seizures as a loss of postural tone preceded by myoclonia and considered myoclonic astatic seizures as a hallmark seizure in MAE—as indeed have most authors (Oguni et al., 2002; Kilaru & Bergqvist, 2007). However, it is difficult to determine whether all reported MAE patients have myoclonic atonic/astatic seizures because of the following: (1) some series group together myoclonic seizures, myoclonic–astatic seizures, and astatic seizures; (2) researchers use different criteria for myoclonic–astatic seizures; and (3) it is difficult to qualify the exact physiologic mechanism of drop attacks without combined EEG/EMG recordings. For example, Oguni et al. (2001) specified that the intensity of myoclonia and atonia should be equal in order for the term myoclonic atonic seizure to be used, and thus myoclonic–astatic seizures were less frequent in his series; and Kaminska et al. (1999) reported drop attacks in 89% of their cohort but did not distinguish this further due to the lack of combined EEG/EMG recordings. In another cohort, ictal EEG of atonic seizures corresponded with spike wave morphology characterized by a positive-negative-deep-positive wave followed by a large negative slow wave (Oguni et al., 2005).

Epileptic drop attacks caused by atonic drop seizures are relatively rare, as demonstrated by video monitoring of epileptic falls on 15 children with LGS, where myoclonic-atonic seizures occurred in only three cases compared with flexor spasms or tonic falls in 13 (Ikeno et al., 1985). In addition, Egli et al. (1985) investigated 45 patients with drop seizures and found that only nine patients each had myoclonic–atonic or atonic seizures. Therefore, neurophysiologic studies to differentiate myoclonic atonic/atonic seizures from other causes of falls may be necessary to distinguish a phenotypically homogenous group for genetic studies.

Myoclonic seizures

Myoclonic seizures, although occurring frequently in MAE, are not characteristic of the syndrome. The frequency of myoclonic seizures varies from approximately 43–100% in MAE (Kaminska et al., 1999; Oguni et al., 2001, 2002; Ohtsuka et al., 2006; Kilaru & Bergqvist, 2007). Myoclonic jerks mainly involve proximal muscles and can be both flexor and extensor (Oguni et al., 2001) and may cause drop attacks. Aicardi described some patients with the so-called myoclonic variant of LGS to have an unusually marked myoclonic component (Arzimanoglou et al., 2004). However, a British neurophysiologic study has demonstrated that myoclonus originates differently in LGS and MAE. In three LGS cases, topographic voltage mapping of the premyoclonic spike peak showed a unilateral frontal distribution, whereas in three MAE cases this mapping showed a diffuse distribution of the electrical field (Bonanni et al., 2002). Therefore, epileptic myoclonus in LGS is hypothesized to originate from a stable generator in the frontal cortex and then spread to contralateral and ipsilateral cortical areas, whereas myoclonus in MAE appears to be a primary generalized epileptic phenomenon. This corresponded to a generalized spike and wave with a median frequency of 1.3 Hz (Hirano et al., 2009). On analysis of four patients with myoclonic seizures on video polygraphic analysis, the seizures primarily involved the trunk and proximal upper extremities and were flexural, sometimes causing the patient to fall forward (Hirano et al., 2009). The occurrence of myoclonic seizures without an atonic component should prompt the consideration of alternate myoclonic epilepsies such as BMEI if onset is <1 year or SMEI if there is a history of fever sensitivity.

Tonic seizures

There is no agreement on the frequency of tonic seizures in MAE, and figures between 0% and 55% have been reported (Kaminska et al., 1999; Oguni et al., 2002; Kilaru & Bergqvist, 2007). Doose stated that tonic seizures occur infrequently in MAE during sleep, and only in rare cases during daytime (Roger et al., 1992). In contrast, 75–90% of LGS patients undergoing sleep EEG recording exhibit tonic seizures (Dulac & N'Guyen, 1993). Tonic seizures may appear later in the course of LGS rather than at onset, and thus it may be necessary to reevaluate MAE patients for this symptom to differentiate the two conditions.

Absences

There may be a whole spectrum of clinical manifestations ranging from typical absences to loss of muscle tone, eyelid myoclonia, and sialorrhea (Nabbout et al., 2003). The occurrence of atypical absences is usually less common than generalized tonic–clonic seizures (GTCS) in MAE.

Generalized tonic–clonic seizures

Febrile and afebrile GTCS are the first seizure type in more than two thirds of MAE cases (Doose et al., 1970; Escayg et al., 2001; Oguni et al., 2002; Kilaru & Bergqvist, 2007). GTCS are also seen during the course of the disease (Roger et al., 1992; Kilaru & Bergqvist, 2007).

Status epilepticus

A status of seizures consisting of a series of myoclonic–astatic seizures or myoclonus and atypical absences is typical and much more common than convulsive status. This contrasts with LGS in which status characteristically involves clouding of consciousness with frequent tonic seizures. Kaminska reported myoclonic status as an important distinguishing factor with a frequency of 14% in favorable MAE, 94.5% in unfavorable MAE, and zero in cryptogenic LGS (Kaminska et al., 1999).

EEG

The EEG often shows noncharacteristic background changes with abnormal centroparietal theta rhythms at the start of the epilepsy. With progression of the disease, brief bursts of 2–5 Hz generalized spike and wave and polyspike-wave complexes become prominent. Focal activity is unusual. Although it is recently recognized that MAE is an epileptic encephalopathy (Engel, 2006), generally, posterior background rhythms and sleep architecture can be normal, which is in contrast to LGS, where there is little or no normal background activity and slower (2–2.5 Hz) spike wave runs for prolonged periods. Slow spike waves may also be seen in MAE in the later course of the disease. However, unlike in LGS, where slow-spike waves are sometimes combined with focal abnormalities, in MAE they are combined with 3 Hz spike wave. During remission, it is typical for a marked diffuse abnormal theta rhythm to develop (Stephani, 2006). Therefore, although there are no pathognomonic EEG signatures for MAE, sufficient EEG features exist to distinguish it from other conditions, when taken in conjunction with a consistent clinical history.

Comorbidity

Remarkably little detail has been reported about the cognitive or behavioral phenotype in patients with MAE. Hyperactivity and behavioral disturbances were reported in 10 of 22 patients in one series (Escayg et al., 2001), although specific measures and difficulties were not. Another study reported one MAE patient with distractibility, behavioral inhibition, and shyness based on the Child Behavior Checklist. The authors claimed that this profile normalized with antiepileptic drug treatment in parallel with clinical improvement and normalization of the EEG (Filippini et al., 2006). There is insufficient evidence to generalize from this case report. Behavioral difficulties occur in general among children with epilepsy, especially if there are coexisting cognitive difficulties. Further studies are required to identify whether a specific cognitive–behavioral phenotype exists in MAE.

Course and prognosis

Predictive factors

Prognosis is variable in MAE. Doose identified the following risk factors for an unfavorable prognosis: onset with febrile and afebrile GTCS during the first 18 months of life, status of minor seizures, persistence of 4–7 Hz rhythms and failure to develop a stable occipital alpha rhythm (Gundel et al., 1981; Roger et al., 1992). Two studies have attempted to differentiate MAE into favorable and unfavorable groups (see Table 3) (Kaminska et al., 1999; Oguni et al., 2002). Using a method of data reduction known as multiple correspondence analysis, Kaminska et al. (1999) found that both groups were indistinguishable at onset but that those with poor outcome after 3 years demonstrated lack of familial antecedents, tonic and absence seizures, myoclonic status and long bursts of irregular spike and slow waves throughout the disorder. Oguni retrospectively compared 55 favorable and 15 unfavorable MAE cases and reported that a positive family history of epilepsy and absence status or minor epileptic status significantly correlated with an unfavorable outcome (Oguni et al., 2002). Putting together the evidence, cases with unfavorable outcome might be characterized by absence or minor epileptic status, tonic seizures and EEG spike and slow wave—all features that shift the overall picture toward LGS. However, when groups of patients with features of MAE and LGS were compared, there was no transition in syndrome diagnosis between the two groups, even though EEG patterns were changeable and some electroclinical features overlapped (Ohtsuka et al., 2006). These studies indicate that there are identifiable but not completely reproducible risk factors for an unfavorable prognosis that may not be present at onset. It would be valuable to test the predictive properties of these proposed risk factors or to identify biomarkers for seizure and cognitive outcomes in large-scale, prospective longitudinal studies.

Seizure remission

In retrospective studies, about two thirds of MAE patients achieve seizure remission (Kaminska et al., 1999; Oguni et al., 2002). Myoclonic and/or astatic seizures disappeared within 1–3 years in 89% of a retrospective cohort but GTCS tended to continue. It is possible that seizure remission rates may be underestimated because of selection bias in follow-up studies Oguni et al., 2002).

Cognitive outcome

Cognitive prognosis tends to be favorable if seizures remit. However, if seizures persist, cognitive prognosis tends to be unfavorable. Therefore, about two thirds of patients show a normal IQ level on final follow-up (see Tables 1 and 3) (Oguni et al., 2002).

Genetic Etiology

Myoclonic–astatic seizures are etiologically heterogeneous and may occur in conditions as diverse as Sturge-Weber syndrome, cerebral folate deficiency syndrome, and LGS (Ramaekers & Blau, 2004; Jiruska et al., 2011). However, there are no known associated causes for the MAE epilepsy syndrome. The only known causes and associations are genetic and this section therefore deals exclusively with genetic data.

Evidence supporting a genetic cause for MAE comprises twin studies, family studies (some with EEG), and gene mutation analyses. Twin studies generally compare monozygotic (MZ) and dizygotic (DZ) twins through a comparison of disease concordance rates. This design is based on the fact that MZ pairs are assumed to be genetically

Table 3. Studies comparing favorable and unfavorable MAE

	Doose et al. (1970)	Kaminska et al. (1999)	Oguni et al. (2002)
Definition of favorable			
Seizure remission	No seizures for 24 months	No seizures for 12 months	No seizures for 24 months
Cognitive outcome	Clinical observation that mental age was not commensurate with chronologic age	Normal IQ > 80 Moderate IQ 50–80 Severe IQ < 50 Educational achievement if IQ not available	Normal IQ > 80 Borderline to mild IQ 60–79 Moderate 30–59 Severe IQ < 30
Study design	Retrospective study 1/3 of study cohort up to 3 years 2/3 of study cohort from 4 to 17 years	Retrospective study >3 or 1 year from last seizure	Retrospective study 36–320 months
Prognostic outcome			
Seizure remission	22/38 (57.9%)	36/55 (65.5%)	55/81 (68%)
Cognition outcome	26% Normal	22/55 (40%) Normal	48/55 (59%) Normal
Poor prognostic features	Absence status	Lack of family history of seizures EEG spike and slow wave Presence of tonic and absence seizures Myoclonic status	Family history of seizures Absence status or minor epileptic status

identical in DNA sequence, whereas DZ twins share approximately 50% of their gene sequence. Genetically influenced characteristics may show a higher concordance in MZ than DZ twins, assuming that both types of twins equally share environmental influences. Family studies examine the distribution of traits among members of a family, but cannot distinguish shared genetic and environmental factors when familial aggregation is present. Genetic linkage studies are used to identify regions of the genome that contain genes that predispose to disease by observations of allele sharing among related individuals. Gene mutation analysis correlates mutations in genes with particular phenotypes comparing cases with controls and sometimes with relatives.

Twin studies

Twin studies of symptomatic or cryptogenic generalized epilepsies (Commission, 1989) have shown a higher concordance rate of 83–94% in MZ pairs compared to 65–71% in DZ pairs (Berkovic et al., 1998; Kjeldsen et al., 2003). A discordant MZ pair was reported within one of these studies, in which one twin had MAE and his co-twin had an unclassified epilepsy (Berkovic et al., 1998). The presence of this MZ twin pair concordant for epilepsy but discordant for syndrome is interesting and suggests that genetic sequence variants may not fully explain the etiology of MAE. The concordance for epilepsy and having different epilepsy syndromes might be explained by epigenetic or environmental factors interacting with a genetic susceptibility. Family studies also suggest that the underlying genetic susceptibility may not be to the syndrome itself.

Family studies—seizures

A positive family history of seizures in first-, second,- or third-degree relatives is seen in about one third of cases (see Table 1) (Doose et al., 1970; Roger et al., 1992; Oguni et al., 2002; Nabbout et al., 2003; Kilaru & Bergqvist, 2007). In Doose and Baier's series, the incidence of afebrile/febrile seizures was higher in siblings (15%) than in parents (6%) (see Table 4). Although this was higher in fathers (7%) compared to mothers (4%), and in brothers (18%) compared to sisters (12%) (Doose et al., 1970; Doose & Sitepu, 1983), these differences were not statistically significant (parents' $p = 0.36$; siblings' $p = 0.38$). This unusual distribution is seen in some idiopathic generalized epilepsies with genetic anticipation (Cvetkovska & Panov, 2011), but recall bias for seizures in the parental generation is a more likely explanation (Ottman et al., 2011). The seizure types present in the relatives were predominantly febrile or afebrile GTCS—myoclonic or myoclonic–atonic seizures occurred in only 3 of 160 siblings (Doose et al., 1970). Doose & Baier (1987) also reported the case of a woman with a past history of MAE and her two children; the daughter had MAE, whereas the son manifested myoclonic seizures and GTCS with a benign course—a suggestion of maternal transmission that is more strongly supported by EEG studies (below).

Table 4. Familial incidence of seizures in families of 107 cases with MAE (Doose & Baier, 1987)

Class of relative	n (%)
Brothers	78 (18)
Sisters	82 (12)
Father	100 (7)
Father's siblings	246 (3)
Mother	102 (4)
Mother's siblings	221 (4)

These family studies of MAE thus suggest a familial susceptibility to generalized seizures much more often tonic–clonic than myoclonic. The low familial aggregation of myoclonic or myoclonic–atonic seizures in families of MAE probands is an interesting observation that remains difficult to explain. One hypothesis is of an interaction between, on the one hand an inherited susceptibility to generalized seizures with, and, on the other hand, a separate and low frequency (genetic, epigenetic, or environmental) factor modifying the phenotype (Berkovic et al., 2006). The situation somewhat resembles the inheritance of different seizure types in adolescent-onset generalized epilepsies, in which there is differential inheritance of GTCS, myoclonic, and absence seizure types in idiopathic generalized epilepsy families (Durner et al., 2001; Pal et al., 2006). Familial EEG studies offer further clues about the exact nature of inherited traits in MAE families.

Family studies—EEG

It is known that individual variability of the human electroencephalography (EEG) is largely genetically determined (Stassen et al., 1988). Doose recorded EEG in family members of MAE probands looking for the transmission of EEG abnormalities. He defined the following pathologic EEG traits: photosensitivity, dysrhythmias including theta rhythms, and generalized spike-and-waves—all traits that are considered genetically determined (Doose & Baier, 1987, 1988; Waltz et al., 1992; Doose & Waltz, 1993). At least one of these EEG traits occurred in 45.8% of siblings, compared to 8.3% of kindergarten and school-aged controls ($p < 0.01$). The most common EEG abnormality was photosensitivity and there seemed to be a clear female excess: present in 16 of 39 sisters compared to 4 of 33 brothers ($p < 0.025$). There was also clear evidence of preferential maternal transmission of the EEG traits: 9 of 37 mothers as opposed to 1 of 32 fathers of MAE probands had a pathologic EEG (see Table 5). Doose et al. (1970) showed that of the 50 families, taking both seizure and EEG data into account, 34 (68%) of families had members (excepting the proband) with some evidence of seizure susceptibility (Roger et al., 1992). These 34 families included 11 families with both pathologic EEG and seizure history, 12 families with pathologic EEG only, and 11 with seizure history only. As not all ascertained families had EEG studies, these cases

Table 5. EEG findings in 72 siblings, 32 fathers, and 37 mothers of 50 probands (Doose et al., 1970)

	Siblings (%)	Parents (%)
Photosensitivity	20 (27.8)	6 (16.2)
Generalized spikes and waves	6 (8.3)	1 (3.1)
Abnormal rhythms	14 (19.4)	3 (8.1)
Total pathologic	33 (45.8)	10 (27.4)

may have been subject to ascertainment bias. It would be valuable to replicate these EEG studies and to explore the use of EEG biomarkers for genetic analysis.

Interpretation of family studies

The very high prevalence of diverse seizure and EEG traits within families of MAE probands cannot obviously be explained by monogenic inheritance. It is more likely that a combination of independent genetic factors give rise to different permutations of seizure and EEG features within individual family members. This may be analogous to the proposed model of oligogenic inheritance in adolescent-onset idiopathic generalized epilepsies in which there are clear shared and distinct genetic influences on seizures and EEG (Durner et al., 2001; Tauer et al., 2005; Pal et al., 2006). The maternal preponderance of EEG abnormalities, along with the male bias for MAE in probands, is intriguing and has several possible genetic explanations (see Table 6). At the same time, EEG features may provide a useful endophenotype in family based genetic studies to shed light on the genetic model. Criteria used for an endophenotype in psychiatric genetics include the following: (1) the endophenotype is associated with illness in the population, (2) the endophenotype is heritable, (3) the endophenotype is state dependent (manifest in an individual whether or not illness is active), (4) the endophenotype and illness cosegregate within families, and (5) the endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population (Gottesman & Gould, 2003). Photoparoxysmal responses and spike waves easily satisfy the criteria for endophenotypes and have been employed before (Waltz et al., 1992; Pinto et al., 2005; Tauer et al., 2005), but theta rhythms may prove more problematical because of their resemblance to physiologic EEG phenomena (Baier & Doose, 1987). So far, the literature we have discussed concerns MAE in its usual context. As with many other ''idiopathic'' epilepsy syndromes, variant Mendelian forms have been described and we next consider what can be learned from such pedigrees.

Table 6. Patterns of maternal transmission and expected offspring sex ratio (Pal et al., 2006)

Maternal transmission	Sex ratio in offspring
X linked recessive	Only boys affected
X linked dominant[a]	Equal
Mitochondrial	Equal with variable expression
Triplet repeat[a]	Equal with anticipation
Ascertainment bias[a]	Female or male excess
Nonpaternity	Equal
Perinatal or pregnancy factors	Variable depending on factors
Paternal imprinting	Equal
Sex dependent penetrance[a]	Female or male excess

[a]Paternal transmission possible.

Gene mutation analyses

Rare Mendelian pedigrees

Three consanguineous multiplex Arab families from Israel and the Palestinian territories have been reported in abstract form, each ascertained through a proband with MAE (Kron et al., 2007). In family 1, 6 of 14 siblings were affected with MAE and one cousin had idiopathic generalized epilepsy (IGE); in family 2, 5 of 12 siblings were affected with MAE, the father had juvenile myoclonic epilepsy, and two other individuals had a benign unclassified generalized epilepsy syndrome; and in family 3, there were two affected cousins with MAE (Kron et al., 2007). The clinical details of these cases are not available to check how well they fit with conventional MAE criteria. Nevertheless, these pedigrees are interesting because MAE multiplex pedigrees are not common, but even among these consanguineous kindreds some individuals are affected with other forms of IGE. These pedigrees support the concept of overlapping genetic influences on separate IGE syndromes.

Genetic studies in phenotypically heterogenous multiplex epilepsy families have revealed several different mutations in MAE patients. *SCN1A* (Escayg et al., 2001; Dimova et al., 2010) and *SCN1B* (Wallace et al., 1998) mutations segregated in three separate generalized epilepsy with febrile seizures plus (GEFS+) pedigrees that included one family member with a MAE phenotype. A *GABRG2* mutation was reported in a case of MAE in a pedigree with childhood absence epilepsy and febrile seizures (Wallace et al., 2001). In each of these pedigrees, only one member was affected with MAE, whereas other members had diverse (febrile and afebrile) seizure phenotypes. However, the distribution of seizure types in these pedigrees is not consistent with earlier family studies of pedigrees ascertained through a proband with MAE (Doose et al., 1970), suggesting that the association of MAE with *SCN1A*, *SCN1B,* and *GABRG2* mutations may be purely ''private'' to these pedigrees yet still providing an example of overlapping genetic influences to generalized seizures albeit within single Mendelian pedigrees.

Sporadic cases

This hypothesis of a private mutation was tested by in 22 ''sporadic'' (i.e., simplex families, not implying that the cases were nongenetic in etiology) French MAE cases and four Japanese MAE cases; *SCN1A*, *SCN1B,* and *GABRG2*

mutations were not found through standard PCR and Sanger sequencing of exons (Ohmori et al., 2002; Nabbout et al., 2003). It is unclear if fever susceptibility was a symptom elicited in the MAE cases in the GEFS+ pedigrees—if so this might be a useful clue to genetic heterogeneity. Outside of GEFS+ pedigrees, *SCN1A* mutation c.3521C>G transversion has been identified in a boy with sporadic MAE, but the pathogenicity is uncertain because the same mutation was also identified in his asymptomatic mother and a control individual (Yordanova et al., 2011). In addition, *SCN1A* mutation analysis was performed in 20 nonfamilial MAE cases and 18 cases with severe idiopathic generalized epilepsy of infancy (SIGEI) and SMEI without myoclonic astatic seizures. The authors defined SIGEI as the presence of generalized and unilateral tonic and tonic–clonic seizures in the first year of life, often provoked by fever, which tend to recur in clusters or status epilepticus; they differentiated this from SMEI by the lack of myoclonic seizures. Novel *SCN1A* mutations in exons 9, 15, and 18 were found in two cases with SIGEI and one with borderline MAE and SIGEI (Ebach et al., 2005). These cases indicate that *SCN1A* mutations are rare in individuals with myoclonic–astatic seizures but do not establish pathogenicity (Klassen et al., 2011).

Recently, mutations in *SLC2A1* have been identified in 4 of 84 MAE cases, suggesting that *GLUT1* deficiency may have a broader phenotype than previously conceived, and these are associated with the seizures types observed in MAE (Mullen et al., 2011). The mutations identified were missense, rather than the deletions, duplications, or amplifications of the *SLC2A1* gene that are associated with classic *GLUT1* encephalopathy. Three of the four MAE patients with *SLC2A1* mutation had an abnormal neurologic examination with speech delay and/or movement disorder. These additional clinical features might provide clues to genetic heterogeneity in MAE. Although the contribution of known genomic sequence variants in MAE is currently modest, although expanding, the etiologic role of structural variation in the genome is much less certain.

Structural genomic variation

The role of rare genomic copy number variations (CNVs) in epilepsy is increasingly recognized (Kim et al., 2007; Mulley & Mefford, 2011). Mefford applied whole genome oligonucleotide array comparative genomic hybridization (average probe spacing 2.5 kb in hotspot regions and 38 kb for whole genome backbone coverage) to 15 cases with a MAE phenotype. Two rare CNVs were detected: one was a duplication in chromosome 5p15.33 (with possible candidate genes *NKD2* and *SLCA18*) inherited from an affected mother, although details of her affectedness were not specified. The other CNV was a deletion in chromosome 7q36.1 inherited from an unaffected father (Mefford et al., 2010). These loci have yet to be replicated and it is difficult to infer causality without further family and functional studies.

Challenges and etiologic hypotheses

Twin and family studies clearly demonstrate genetic influences on MAE. It is equally clear that the nature of the genetic influence(s) is not straightforward to determine. The key challenge is to identify and control sources of genetic heterogeneity. As the definition and boundaries of MAE have evolved, so too has the evidence of genetic heterogeneity been revealed. Over time, the distinction between MAE and LGS has become better defined, and several distinct syndromes such as BMEI and SMEI, with genetically heterogeneous backgrounds to MAE, have been disentangled from the original MAE grouping. Lately, gene mutations in *SCN1A* and *SLC2A1* have been observed in a small but appreciable proportion of MAE cases. Most *SCN1A* mutations in MAE are found in individuals within GEFS+ pedigrees rather than in ''sporadic'' MAE cases. *SLC2A1* mutations have, on the other hand, been found in approximately 5% of sporadic cases, and it remains to be seen if subtle clinical features are predictive of *SLC2A1* mutations in MAE (e.g., speech delay) or whether more subtle *SLC2A1* mutations (e.g., missense or intronic SNPs) are found in MAE cases compared with more typical *SLC2A1* mutations seen in established *GLUT1* phenotypes. At present there is scant evidence of a significant role for CNVs in the disorder, although such investigations are at an early stage in MAE. Nevertheless, the most MAE etiology remains unexplained and insightful findings arising principally from family studies lead us to a number of research questions and hypotheses.

Family studies, both in relatives of typical MAE cases and in rare consanguineous kindreds, show that different family members are often affected with IGE subtypes different from MAE. This strongly suggests an etiologic model comprising more than just one single gene. Up to two thirds of family members were affected with seizures or EEG abnormalities in Doose's original studies, although this incidence may be less if we were now to separate out families of BMEI and SMEI probands. Nevertheless, even if this figure was reduced to 50%, this suggests that the genetic influence on MAE is major. Major genetic influences should be amenable to elucidation by linkage analysis, and linkage designs should incorporate phenotypic (seizure and cognitive) as well as endophenotypic (e.g., EEG) data from all informative family members to maximize the statistical power of the method. However, it is not certain if all the EEG abnormalities described by Doose can be successfully employed as endophenotypic markers. In addition, the existence of an MZ twin pair, discordant for MAE but concordant for (generalized) epilepsy, suggests a role for epigenetic factors. Two other intriguing observations, a male sex bias and strong evidence for maternal transmission of EEG abnormalities, are open to several genetic or epigenetic interpretations. Therefore, we propose two alternative but nonconflicting genetic models: one involving a combination of major genetic factors, and the other combining major

genetic and epigenetic factors. By analogy with findings in adolescent-onset IGE (Durner et al., 2001), we hypothesize that some loci are shared between EEG abnormalities and generalized seizures, whereas other loci or epigenetic marks uniquely influence myoclonic seizures.

Genetic Strategies to Elucidate Etiology

There are three major gaps in our knowledge of MAE etiology. The first is the broader neurodevelopmental and neuropsychiatric phenotype in cases and relatives, and tied with that the prognostic features at onset. The second is the role of CNVs in disease causation and their possible correlation to aspects of phenotype. The third is of course the genetic basis for approximately 95% of MAE. The foundation for answering these questions lies in detailed (''deep'') phenotyping of clinical characteristics, cognitive and neuropsychiatric features, and seizure and EEG traits.

Deep phenotyping is increasingly recognized as critical in genetic analysis (Greenberg & Subaran, 2011; Joober, 2011) and is important to identify (see the following): (1) endophenotypes that could be used as biomarkers, (2) prognostic features (Moschetta et al., 2011), (3) and phenotypic clues to genetic heterogeneity. Subsequently, we can start to identify and control sources of genetic heterogeneity, testing the hypotheses that clinical features and family history can predict *SCN1A* and *SLC2A1* mutations, and that cases from densely multiplex pedigrees are genetically heterogeneous from typical MAE cases. Dense multiplex pedigrees may also be enormously instructive and should be investigated separately.

CNVs are increasingly recognized for their role in neurodevelopmental disorders and in epilepsies (Mefford et al., 2010). Their role in MAE is little explored, and it would be interesting not only to assess the role of recurrent and novel CNVs but also to test the hypothesis that CNVs are more frequent in the MAE subgroup with unfavorable cognitive or seizure prognosis, that is, neurodevelopmentally comorbid individuals.

The most challenging question is how to unravel the genetic basis for the large majority of MAE cases. The existence both of multiple phenotypes within families and maternal EEG transmission multiply this challenge, even after genetic heterogeneity has been limited. However, the evidence of major genetic effect provides grounds for optimism, and the phenotype data from relatives can be fully exploited to investigate shared and distinct genetic influences on seizure, EEG, and cognitive features. Two approaches are feasible for this relatively uncommon disorder: the first, linkage analysis, relies on the use of rich family data across multiple pedigrees and has been successfully employed in idiopathic generalized and focal epilepsies with sample sizes of 20–50 families (Durner et al., 2001; Strug et al., 2009); the second, next-generation sequencing (NGS), is a promising tool that has been used in rare disorders. Both linkage and NGS approaches are able to identify allele-specific inheritance, and could therefore potentially address the hypothesis of maternal transmission of susceptibility (Heinzen et al., 2010; Azmanov et al., 2011). The main methodologic challenge of NGS, now that technical costs have dropped, is to reduce the number of variants identified in a single case by comparison with phenotypically similar cases or with affected relatives and with control data. A number of articles have described success in trios or with a handful of cases (Ng et al., 2010; Regalado et al., 2011), but whether such success can be reproduced in diseases with different (unknown) genetic architecture is a matter of conjecture. Nevertheless, several international collaborative ventures (for example, EuroEpinomics; Epilepsy Phenome Genome Project/EP14K) are focused on the elucidation of etiology in rare epilepsies, and we anticipate that these methodologic challenges will be overcome in the near future. It is also evident that answers to the etiology of MAE can most speedily and efficiently be achieved through the pooling of clinical and scientific resources. To conclude, careful clinical observation has revealed genetic heterogeneity in this field over the last 40 years and as such detailed phenotyping undoubtedly holds the key to further genetic advances in an era when we are able to investigate multiple genetic and epigenetic mechanisms only hinted at before.

Disclosure

None of the authors have any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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