ogressive myoclonic epilepsy could be suspected, y ceroid-lipofuscinosis, but at this age it runs a dif- course and can be eliminated by biological, neuro- ological, and ophthalmological investigations.

rly cryptogenic focal epilepsy may have the same with complicated febrile seizures rapidly associ- with focal seizures; these patients do not present al absences or myoclonic jerks. This diagnosis is ly when hemiclonic seizures alternate affecting sides and when partial motor seizures affect differ- arts of the body (Sarisjulis et al., 2000). However, atients have been reported with focal epilepsy shar- linical features with SMEI and also carrying an *A* mutation (Okumura et al., 2007). These cases the problem of the limits of the Dravet syndrome. her patients with a complete picture of SMEI to families in which other members present with febrile seizures or another type of epilepsy and an *SCN1A* mutation, which constitutes the S+ syndrome (see Chapter 59).

cently, the discovery of mutations in PCDH19, the ncoding the protocadherin 19 on the Xq22 chromo- in *SCN1A*-negative female patients presenting clinical picture resembling the borderline SMEI diagnostic question: are these patients affected orderline SMEI (Depienne et al., 2009b) or by a dif- disease, "Epilepsy and mental retardation limited males (EFMR)," as described by Scheffer et al. Further studies are needed to solve this problem.

DIAGNOSTIC WORKUP

onset, the diagnosis is uneasy and based on the findings described above. Hattori et al. (2008) sed an interesting set of criteria for an early diag- during the first year of life. The severity of the sei- contrasts with the scarcity of EEG paroxysmal lies, the negativity of the etiological investiga- and the initial good psychomotor development. MRI are usually normal except for a few cases ation of the cisterna magna or slight diffuse at- Dravet et al., 2005). One must underline the great of the triggering factors. The provocative effect temperature variations, without true fever, fections is characteristic, as well as that of vac- In this context, one genetic analysis must be ed for the patient and his parents, bearing in hat the absence of one *SCN1A* mutation does clude the diagnosis and other mutations need searched for (Depienne et al., 2009b). Later on, and pattern sensitivity are also frequent, including mental light, and can lead to autostimulation, es by only eye closure. Many other stimuli gger seizures: hot baths (Awaya et al., 1989), physical exercise (Dravet et al., 2005), noisy environments, and emotion. These patients have a very high susceptibility to convulsions. During the second year, the appearance of other seizure types and EEG anomalies, as well as the slowness of the psychomotor progresses and the changes in behavior, which becomes hyperactive, allow the diagnosis of SMEI to be confirmed. It is also of value to perform repeated cognitive assessments which can detect sectorial deficits (language, visual-perceptive, visual-motor skills).

Neuroimaging and other ancillary investigations remain normal; however, in rare patients the MRI performed during the course of the epilepsy displays hippocampal sclerosis (Siegler et al., 2005; Striano et al., 2007a).

GENETIC FACTORS

Patients with SMEI have a family history of epilepsy or febrile seizures (FS), ranging in incidence from 25 to 71% (Hurst, 1987; Ohki et al., 1997; Oguni et al., 2001). In a series from Marseille (60 cases), family antecedents were found in 22 cases (36%), FS in 10 families (16.6%), and epilepsy in 12 families (20%), which included three with FS also (Dravet et al., 2005). In addition, there are several familial case reports in which siblings were also affected by SMEI, including affected monozygotic twins (Fujiwara et al., 1990; Dravet et al., 1992; Ohki et al., 1997; Miyama et al., 2008) and dizygotic twins (Ohtsuka et al., 1991). These clinical studies suggested a strong genetic predisposition in SMEI. A marked breakthrough in identifying the underlying cause of SMEI was made through the discovery of voltage-gated sodium-channel gene α1 subunit (*SCN1A*) mutations causing a unique epileptic syndrome designated as generalized epilepsy with febrile seizures plus (GEFS+) (Scheffer and Berkovic, 1997; Wallace et al., 2001). Singh et al. (2001) found SMEI patients among members of GEFS+ families, and proposed a GEFS+- spectrum, with FS being the most benign phenotype and SMEI being the most severe. Eventually, Claes et al. (2001) identified new *SCN1A* mutations in all seven probands with SMEI that they studied. These mutations were more severe than those observed in the GEFS+ families and occurred *de novo*. The proportion of cases carrying the *SCN1A* mutation reported before now ranged from 33 to 100% (Claes et al., 2001; Ohmori et al., 2002; Sugawara et al., 2002; Fujiwara et al., 2003; Nabbout et al., 2003; Wallace et al., 2003; Fukuma et al., 2004; Depienne et al., 2009a), although current estimates reach 70 to 80%, owing in part to the methodological advances (Madia et al., 2006; Mulley et al., 2006; Nakayama et al., 2010). *De novo* *SCN1A* mutations were shown to arise largely from the paternally derived chromosome, and may occur at

any time, from the premorula stage of the embryo (causing disease in the subject) to adulthood (with mutations in the germline cells of parents causing disease in offspring) (Heron et al., 2010; Vadlamudi et al., 2010). The number of reported SMEI-associated mutations of *SCN1A* now exceeds 330 (Lossin, 2009). Approximately two-thirds of these are truncating mutations including frameshift and nonsense mutations, and the remaining third are missense mutations. Correlations between phenotypes and genotypes have been studied by different authors (Nabbout et al., 2003; Ohmori et al., 2003; Ceulemans et al., 2004; Fukuma et al., 2004; Oguni et al., 2005) but no consensus has been reached. The most recent study by Zuberi and colleagues analyzing 273 of their own and 546 published cases demonstrated that truncating mutations were significantly associated with earlier mean onsets of prolonged seizures, myoclonic seizures, and atypical absence seizures, as compared to missense mutations (Zuberi et al., 2011). Recently, intrafamilial clinical variability in epilepsy phenotype was reported as well as severity of epilepsy in several familial cases showing the same missense mutations or even the same truncating mutations, i.e., proband with SMEI core phenotype, sibling with SMEI borderline phenotype, or parent with FS or even no symptoms (Fujiwara et al., 2003; Nabbout et al., 2003; Kimura et al., 2005; Morimoto et al., 2006; Guerrini et al., 2010; Suls et al., 2010). These cases suggest the presence of other modifying factors such as genes or environmental influences, and also somatic or germline mosaicisms (Kimura et al., 2005; Gennaro et al., 2006; Morimoto et al., 2006). Recently, *SCN9A* variants have been suggested to modify the clinical symptoms of SMEI through interaction with *SCN1A* mutations (Singh et al., 2009).

Research aimed at identifying mutations in other genes in the remaining 20–30% of *SCN1A*-negative SMEI patients has been largely unsuccessful (Sugawara et al., 2002; Gennaro et al., 2003; Madia et al., 2003; Fukuma et al., 2004), apart from a *GABRG2* mutation and a *SCN1B* mutation found in two different patients (Harkin et al., 2002; Patino et al., 2009). However, the recent identification of protocadherin 19 mutations in *SCN1A*-negative SMEI patients could account for 5% of all SMEI patients, because their clinical picture is shared with those of SMEI borderline phenotype (Depienne et al., 2009b). In another study, 7 (37%) of the 19 patients with *SCN1A*-negative SMEI were found to have *PCDH19* mutations (Marini et al., 2010).

Recently, *SCN1A* knockout and knockin mouse models were developed to clarify the underlying mechanism of SMEI (Yu et al., 2006; Ogiwara et al., 2007). They beautifully reproduced the characteristic temperature- and age-dependent seizures and EEG manifestations shown in the human counterpart (Oakley et al., 2009). In these mouse models, a decrease in the Na [illegible] was recognized in the GABAergic interneurons [illegible] than pyramidal neurons, suggesting that dysfunction [illegible] inhibitory neurons plays an important role in gen[illegible] seizures. It was also shown that the α type I sodium [illegible] nel (Nav1.1) protein was expressed predominantly [illegible] axons and somata of inhibitory neurons but was neg[illegible] in pyramidal cells (Ogiwara et al., 2007). In heterozy[illegible] mutations, there is a 50% reduction in the sodium [illegible] density in interneurons without changes in the kinet[illegible] the channels. Thus, the pathogenesis of SMEI is pri[illegible] considered to be a dysfunction of inhibitory interne[illegible] caused by haploinsufficiency derived from *SCN1A* [illegible] tions. However, the phenotypic variability of SME[illegible] tients remains unexplained.

LONG-TERM COURSE

The outcome of SMEI is unfavorable. Three [illegible] reported patients with a follow-up to more than 40 [illegible] of age and their findings are convergent (Jansen [illegible] 2006; Dravet et al., 2009; Akiyama et al., 2010). Th[illegible] zures persist in adolescence and adulthood, even if [illegible] frequency and severity decrease. Partial seizures can [illegible] appear and myoclonic jerks disappear or attenuate. C[illegible] vulsive seizures mainly take place at the end of the [illegible] They usually present as secondarily generalized. T[illegible] perature variations remain a triggering factor and [illegible] still provoke epileptic status. Neurological anom[illegible] either remain stable or aggravate and are associated [illegible] orthopedic deformities (cyphoscoliosis, "crouch" [illegible] pes planus, etc.). The EEG features are variable [illegible] prominence of multifocal anomalies. All patients [illegible] cognitively impaired (severely in 50%) but deterior[illegible] after the age of 4 years is unusual (Wolff et al., 2[illegible] Many of them also have behavioral and personality [illegible] orders, including psychosis.

In 1992, we found a high rate of early mortality – [illegible] due to accidents, drowning, severe status epilepti[illegible] infections, sudden unexplained death (SUDEP) – [illegible] this figure is probably overestimated and a recent su[illegible] in Japan found a mortality rate of 10.1% (Sak[illegible] et al., 2011). However, SUDEP remains frequent, pr[illegible] bly more than in other infantile epilepsies. It occurs [illegible] often in small children (<5 years) but also in adults [illegible] not related to a previous worsening of epilepsy. Se[illegible] status epilepticus represents the second most com[illegible] cause of deaths.

TREATMENT AND MANAGEMENT

Treatment outcome is disappointing and a close inter[illegible] tion between doctors and families is mandatory. [illegible] early diagnosis is necessary in order to avoid the ant[illegible] leptic drugs (AEDs) that can aggravate the seizures. [illegible]

bamazepine and lamotrigine (Guerrini et al., 1998). roate, benzodiazepines (diazepam, clonazepam, am), stiripentol, and topiramate are the most use- EDs. When an infant starts to present with long and ed convulsive seizures before 1 year, continuous ent is indicated even if the diagnosis is not yet ed. as well as rectal injection of benzodiazepine time of the seizure. Valproate is commonly used ce but potassium bromide can allow good control convulsive seizures and is largely used in Germany pan (Oguni et al., 1994; Doose et al., 1998). When zures cannot be controlled and tend to realize sta- the most efficacious treatment is the association ipentol, clobazam, and valproate. Stiripentol, a ED. is the only drug which has been proved to icacious in the majority of these patients by con- trials (Chiron et al., 2000). It has been approved European Medicines Agency and is progressively ed in European countries. Topiramate can also be ious (Coppola et al., 2002) but its side-effects be carefully monitored: loss of weight, hypona- slowing of language acquisitions. The benefit of genic diet has been demonstrated in several pa- (Fejerman et al., 2005; Caraballo, 2011). Ethosux- can be used for myoclonic and absence seizures nobarbital for convulsive seizures when the other have failed. Levetiracetam seems promising for seizure type (Striano et al., 2007b). When the are photosensitive the use of a special blue lens ppress or decrease the light-induced seizures shi and Tsukahara, 1992; Capovilla et al., 1999) the pattern sensitivity is difficult to control. It important to avoid the long, generalized, or uni- seizures by preventing infectious diseases and hy- mia, which are their triggering factors. In this no pharmacological treatment has ever allowed press the epileptic seizures completely. So we not give many AEDs together because they have erious effect on behaviour and acquisitions. The the treatment should not be to make the seizures ear, but to decrease their number and duration favoring a good cognitive development.

management of statuses is still controversial, but of rectal (diazepam), buccal/nasal (midazolam), venous benzodiazepines is generally indicated, ed that the doses remain reasonable. In the same hen the benzodiazepines have failed to control zures, and intravenous phenytoin and barbiturates g considered, careful monitoring of plasma is required in order to avoid the complications verdosing (Chipaux et al., 2010). Recently, anec- sults have been obtained with intravenous levetir- but further studies are needed to evaluate its alue.

Repeated cognitive evaluations are recommended in order to understand better the factors responsible for the cognitive defects and the respective roles of seizures and AEDs. One must keep in mind that an infant with Dravet syndrome is at risk of becoming a handicapped child, adolescent, and adult, and it is possible to decrease the degree of this handicap by offering him or her a good environment with appropriate educative and rehabilitative methods (psychomotricity, speech therapy, ergotherapy) (Granata, 2011). Management of the behavioral disturbances is not easy and psychological support by a specialized team can help the family, as well as involvement with an association of families of children with Dravet syndrome (Black and Baker, 2011).

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Chapter 67

Lennox–Gastaut syndrome and epilepsy with myoclonic–astatic seizures

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...NEATING EPILEPTIC GENERALIZED NONSYMPTOMATIC EPILEPSY SYNDROMES IN CHILDHOOD

...at variability of outcome in childhood epilepsy ... a challenging condition, particularly for non-...matic cases. The syndromic approach has proved ...o predict outcome and is presently one of the ma-...es for nosology of epilepsies (Commission on ...ication and Terminology of the International ... Against Epilepsy, 1989). There is also growing ... that the appropriate choice of medication at ...set of the disorder should be decided based on ...e of syndrome involved and the knowledge that ...patients may be worsened by inappropriate medi-... (Guerrini et al., 1998; Perucca et al., 1998). Further-... the syndromic approach contributes to etiology, ... some syndromes are known to be idiopathic ... others are mainly symptomatic.

...wever, the concept of syndrome has a number of ...acks. First, many epilepsy syndromes lack one or ... major features at onset, making their recognition ...t until the full pattern has developed. Second, ... syndromes seem to be rather poorly delineated ...agnosis may vary among different clinical teams ...ng in the field. This is the case for syndromes in ... the patients exhibit several types of seizures, par-...ly for syndromes occurring in the same age range ... share one or several seizure types or electroen-...lography (EEG) patterns. In this context, statistical ...tion of the diagnostic criteria that distinguish syn-...es is required. It should demonstrate that the items ... define a given syndrome are linked, since this de-... the concept of "syndrome," that goes together.

One of the most challenging fields is that of severe generalized epilepsies of childhood that exhibit several types of seizures. Nonprogressive symptomatic cases with tonic and atypical absence seizures, mental retardation, and slow spike-waves are universally labeled Lennox–Gastaut syndrome (LGS) (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). However, in nonsymptomatic cases, particularly when there is myoclonus and deterioration, it may be difficult to draw the border between nonsymptomatic LGS and the condition defined by Doose et al. (1970). These nonsymptomatic cases are particularly difficult to address for historical reasons.

Soon after Gibbs and colleagues (1939) had shown that patients with the "petit mal variant" pattern differ from those with typical absences, Lennox and Davis (1950) showed that the former exhibit drop attacks, atypical absences, and a variety of brain lesions, and that most of them remained intractable. The clinical and EEG pattern was further delineated by Gastaut et al. (1966) and Dravet (1965) who showed that tonic seizures and atypical absences were the most characteristic seizure types. The condition was therefore named Lennox–Gastaut syndrome.

CLASSICAL PATTERN OF THE LENNOX–GASTAUT SYNDROME

Pathophysiology of LGS remains unknown; there are no familial cases and no evidence for genetic predisposition. Prevalence is estimated to be around 2–3% of pediatric epilepsy cases. Onset is often insidious and imprecise, between 3 and 10 years of age. It is earlier when preceded by other types of epilepsy, infantile

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spasms, or partial epilepsy. Around 70% of the cases are symptomatic, affecting children with psychomotor delay or neurological antecedents (malformations, hypoxic–ischemic encephalopathy, postinfectious, tumors, post-irradiation, etc.) (Beaumanoir and Blume, 2005).

The course is often unfavorable with intractable epilepsy, frequent episodes of atypical absence, tonic or mixed status epilepticus, and mental deterioration or stagnation (Beaumanoir et al., 1988). Atypical absences may be difficult to identify because of progressive onset and outset and incomplete loss of contact, and the patient may continue automatically with his or her previous activity although he or she experiences slow forward drop of the head while the EEG records generalized irregular 1–2.5 Hz slow spike-waves (SW) lasting from 5 to 20 seconds (Fig. 67.1). Diurnal and nocturnal tonic axial seizures comprise progressive flexion of the head and trunk, flexion, or extension of the upper limbs, upward deviation of the eyes and brows, and often autonomic manifestations while the EEG discloses generalized fast low-amplitude rhythmic activity (Fig. 67.2). Atonic seizures produce sudden loss of tone that may involve the whole body or no more than the head, and may be combined with either slow SW or fast EEG activity.

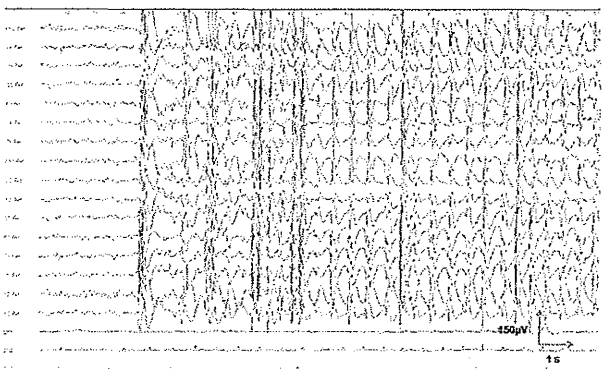


Fig. 67.1. A 12-year-old adolescent with Lennox–Gastaut syndrome. Awake tracing shows atypical absence, sequence of slow spike-waves around 1–2 Hz, diffuse and synchronous, predominating on both frontal areas.

There may be other seizure types: partial seizures, epileptic spasms, tonic–clonic seizures, and myoclonus, though they are not characteristic of LGS.

Awake interictal EEG shows more or less prolonged or even subcontinuous sequences of diffuse slow spike-waves (SW) identical to that of atypical absence. There are frequent focal anomalies consisting of slow waves or spikes that correlate with the topography of an eventual brain lesion. In sleep, physiological features and organization are decreased or even missing, and replaced by generalized bursts of high-amplitude slow spikes similar to the ictal record of a tonic seizure, characteristic of LGS (Fig. 67.3).

Pathophysiology, including that of slow SW remains unknown; as for West syndrome at least two factors are involved: nonspecific brain lesion and specific age-related to brain maturation. The bifrontal predominance of interictal EEG anomalies, "frontal" semiology of seizures, and cognitive defect could be linked to maturation of the frontal cortex at this age. Although some brain lesion is likely the triggering factor, the paroxystic activity affects the whole cortex, particularly the frontal lobes. Indeed, measures of propagation time across the corpus callosum of a series of slow SW with focal onset show that time lag decreases during the discharge, demonstrating that a unilateral discharge rapidly generates a bilateral and synchronous activity (Kobayashi et al., 1997; Ohtahara et al., 1995). Long-term potentiation and synaptic remodeling mechanisms, or lack of synaptic pruning during maturation of thalamo-frontal pathways and primary bisynchrony could contribute to the maintenance of autonomous slow SW activity (Dulac and N'Guyen, 1993; Blume et al., 1973; Blume, 2001; Markand, 2001).

MYOCLONIC VARIANT OF LENNOX–GASTAUT SYNDROME AND DOOSE'S ETIOLOGICAL APPROACH

During the years following the identification of LGS, variants were reported, particularly the nonsymptomatic

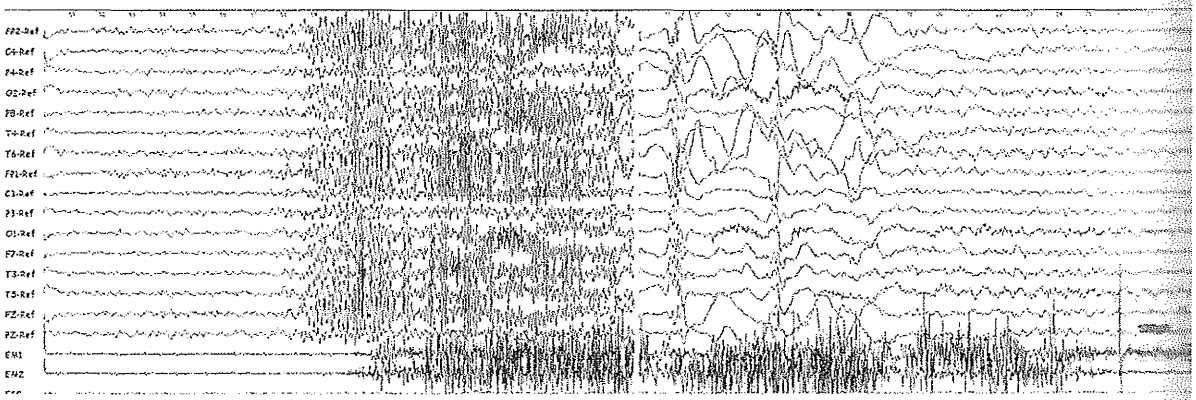
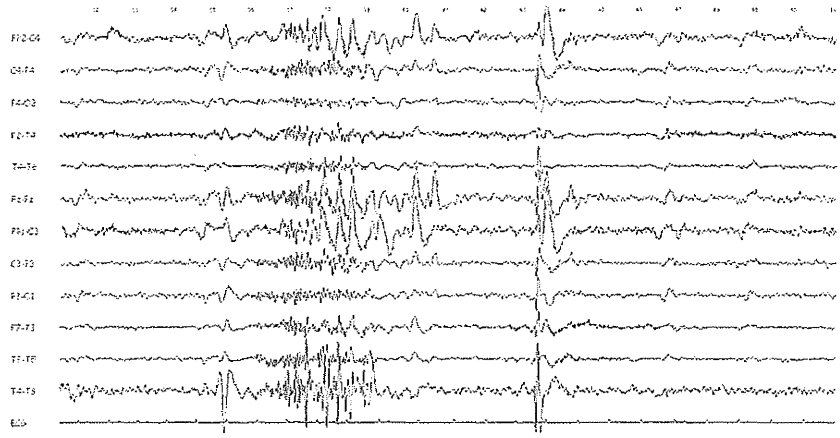


Fig. 67.2. A 15-year–old adolescent with Lennox–Gastaut syndrome. Axial tonic seizure in sleep. Rapid rhythms follow



67.3. A 13-year-old adolescent with Lennox–Gastaut syndrome. Sleep tracing shows a sequence of diffuse rapid rhythms.

clonic variant bearing a better prognosis (Aicardi and rie, 1971; Giovanardi Rossi et al., 1988). In this variant, mean age of onset was 3 years, patients exhibited mas- and erratic myoclonus, atypical absences and tonic sei- s, and EEG showed slow SW. These patients had ent episodes of myoclonic status during which they drowsy with erratic myoclonus (Beaumanoir, 1981). condition was reported as "idiopathic Lennox– ut syndrome" by Boniver et al. (1987), and shows incidence of familial antecedents (47%), frequent clonus, and delayed occurrence of tonic seizures.

the meantime, Kruse (1968) and Doose et al. (1970) attention to genetic predisposition to the occur- e of myoclonic seizures in early childhood. Thus, ntrast with the *syndromic* approach of the previous hors, they defined an *etiological* approach and termed rencephalic myoclonic–astatic petit mal" a hetero- eous condition that shared massive myoclonus and background activity with generalized SW on EEG, which some patients had a single type of seizures, rs several, some patients exhibited long lasting epi- es of status epilepticus, others did not, some patients vered whereas others remained with intractable epi- y. The view of the authors was that all these patients ed a polyfactorial genetic predisposition to general- epilepsy, but the cause of the wide variety of clinical ression and outcome remained unclear.

The description of several detailed cases helped to gnize within Doose's (1992) population of children cific clinical and EEG patterns corresponding to ep- y syndromes more recently identified. Indeed, some ents exhibit massive myoclonus combined with gen- zed spike-waves as a single type of seizure together favorable outcome, corresponding to the "benign clonic epilepsy of infancy" delineated by Dravet Bureau (1981) but presently called "myoclonic epi- y in infancy" (Classification, 1989) because of the able course. Others with onset in the first year of life suffer generalized or unilateral clonic seizures without interictal EEG abnormalities during the first months of the disease, whereas myoclonus and spike-waves occur one to several years after onset and the course is protracted, corresponding to the "severe myoclonic epilepsy of infancy" delineated by Dravet et al. (1982).

Within Doose's group, patients with later onset (after 2 years of age) and several types of seizures also exhibit various outcomes. Some patients recover after a few months to 1 or 2 years (Dulac et al., 1990) whereas others have long-lasting episodes of myoclonic status and tonic seizures, and remain intractable. This latter group shares with the "myoclonic variant of LGS" (Aicardi and Chevrie, 1971) a high incidence of familial antecedents, several types of generalized seizures, episodes of myoclonic status, late occurrence of tonic seizures, and mental deterioration together with pharmacoresistance, and lack of etiology.

In order to conciliate these two approaches (syndromic vs. etiological) the concept of a biological continuum ranging from LGS to myoclonic epilepsy was developed, with the myoclonic variant of LGS being intermediary between these two conditions (Aicardi and Chevrie, 1972; Aicardi, 1973; Aicardi and Levy-Gomes, 1988). According to this model, the main cause of different clinical expression of epilepsy would be the age of onset (Aicardi and Chevrie, 1971).

MULTIPLE CORRESPONDENCE ANALYSIS TO VALIDATE THE DISTINCTION BETWEEN LENNOX–GASTAUT SYNDROME AND EPILEPSY WITH MYOCLONIC–ASTATIC SEIZURES

In 1999, we applied a mathematical method to data from a group of 72 children followed in the pediatric neurology unit of Saint-Vincent de Paul Hospital; these children had their first seizure between 1 and 10 years of

age, despite normal previous psychomotor development and negative cerebral MRI, and had at least two types of generalized seizures excluding epileptic spasms (Kaminska et al., 1999). In these patients, there was great variability in terms of response to medication and outcome. The challenge was to determine whether distinct epilepsy syndromes could be recognized. For this, we used a well-adapted method called Multiple Correspondence Analysis (MCA) (Benzécri, 1992). Each patient is represented in a multidimensional space; hence there is a "cloud" of patients in which the distances between patients reflect the similarities between individuals. The cloud of patients is projected onto subspaces that account for most of the variance and permit visualization. Clusters were then identified within the cloud. This method avoids any *a priori* classification and permits the most discriminate variables to be identified.

The study was first performed on the combined clinical and EEG items collected throughout the follow-up period which permitted the identification of three groups (Fig. 67.4). The most contributive items for the classification were age of onset and duration of the seizure disorder, seizure types, mental retardation, and EEG patterns (Table 67.1). One group was differen[t] the two others because of late onset (after 5 [y] age), persistence of seizures for over 3 years, [a] mental retardation at the end of follow-up, [a] of myoclonus. In a second group seizures also p[er] for over 3 years with severe mental retardation a[t] of follow-up and long bursts of irregular spikes [a] waves but there was myoclonic status for over [1] and vibratory tonic seizures. The third group lack[s] vere mental retardation on follow-up and s[ei] ceased within the first 3 years of the disorder. Thi[s] provided therefore the first statistical demonstrat[ion] the existence of discrete groups of patients sha[ring] combination of clinical and EEG characteristics, [a] distinguishing and defining precisely well delineat[ed] ilepsy syndromes.

In a second MCA only items involving the firs[t] of the disease were included, in order to dete[r]mine whether the previously identified groups could be r[e]cognized from the onset of the seizure disorder, or if [it] only appeared during the course of the disease, [as] could be a consequence of treatment (Fig. 67.5). [The] most contributive features for the classificatio[n]

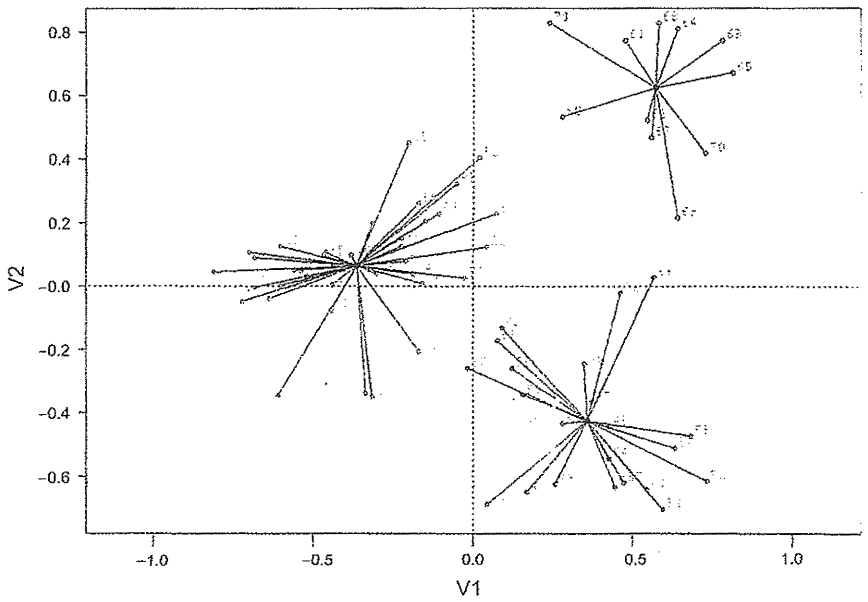


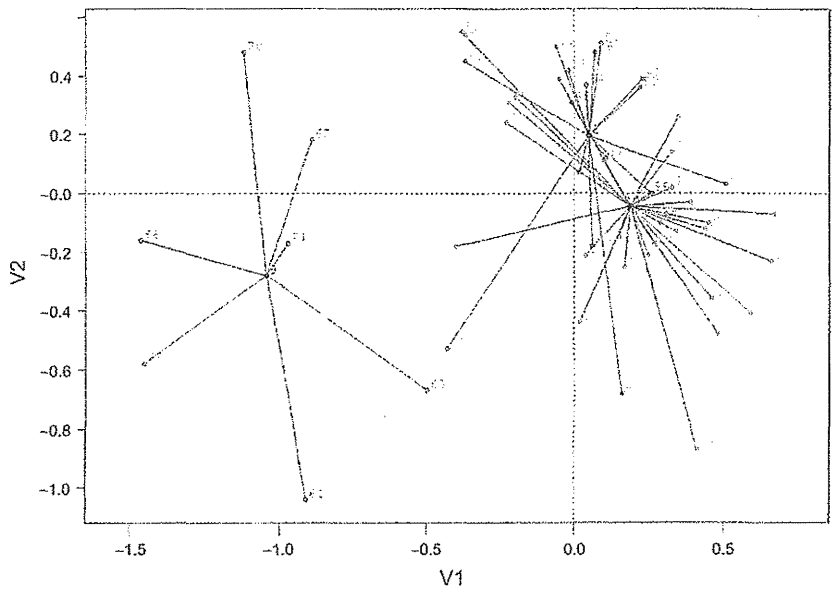
Fig. 67.4. Multiple correspondence analysis with overall clinical and EEG variables (72 individuals and 23 variables). [The] method identifies groups of individuals that share specific features, thus corresponding to the definition of syndromes. Notice [that] there are three distinct groups identified by this method. Group 1 is on the left. Group 2 is on the lower right. Group 3 is on the [upper] right. Numbers represent subjects. Axes 1 and 2 comprise the most contributive variables (78.4% of the variance – axis 1: 54.[6]% axis 2: 23.8%). The first axis V1 comprises in order of decreasing importance: negative values: no mental retardation > no [absence] seizure > duration less than 3 years of the disorder > no other tonic seizures > JME; positive values: D EEG pattern > severe [mental] retardation > seizure disorder lasting over 3 years > vibratory tonic seizures > tonic status epilepticus > absences status epilep[ti]cus. The second axis V2 comprises in order of decreasing importance: negative values: myoclonic status epilepticus > vibra[tory] tonic seizures > A EEG pattern; positive values: absence of massive myoclonus > age of onset of seizure disorder between 5 and [6] years > no drop attacks > no myoclonic status epilepticus. Reproduced from Kaminska A, Ickowicz A, Plouin P, et al (19[99]) Delineation of cryptogenic Lennox–Gastaut syndrome and myoclonic–astatic epilepsy using multiple correspondence analysis. Epilepsy Res 36: 15–29, with permission.

7.1

features that distinguish each given group from the two others

Group 1	Group 2	Group 3
No vibratory tonic seizures	Disorder duration > 3 years	Absences, no familial antecedents, no myoclonic status, no febrile convulsions
Frequent massive myoclonus, no partial seizures, no absence status, no C, no D EEG pattern	Frequent massive myoclonus, drop attacks, tonic–clonic seizures, no familial antecedents, no febrile convulsions, no C EEG pattern	Other tonic seizures, disorder duration > 3 years, no A EEG pattern, no tonic status, no Juvenile myoclonic epilepsy (JME)
Drop attacks, age of onset 2–4 years, disorder duration < 3 years, no E EEG pattern, no tonic–clonic status, no familial antecedents	Boys, tonic vibratory seizures, myoclonic status, presence of A EEG pattern, no partial seizures	D EEG pattern, no B EEG pattern, no tonic–clonic status, no vibratory tonic seizures

are drawn from the first MCA study including characteristics from throughout the seizure disorder.
terns: (A) long sequences of generalized irregular spike-and-slow wave (SSW) activity with disappearance of physiological rhythms, (B) quences of 3 Hz spike-waves (SW) with persistence of basic activity, (C) short sequences of SSW activity predominating over the frontal D) long sequences of SSW activity with frontal predominance, and (E) focal paroxysmal activity.
racters correspond to positive characteristics.



67.5. Multiple correspondence analysis with initial clinical and EEG parameters (59 individuals and 15 parameters). Notice here are two identifiable groups. On the left, patients assigned to Group 3, and on the right the combination of those assigned to ps 1 and 2 by the first multiple correspondence analysis applied to all clinical and EEG parameters. Thus, Groups 1 and 2 could be distinguished at the beginning of the disorder. Numbers represents subjects. Axes 1 and 2 comprise the most contributive ables. The first axis V1 comprise in order of importance: negative values: age of onset over 5 years > no massive clonus > E EEG pattern > no drop attacks > D EEG pattern > rare massive myoclonus > tonic seizures; positive values: no ence seizures > no other tonic seizures > frequent massive myoclonus Reproduced from Kaminska A, Ickowicz A, Plouin al (1999). Delineation of cryptogenic Lennox–Gastaut syndrome and myoclonic–astatic epilepsy using multiple correspon- ce analysis. Epilepsy Res 36: 15–29, with permission.

age of onset of the disorder, seizure types including massive myoclonus and drop attacks, and EEG patterns. Only the first group which had the characteristics of LGS could be recognized from the first year of the disorder. The two other groups were myoclonic epilepsy but could only be distinguished after the first year of the disorder, following a long-lasting episode of myoclonic status epilepticus.

EPILEPSY WITH MYOCLONIC–ASTATIC SEIZURES

Epilepsy with myoclonic–astatic seizures (EMAS), a genetically determined epilepsy syndrome, is characterized by onset between 18 and 53 months of age in a previously normal child, more frequently boys (75%), with nonfebrile generalized mainly tonic–clonic, clonic, and a few days or weeks later, myoclonic, atonic (or astatic) (positive or negative myoclonus), myoclonic–astatic, and eventually atypical absence seizures, or a combination of the latter. In addition, some patients have tonic seizures. Febrile seizures may have preceded nonfebrile seizures by a few months. Within a mean 3 months seizure frequency gradually increases and patients exhibit frequent seizures of several types.

Patients become ataxic, but there is no other abnormality on neurological examination. IQ is in the normal range during the first months of the disease although parents complain of their severe hyperkinesia. EEG shows slowing of background activity with diffuse theta rhythms predominating on central areas and generalized bursts of around 3 Hz spike-waves concomitant or not with myoclonic axial or segmentary seizures (Fig. 67.6).

For the following months, the course may be favorable, with seizures mainly myoclonic–astatic and tonic–clonic, and the EEG shows short bursts of spike-waves. Within 2, rarely 3, years from the onset tients experience sudden arrest of seizures. A cognitive outcome is favorable, there is dysarthria dyspraxia with poor manual dexterity. Up to one of the patients exhibit massive myoclonic and/or generalized tonic–clonic seizures in adolescence. These tients correspond to group 1 identified by MCA.

In other cases, the course is altered by the occurrence of a long-lasting episode of myoclonic status epilepticus (MS), which occurs at a mean 53 months of age (35 a mean 17 months from seizure onset. During these isodes, vigilance is altered, with loss of contact with surroundings or somnolence. There is drooling, speech disorders ranging from dysarthria to mutism. Patients exhibit erratic myoclonus predominating the face and extremities of the upper limbs, massive eyelids, mouth, tongue, and fingers; they are ataxic hypotonia and tremor, and walking is difficult or impossible. These episodes usually start insidiously and difficult in most instances to determine the precise of onset since the diagnosis is often retrospective the patient is admitted to hospital for an increase in zure frequency. Parents only notice that the child been less interactive than previously. Other types of zures often occur during these episodes, including sences, eyelid jerks, drop attacks, massive myoclonus and generalized tonic or tonic–clonic seizures. shows lack of basic activity and diffuse and irregular spikes and slow waves persisting continuously throughout the episode of MS, in combination with erratic myoclonus recorded on electromyogram (Fig. 67.7). These MS episodes last for several weeks and may until the age of 8 years. In addition to MS, patients suffer from other types of status, absence, tonic, tonic–clonic seizures. Later, these patients with unfavorable outcomes are left with tonic seizures at the night sleep that exhibit a vibratory component and persist by the end of the second decade. In addition, is significant cognitive decline, and patients are left a major mental defect, the IQ being under 50 in instances, with slowness, lack of initiative, and perseverations (Kieffer-Renaux et al., 2001). These correspond to group 2 identified by MCA.

The significance of these two groups remains unclear. There are two likely possibilities. The first possibility is the etiology is the same at onset – namely there is some genetic predisposition according to Doose's hypothesis. In this case, a change in the course of the disease could result from adverse effects of medication when drugs such as carbamazepine or phenytoin are administered early in the course of the disease. This hypothesis is consistent with the fact that groups 1 and 2 cannot be distinguished during the first year of

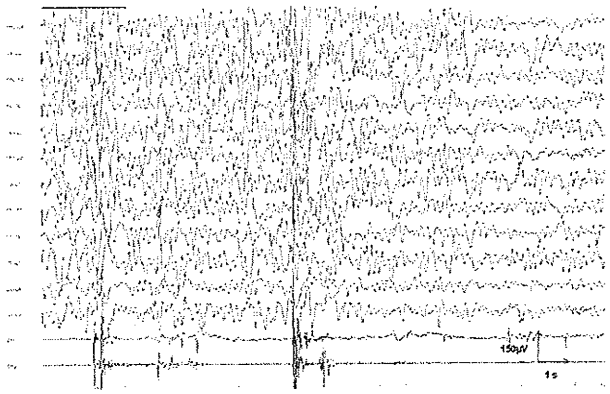
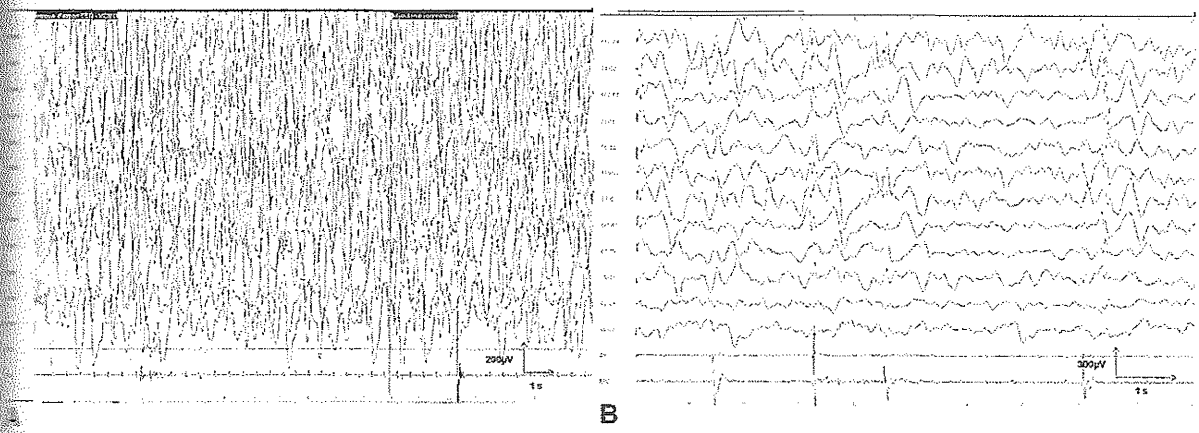


Fig. 67.6. A 3-year-old child, awake, at onset of MAE. Slow basic rhythm with many diffuse theta rhythms predominating in central regions. Bursts of diffuse and irregular spike-waves combined with axial jerks (contraction of deltoid muscles is shown on EMG).



67.7. (A) A 4-year-old boy, a few months after onset of MAE, during an episode of myoclonic status of myoclonus during fulness. Lack of physiological figures, very high amplitude diffuse, asynchronous delta slow waves, mixed with multifocal es. some combined with segmentary or erratic myoclonus. (B) Awake. Status of erratic myoclonus, during the same recording A. with decreased amplitude and time analysis (20μV/mm, 30mm/sec). High amplitude and diffuse delta slow-wave activity, ached on by multifocal spikes, some combined with segmentary myoclonus.

ase. In addition, in our series only half the group 1 ents received carbamazepine for a short period dur- which they experienced worsening of the epilepsy, reas in group 2 all patients received carbamazepine experienced worsening. An alternative hypothesis is the genetic background is not similar. Indeed, from first year of the disease twice as many patients from up 2 than from group 1 had tonic seizures, and they more bursts of slow SW than 3 Hz SW compared patients from group 1. However, these differences subtle and do not permit a clear distinction between ups in the first year of the disease. In addition, the rch for a specific genetic background has been unsuc- sful (Nabbout et al., 2003).

A long-term follow-up study by Oguni and colleagues 1 patients showed a similar evolution which was clas- d into favorable, intermediate, and unfavorable ms according to the ultimate seizures outcome guni et al., 2005). There were no clear differences e clinical and EEG characteristics as well as the prog- s between the atonic seizures (AS) and myoclonic ures (MS) groups. All attacks corresponded to gen- zed spike-wave or polyspike-and-wave complexes. inguishing between myoclonic or atonic seizures not influence the outcome of this unique epileptic drome. Thus, electrophysiological events underlying AS may be merely a consequence of genetically rmined thalamocortical excitability that generates generalized spike-and-wave complex and in turn, ctly or indirectly produces myoclonic, myoclonic– tic, or atonic seizures, depending on the predomi- ce of inhibition or excitation of neuronal activity.

Cumulative percentage remission of MS/AS after on- of attacks reached 40% within 6 months, 63% within 1 year, and 89% within 3 years (Oguni et al., 2005). Thus MS/AS in 89% of 81 patients disappeared within 1 to 3 years despite initial resistance. However, other combined convulsive or nonconvulsive seizures (GTCS or GCS) tended to persist after cessation of the MA/AS (Oguni et al., 2005). Based on the seizure prognosis, authors separate patients into three subgroups, favorable, intermediate, and unfavorable outcome. However, even in 55 children with a favorable clinical course, the attacks were initially resistant to AEDs, sometimes requiring additional corticotropin (ACTH) or ketogenic treatment. Interestingly, at least 21 patients among the favorable and intermediate groups appeared to enter into spontaneous remission, either suddenly or gradually, despite initial resistance to treatment for months or a few years. Approximately half of 15 patients with an unfavorable outcome were characterized by a combination of MA/AS, atypical absence seizures, minor status epilepticus, and recurrent GTCS at the early clinical course. Later, these seizures were accompanied by nocturnal GTS or generalized tonic vibrating seizures. Eleven patients with an intermediate outcome resembled the clinical course of those with BME, to some extent, experiencing recurrence of GTCS after a long remission period with a mean of 9 years and 2 months. GTCS were controlled easily by restitution or increasing the dosage of AEDs.

As to the intellectual outcomes of the 81 patients with myoclonic–astatic seizures (MEA) in the Oguni study, 49 patients or 59% showed a normal IQ level at the final follow-up, 20% were borderline or had mild retardation, and 21% had moderate retardation at most. The earlier the remission of epilepsy was, the better the IQ levels were. Among clinical factors, a positive family history of epilepsy and incidences of absence status or minor

epileptic status appeared to be the risk factors for unfavorable outcome.

MAE is considered a unique age-dependent epileptic encephalopathy, in which epileptogenesis progresses to a peak within 1 year after the onset. Recurrent GTCS, daily myoclonic/atonic seizures, or minor epileptic status are initially resistant to treatment. They gradually decrease within 2 to 3 years when seizures become more easily controlled or spontaneously remit. At present MAE should be recognized as an epileptic syndrome with a relatively wide clinical spectrum in which the main seizure types range from myoclonic to atonic. Intellectual outcomes range from favorable to unfavorable.

FROM LENNOX–GASTAUT SYNDROME TO EPILEPSY WITH MYOCLONIC–ASTATIC SEIZURES: A BIOLOGICAL CONTINUUM OR AN ETIOLOGICAL COMBINATION?

EMAS with favorable outcome and nonsymptomatic LGS are clearly distinct since they do not share any clinical or EEG feature. On the other hand, EMAS with unfavorable outcome appears as an intermediary condition: it comprises genetic predisposition, myoclonus, tonic–clonic seizures, and 3 Hz SW as EMAS with favorable outcome, but also tonic seizures, atypical absences and slow SW as LGS. It begins as EMAS with favorable outcome but in the long term it is similar enough to LGS to be called "the myoclonic variant of LGS" (Doose et al., 1970; Aicardi and Levy-Gomes, 1988), and adult neurologists who are not aware of the mode of onset see no difference from LGS. This condition has therefore a genetic predisposition. The difficult question is why it looks like LGS. This brings us to the reason why in childhood, epilepsy related to brain lesion may generate the LGS pattern. The clue is of course in the term "childhood," thus a maturation component is involved (see Chapter 47). Rapid maturation of the frontal lobes in this age range is known to be epileptogenic, and it could alter the course of epilepsy due to various causes, i.e., a brain lesion (LGS) or genetic predisposition (EMAS) (Doose and Baier, 1987; Chiron et al., 1992; Wasterlain and Shirasaka, 1994). This could explain why features of both types of epilepsy – LGS and EMAS – are shared (tonic seizures, atypical absences, and the slow SW and fast activity EEG patterns). In this case, the apparent biological continuum results from partly shared etiology–brain maturation.

ELECTROPHYSIOLOGICAL CHARACTERISTICS OF MAE

A series of 81 patients with EMAS, followed and extensively investigated at Tokyo Women's Medical University permitted a better description of seizure types and long-term outcome of patients with EMAS (Oguni et al., 2005). Video-EEG analysis with polygraphic recording (EMG placed on the trapezius, sternocleidomastoideus (SCM) and paraspinal muscles) of drop seizures in EMAS identified three seizures types according to postural change, temporal sequence of jerking, and associated EMG potential (Oguni et al., 1992):

1. *Myoclonic* flexor characterized either by sudden flexion (or extensor) (Oguni et al., 1992; Kim et al., 2009) of the head and trunk, causing the patient to fall, the fall either forward or backward resulting from massive flexion of the trunk at the hip or extension of the trunk: on the video the patient appears to be hurling toward the ground rather than slumping or collapsing (Fig. 67.6).
2. *Myoclonic-atonic*, with the same initial change as for the myoclonic flexor type, but subsequent falling caused by loss of muscle tone, not from massive flexion (Fig. 67.8). Polygraphs show initial myoclonic EMG potentials immediately followed by the interruption of ongoing EMG activity, corresponding to the myoclonus and atonia, respectively. Another type of myoclonic–atonic seizure is associated with the sound "u" presumably caused by a momentary contracture of the chest, immedi-

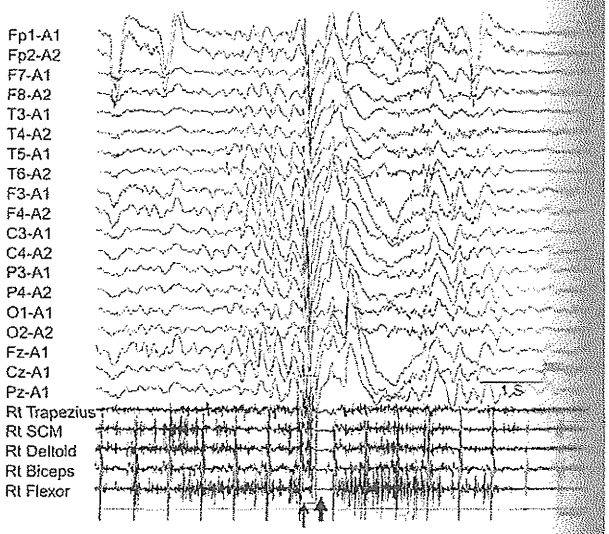


Fig. 67.8. Polygraph of a myoclonic–atonic seizure in a 5 years and 8 months old boy with unfavorable MAE while sitting on the bed. Sudden flexion of the head downward with momentary vocalization, immediately followed by slumping of the trunk onto the bed. The attack corresponded to a generalized, irregular spike-and-wave complex at 1.5 Hz. The massive myoclonic EMG activity, involving the right trapezius, sternocleidomastoid and deltoid muscles (arrow), was followed by interruption of EMG potentials for approximately 400 ms (bold arrow).

followed by atonic falling. The myoclonic and atonic components appeared to be equal in intensity, suitable for designating myoclonic–atonic seizures. *Atonic* seizures are characterized by sudden slumping or collapsing to the floor as a result of transient loss of muscle tone (Fig. 67.9). The detailed polygraphic analysis shows the sudden interruption of the ongoing EMG activity in all axial muscles for up to 400 ms. It may identify preceding small EMG discharges on the extremities prior to the onset of atonia, but is only visible on the ictal video by careful slow-motion analysis.

Generalized bilaterally synchronous single or multiple spike-and-wave discharges are common to all seizure types although spike-waves are briefer for myoclonus (Fig. 67.9). The temporal relation between spike-wave discharge and the clinical seizure show that the EMG phenomena of both myoclonic and atonic seizures correspond to the period between the spike component and the ascending portion of the slow wave. Interruption of EMG potentials lasts 300–500 ms. A spectrum of intensity may exist in the initial myoclonic phenomena, ranging from the slight to relatively high intensity observed in "myoclonic–astatic" seizures and even the high intensity observed in myoclonic flexor type.

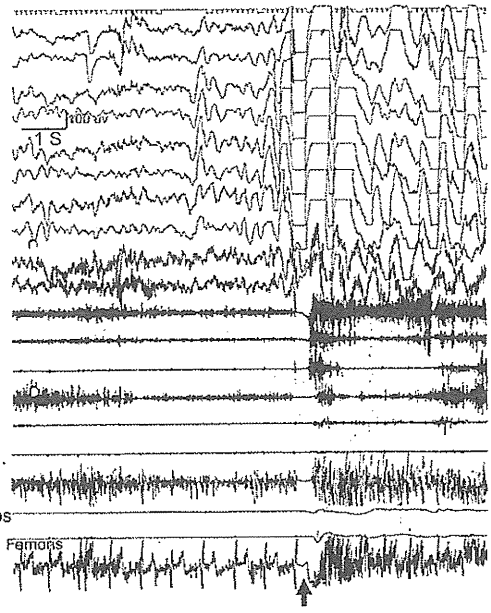


Fig. 67.9. Polygraph of an atonic seizure in a 3 years and 3 month old girl with favorable EMAS. Before the seizure, she was standing in the EEG room. She suddenly collapsed straight downward, landing on her buttocks at the arrow point. However, she immediately recovered. EMG potentials are suddenly interrupted for approximately 400 ms, involving the right trapezius, sternocleidomastoid, biceps, paraspinal, and anterior tibialis muscles. The corresponding EEG shows generalized high-amplitude spike-and-slow-wave complex at 3 Hz. There are no visible EMG potentials immediately before the EMG interruption.

Other seizures types in EMAS

The most common accompanying seizures are GTCS that occur during both wakefulness and sleep. The clonic component frequently resembles the repetition of massive myoclonic attacks. Rhythmic opening of the mouth and movement of the arms and legs start after a sudden collapse backward on the floor, when the patient is sitting. These seizures are considered generalized clonic rather than repetititive myoclonic attacks because of the presence of postictal suppression of background activity. Nocturnal convulsive seizures are generally resistant to treatment and tend to continue for a long time after cessation of MS/AS. Generalized vibrating tonic seizures with a few clonic components during sleep mainly affect the course of the unfavorable outcome group, and they are most resistant to treatment. In some patients, only eye opening occurs with irregular respiration for 10 seconds or more, corresponding to bursts of generalized multiple spikes, during sleep and eventually wakefulness. Atypical absence seizures correspond to runs of generalized irregular SW at 2–3 Hz. Some patients also have recurrences of prolonged clouding of consciousness with random segmental myoclonus. Their ictal EEG shows disorganized markedly slow background activity with random SW discharges, identical to minor seizure status. This peculiar seizure tends to start after awakening and last for hours.

DIFFERENTIAL DIAGNOSIS

Main differential diagnoses of LGS and MAE are conditions in which seizures produce drop attacks, and the EEG exhibits slow spike-waves. Secondary bilateral synchrony related to focal frontal epilepsy may be associated with atypical absences (Gastaut and Zifkin, 1988). Although infantile spasms classically occur before the age of 1 year, clusters of spasms may begin later resulting from frontal or temporal lesions (i.e., herpetic encephalitis), until adulthood. In nonsymptomatic cases beginning between 1 and 4 years of age, spasms in clusters were reported under the term of cryptogenic late onset infantile spasms (Eisermann et al., 2006). In addition to the spasms that may at that age produce drop attacks and are often difficult to distinguish from myoclonic seizures until recorded with video and EMG, patients exhibit atypical absences and tonic seizures, and the EEG exhibits both slow spike-waves and focal spikes and slow waves in the temporal areas.

Atypical benign focal epilepsy also causes drop attacks with major activation of the focal spike activity

that becomes bilateral in sleep (Aicardi and Chevrie, 1982). Epileptic encephalopathy with continuous spikes and waves during slow sleep is the extreme form of the latter (Tassinari et al., 2005) and may result from a focal brain lesion (see Chapter 66). Myoclonic epilepsy of infancy comprises massive myoclonus as the only type of seizures that usually does not cause the children to fall because of younger age of onset (see Chapter 69). Ring chromosome 20 syndrome, which usually begins in childhood, is another cause of long-lasting atypical absence seizures (see Chapter 57 on chromosome disorders) (Gobbi et al., 2005). Subacute sclerosing panencephalitis may also cause drop attacks due to the periodic jerks (see Chapter 123 on Subacute sclerosing panencephalitis and chronic viral encephalitis). The late infantile variant of ceroid lipofuscinosis may appear as LGS or MAE (see Chapter 173 on Neuronal Ceroid Lipofuscinoses).

TREATMENT OF LENNOX–GASTAUT SYNDROME

Although LGS is usually considered pharmacoresistant, this is indeed the case for conventional antiepileptic drugs that have been developed for totally different conditions. Compounds efficient in partial epilepsy may even worsen LGS, probably because the mechanism of the disease is different. Therefore, carabamazepine, oxcarbazepine, phenytoin, phenobarbital, vigabatrin, and gabapentin should be avoided as soon as the diagnosis is suspected. This may be challenging at onset since the slow SW activity often predominates in the frontal regions (probably for maturation reasons) and patients are often considered as having frontal epilepsy until a proper diagnosis is established. Benzodiazepines raise a difficult issue since it is in the course of the disease that worsening may occur (Tassinari et al., 1972) and their use therefore requires special attention.

However, some conventional drugs are efficient in LGS, particularly lamotrigine in combination with valproate (Motte et al., 1997; Eriksson et al., 1998), and topiramate (Bitton et al., 1999; Sachdeo et al., 1999). More specific is the effect of felbamate, a compound difficult to administer because of the bone marrow and hepatic toxicity (Dodson, 1993; Felbamate Study Group in Lennox, 1993; Pellock and Watemberg, 1997). Nevertheless, it often offers the only means to control drop attacks efficiently, and it is certainly worth monitoring blood values of transaminases and cells twice a month. Rufinamide is a promising compound that still requires clinical experience (Kluger et al., 2010).

Status epilepticus may be precipitated by various modifications in the conditions of life, including a change in the institution, probably as a consequence of altered quality of sleep. Change in drug treatment is however the major precipitating cause of SE. Treatment cannot follow the classical scheme dedicated to the treatment of convulsive status epilepticus since the drugs advised for the latter comprise a risk for worsening although phenytoin may be helpful when tonic seizures are a prominent component of the status. A ketogenic diet and steroids are however more likely to contribute to controlling seizures in this context.

TREATMENT OF EPILEPSY WITH MYOCLONIC–ASTATIC SEIZURES

The major issue is to reach the diagnosis early enough to have time to start treatment before seizures become daily or even occur several times a day. Indeed, no drug has proved efficient in monotherapy and the most efficient combination is that of valproate and lamotrigine. However, the build-up of this combination without a rash requires at least 6 weeks. Other potentially efficient drugs are levetiracetam and zonisamide, but they were not tested with dedicated trials that could confirm this indication from the onset of the disorder. For myoclonic status, the most effective treatment is a ketogenic diet followed by corticosteroid treatment. Benzodiazepines are also effective particularly in acute administration but they should be decreased very slowly to avoid relapse. In the Oguni series the most effective treatment of MS/AS was a ketogenic diet, followed by ACTH and ESM, supporting the suggestion of Doose that ESM appears to be the most favorable AED for myoclonic–astatic seizures and that high-dose ESM, in combination with VPA, appears better at controlling MS/AS (Oguni et al., 2001). Aggravation was reported with carbamazepine, phenytoin, phenobarbital, and vigabatrin. The question is when to stop treatment of responders, given the possible recurrence of myoclonic seizures in adolescence.

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Genetic variations of immunoregulatory genes associated with Rasmussen syndrome

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Summary
Objective: To elucidate the genetic predisposition of Rasmussen syndrome (RS).
Methods: In 29 Japanese patients, we examined the genome sequences of *cytotoxic T-lymphocyte-associated protein 4 (CTLA4)*, *programmed cell-death 1 (PDCD1)*, and *T-bet (TBX21)* genes by direct sequencing, and evaluated the significance of SNPs (single nucleotide polymorphism) by comparison with Hap Map data.
Results: In all patients, no disease-causative mutations were found in *CTLA4*, *PDCD1*, and *T-bet*. However, rs231775 SNP in exon 1 of *CTLA4* showed significant positive genotypic ($p = 0.0363$) and allelic associations ($p = 0.0137$) with onset of RS compared with Japanese controls, as did rs231779 SNP in intron 1 of *CTLA4* ($p = 0.0467$ and 0.0188, respectively). Also, rs2227982 SNP in exon 5 of *PDCD1* showed significant positive genotypic and allelic associations with RS ($p = 0.0145$ and 0.0114, respectively). Poor cognitive outcome (IQ below 50) was found in 0% of wild type (C/C), 9% of heterologous (C/T) and 25% of homologous (T/T) genotype of rs2227982. Quadriplegia was found only in homologous (T/T) genotype, and hemiplegia was in heterologous (C/T) and homologous (T/T) genotype of rs2227982. No association between SNPs of *T-bet* and RS onset

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was found. Regarding SNPs in promoter regions (rs4794067 and rs17250932) of *T-bet*, however, IQ below 50 was found in 19% of wild type (T/T) and 0% of heterologous (T/C) genotype of rs4794067, and in 19% of wild type (T/T) and 0% of heterologous (T/C) genotype of rs17250932. Quadriplegic patients were found only in wild-type patients (rs4794067 and rs17250932).
Conclusions: We identified three SNPs (rs231775, rs231779, rs2227982) as some of the SNPs associated with onset of Japanese RS. We need further studies in other populations to confirm these genetic predispositions in RS.

Rasmussen syndrome or Rasmussen encephalitis (RS) is a slowly progressive, autoimmune neurological disease, and shows intractable epileptic seizures including epilepsia partialis continua (EPC) (Rasmussen et al., 1958; Bien et al., 2005; Takahashi, 2006). Infection occurring around two weeks prior to onset is observed in 38% of the patients (Takahashi, 2006). Histological examination usually shows inflammatory lesions with T cell infiltration. The immunopathology of RS is attributed mainly to activated cytotoxic T cells (CTLs) (Bien et al., 2002). The CSF levels of IFNγ, IL-12, and granzyme B levels are elevated in the early stage, suggesting Th1 and CTL involvement (Takahashi et al., 2009). Immunomodulatory therapies using intravenous immunoglobulin, plasmapheresis and tacrolimus have been reported to improve outcome (Bien et al., 2005; Takahashi et al., 2013). These data suggest that incomplete inhibition of CTLs activated by acute infection may contribute to the pathophysiology of RS.

Cytotoxic T-lymphocyte-associated protein 4 (CTLA4) (MIM:123890) is a negative regulator of the immune system, resulting in inhibition of activated T cells. Ctla4 knockout mice show lethal lymph-proliferative inflammation (Waterhouse et al., 1995). Gene association studies reported a strong association of polymorphism of *CTLA4* with autoimmune diseases (Ghaderi, 2011). Programmed cell-death 1 (PDCD1) (MIM:600244) is also a negative regulator of the immune system, resulting in inhibition of activated T cells. *Pdcd1* knockout mice are susceptible to autoimmune diseases (Keir et al., 2008a). These mice have regulatory T cell dysfunction, resulting in susceptibility to experimental autoimmune encephalomyelitis (Wang et al., 2010). T-bet (TBX21) (MIM:604895) promotes differentiation of naïve T cells into Th1 cells that are essential for autoimmunity (Lazarevic and Glimcher, 2011), and expression of granzyme B in $CD8^+$T cells (Ji et al., 2011). We examined the associations of disease-causative mutations and polymorphisms in these immunoregulatory genes with Japanese RS.

Patients and methods

This retrospective study was performed at the National Epilepsy Center, Japan, after obtaining approval from the ethical committee.

Patients

We identified 57 Japanese patients who presented with a diagnosis of RS and were referred to the National Epilepsy Center from all over Japan between 1991 and 2012. We reassessed the diagnosis basically according to the European diagnostic criteria for RS (Figure A1) (Bien et al., 2005). Of 57 patients, two patients who had no frequent partial seizures, and six patients who had no unihemispheric cortical dysfunction were initially excluded from a diagnosis of RS. Of the six patients without unihemispheric cortical dysfunction, five were subsequently diagnosed as having RS based on characteristic histology, elevated granzyme B in CSF, or high intensity lesion on MRI characteristic of RS (Bien et al., 2005; Yamazaki et al., 2011). Of 49 patients with unihemispheric cortical dysfunction, one patient was excluded by histological findings. From the 53 patients with a confirmed diagnosis of RS, we examined only 29 patients who were actively treated in our epilepsy center and Nishi-Niigata hospital by the experimental costs. All 29 patients gave informed consent by the methods approved by the ethical committee.

Methods

Clinical characteristics were examined based on clinical records and referral letters from other hospitals. Outcome was evaluated by findings at the last observation. Seizure outcome in surgically treated patients was evaluated by the findings just before surgical intervention. Intelligence quotient (IQ) was measured by Tanaka–Binet, WISCIII, and WAISIII, dependent on the age at examination. We used full scale IQ (FSIQ) for evaluation.

Genomic DNA was extracted from EDTA blood samples using MagNA Pure (Roche Applied Science, Tokyo) and sent as anonymous samples to a commercial laboratory that performed genome sequencing (Takara bio, Co LTD, Yokkaichi). *CTLA4* from 5′ non-coding region to 3′ non-coding region was divided into 10 regions, and each region was amplified by PCR using primers (Table A1). *PDCD1* from the promoter region to 3′ non-coding region was divided into 16 regions, and subjected to PCR amplification using primers (Table A1). The promoter region, six exons and 3′ non-coding region of *T-bet* were divided into 10 regions, and amplified by PCR using primers (Table A1). PCR reaction was performed in a final volume of 20 μl containing 2 μl of genomic DNA (10 ng/μl) by the following cycling conditions: initially 94 °C for 4 min, followed by 35 cycles of 30 s at 94 °C, 30 s at 59 °C and 1 min at 72 °C. Thereafter, PCR products were purified with exonuclease and alkaline phosphatase, and the purified PCR products were subjected to forward and the reverse reactions using BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, Carlsbad, CA, USA). The reaction solution was purified by XTerminator (Applied Biosystems, Carlsbad, CA, USA). Sequencing was done using ABI3730×1 (Applied Biosystems, Carlsbad, CA, USA). Mutations and polymorphisms were detected using Phred/Phrap/PolyPhred software (CodonCode Corporation, MA, USA).

Data of mutations and polymorphisms were compared with the data of Japanese and other populations obtained from Hap Map data (http://hapmap.ncbi.nlm.nih.gov/index.html.en). Hap Map project is a public international resource that will help researchers find genes associated with human disease. As HapMap data provide no phenotypic information about the samples from volunteers, we do not know their medical conditions. However, ages of volunteers were restricted above 20 years old, and they could understand the context of informed consent. As the age of volunteers is much older than the RS patients (6.8 ± 10.7), we suggest that the volunteers have few risks of RS. Current data from Japanese controls by HapMap may be used as tentative controls, until we will collect many new controls, to facilitate the genomic association study of RS.

For statistical analyses, chi-square test for trend and chi-square test were used. A p value less than 0.05 was considered as indicating a significant difference.

Results

Mean onset age of epilepsy in 29 patients (14 males, 15 females) was 6.8 ± 10.7 (mean $\pm$ SD) years (Table A2). The dominant hemisphere was involved in 15 patients, and non-dominant hemisphere in 14. Ten patients underwent surgical intervention and histological examination revealed typical features including microglia nodule, vasculogenesis on brain surface, endothelial proliferation, spongy degeneration and perivascular cuffing in ten patients; focal cortical dysplasia in four patients; and mesial temporal sclerosis in one patient with status epilepticus.

For *CTLA4*, the region downstream of exon 4 could not be examined by the (AT) 28 repeat at position 54947468–54947524, in spite of several modifications of sequencing conditions. Genomic sequencing revealed no disease-causative mutation, but detected two significant single nucleotide polymorphisms (SNPs) in *CTLA4* (Table 1). The rs231775 SNP in exon 1 (Thr 17 Ala) and rs231779 SNP in intron 1 showed significant positive genotypic and allelic associations with RS compared with Japanese controls. Mean age of onset was not significantly different between heterologous (A/G) and homologous (G/G) genotypes of rs231775. Frequencies of patients with EPC were not significantly different between heterologous (A/G) and homologous (G/G) genotypes of rs231775. The rs231776 (Intron 1), rs231777 (intron 1), rs231778 (intron 1), rs231780 (intron 1) and rs231721 (3′near) SNPs showed no significant association compared with Japanese controls. The rs231781 SNP (intron 3) had no significant association with RS onset compared with Asian controls. Rs231775 and rs231779 formed haplotypes in RS patients. In 25 patients (excluding two patients with deterioration after prolonged anesthesia) analyzed for cognitive outcome, mean IQ was not different between heterologous (A/G) and homologous (G/G) genotypes of rs231775 (Fig. 1). In 22 patients (excluding five patients with functional hemispherectomy and two patients with deterioration after prolonged anesthesia) analyzed for motor outcome, the proportion of patients without motor impairment was 4/16 (25%) in homologous genotype (G/G) and 1/6 (17%) in heterologous genotype (A/G) of rs231775.

Table 1 Single nucleotide polymorphisms (SNPs) in *CTLA4*, and *PDCD1*.

SNP	Subject	Genotype			Allele		HWE	Genotype	Allele frequency	
					Reference	SNP	χ^2	p-Value	p-Value	Odds ratio (95%CI)
rs231775		A/A	A/G	G/G	A	G				
(*CTLA4*, Exon 1,	RS	0	12	17	12	46	1.97	$p=0.0363$	$p=0.0137$	2.344 (1.175–4.676)
Thr17Ala)	Controls	15	55	42	85	139	0.20			
rs231779		C/C	C/T	T/T	C	T		$p=0.0467$	$p=0.0188$	2.257 (1.131–4.503)
(*CTLA4*, Intron 1)	RS	0	12	17	12	46	1.97			
	Controls	14	55	43	83	141	0.31			
rs34819629		G/G	G/A	A/A	G	A			$p=0.0195$	2.301 (1.134–4.671)
(*PDCD1*, Intron 2)	RS	4	9	9	17	27	0.41			
	Controls				49(CHB + JPT)	71(CHB + JPT)				
rs2227982		C/C	C/T	T/T	C	T		$p=0.0145$	$p=0.0114$	2.151 (1.179–3.924)
(*PDCD1*, Exon 5,	RS	4	12	13	20	38	0.21			
Ala215Val)	Controls	33	54	26	120	106	0.19			
rs10204525		G/G	G/A	A/A	G	A		$p=0.2979$	$p=0.2584$	1.57 (0.7145–3.450)
(*PDCD1*, Exon 5	RS	2	5	15	9	35	2.00			
(3′UTR))	Controls	10	45	58	65	161	0.09			

RS, Rasmussen syndrome; Controls, Japanese in Tokyo (JPT); CHB, Han Chinese in Beijing; HWE, Hardy-Weinberg Equilibrium values; p, chi square test.