ELSEVIER

Epilepsy Research 36 (1999) 15–29

Epilepsy Research

Delineation of cryptogenic Lennox–Gastaut syndrome and myoclonic astatic epilepsy using multiple correspondence analysis

A. Kaminska [a], A. Ickowicz [b], P. Plouin [a], M.F. Bru [c], G. Dellatolas [d], O. Dulac [a,e,*]

[a] *Hopital Saint Vincent de Paul, 82 Avenue Denfert Rochereau, F-75674 Paris Cx 14, France*
[b] *Ecole Normale de Lyon, Lyon, France*
[c] *UFR Mathématiques, Paris VII, France*
[d] *Inserm 169, Hopital Paul Brousse, Villejuif, France*
[e] *Inserm U29, Hôpital Port-Royal, 121–123 Boulevard de Port-Royal, 75014 Paris, France*

Received 10 October 1998; received in revised form 20 January 1999; accepted 30 January 1999

Abstract

Purpose: To distinguish various types of childhood severe cryptogenic/idiopathic generalised epilepsy on the basis of reproducible diagnostic criteria, using multiple correspondence analysis (MCA). *Methods*: We applied MCA to a series of 72 children with no evidence of brain damage, starting epilepsy between 1 and 10 years, with two or more types of generalised seizures. We excluded patients with infantile spasms or typical absences. MCA was performed on all clinical and EEG parameters, first throughout follow-up, then restricted to the first year of the disease. *Results*: When including all follow-up variables, there were three groups: (1) Thirty-seven children with male predominance, familial history of epilepsy, simple febrile convulsions, massive myoclonus, tonic–clonic fits. Outcome was favourable, with no seizures and mildly affected cognitive functions. Interictal EEG showed short sequences of irregular 3-Hz spike-waves. (2) In 18 children, clinical characteristics were similar to those of the first group at the early stage, but 95% exhibited myoclonic status and vibratory tonic seizures, with persisting seizures on follow-up. EEG showed long sequences of generalised irregular spike and slow waves. Those two groups meet the characteristics of childhood onset myoclonic-astatic epilepsy (MAE) with respectively, favourable and unfavourable outcome. (3) Eleven children had later onset, atypical absences, tonic and partial seizures, and no myoclonus, or vibratory tonic seizures. All had mental retardation and persisting seizures. EEG showed long sequences of slow spike-wave activity and half the patients had spike and slow wave foci. These patients met the major characteristics of Lennox–Gastaut syndrome. Initial parameters failed to distinguish the first two groups, but Lennox–Gastaut syndrome (the third group) was distinct from both groups of myoclonic astatic epilepsy from the onset. Within MAE groups combined, clinical and EEG risk factors for mental retardation could be identified. *Conclusion*: It is possible to validate statistically the distinction between discrete epileptic syndromes. Myoclonic astatic epilepsy is therefore distinct from Lennox–Gas

* Corresponding author. Tel.: +33-1-40488055; fax: +33-1-40488046.
E-mail address: o.dulac@svp.ap-hop-paris.fr (O. Dulac)

0920-1211/99/$ - *see front matter*
PII: S0920-1211(99)00021-2

taut syndrome, and the distinction appears from the first year of the disorder.

Keywords: Generalized epilepsy of childhood; Lennox–Gastaut syndrome; Myoclonic astatic epilepsy; Multivariate analysis; Multiple correspondence analysis

1. Introduction

The great variability of outcome in childhood epilepsy makes it a challenging condition, particularly for patients without evidence of brain lesion. The syndromic approach proved useful to make therapeutic decisions and predict outcome, and is now one of the major basis for classification of epilepsies (ILAE, 1989).

However, the concept of syndrome has a number of drawbacks. Firstly, many epileptic syndromes lack one or several of these major features at onset, making their recognition difficult until the full pattern has developed. Secondly, some syndromes seem to be so poorly delineated that the same diagnosis may not be achieved among different teams working on the basis of syndromic criteria. This happens to be the case for syndromes where the patients may exhibit several types of seizures, and when several of these complex syndromes occur in the same age range and share one or several seizure types or EEG patterns. In this context, statistical validation of various clinically defined syndromes might be useful, by demonstrating that the characteristic items that define it are sufficiently linked, which is by definition the concept of 'syndrome', that goes together.

One of the most challenging fields is that of severe generalized epilepsies of childhood comprising several types of seizures. Non progressive symptomatic cases with tonic and atonic absence seizures, mental retardation and slow spike-waves are universally labeled Lennox–Gastaut syndrome (LGS) (ILAE, 1989). However, it may be difficult to draw the border between cryptogenic LGS and myoclonic astatic epilepsy (MAE) as defined by Doose et al. (1970, 1998) particularly for patients exhibiting myoclonus and deterioration. These non symptomatic cases are particularly difficult to address for historical reasons. Some consider that there is a continuum ranging from LGS to the cases of MAE with good outcome with an intermediary condition called 'the myoclonic variant of LGS' (Giovannardi Rossi et al., 1988; Aicardi, 1995). Others that LGS is symptomatic and therefore etiologically distinct from MAE that is genetically determined (Doose et al., 1970). Conditions clinically indistinguishable from 'the myoclonic variant of LGS' are considered in this context to belong to MAE and result from genetic predisposition.

The aim of this study was to apply a mathematical method, multiple correspondence analysis, in order to determine whether discrete groups of patients with LGS and MAE could be identified, whether the distinction of these various groups could be statistically validated and whether the early electroclinical pattern permitted to predict outcome.

2. Materials and methods

2.1. Patients

Among all the patients who had been referred to the pediatric neurology unit of the Hopital Saint Vincent de Paul between January 1980 and December 1991, and who had had their first seizure between 1 and 10 years of age (approximately 2500 patients), we selected those who had no evidence of brain lesion detectable by magnetic resonance imaging scans and no evidence of an inborn error of metabolism, who had normal psychomotor development until the first seizure (however, a mild speech delay did not prevent inclusion), who had at least two types of generalized seizures excluding epileptic spasms and typical absences, for whom at least three awake and sleep EEG recordings were available for review, and who were followed in our department from the first year of the seizure disorder and for at

least 3 years or, if becoming seizure-free, for 1 year after the last seizure. Seventy-two patients were selected. EEG recordings were either standard, lasting at least 20 min, or prolonged for several hours. Repeat recordings covered the follow-up period.

2.2. Methods

For each patient, the following items were analyzed: age of onset of seizures, sex, familial history of epilepsy or febrile convulsions, personal history of febrile convulsions, seizures types, status epilepticus, disorder duration, different EEG pattern and mental retardation.

The various seizure types, whether present or absent, comprised massive myoclonus, absences, tonic, tonic–clonic and partial seizures, and drop attacks. Tonic seizures were easily distinguished as either '*vibratory tonic*', occurring at the end of night sleep and very intense with vibration of the upper limbs (Fig. 1), or '*classical tonic*' seizures which appeared when awake or falling asleep and were milder comprising upper deviation of the eyes and modification of the respiration. Regarding drop attacks, for those patients who lacked polygraphic recording, we could not distinguish whether they were myoclonic, atonic or myoclonic–astatic.

Episodes of status epilepticus, whether myoclonic, tonic, tonic–clonic or absence were identified, together with their age of onset and overall duration. The duration of the seizure disorder, and eventual mental retardation at the end of follow-up were the major long-term items, together with the eventual recurrence of myoclonic

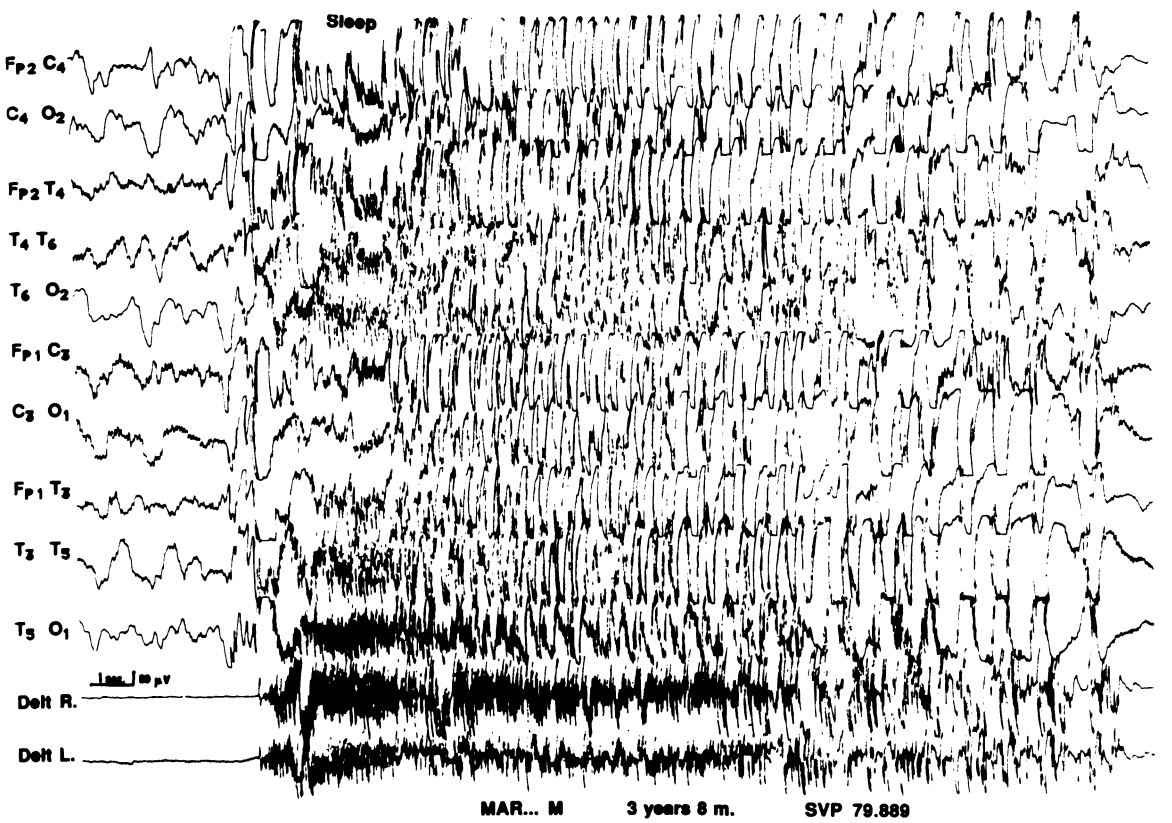

Fig. 1. Vibratory tonic seizure; notice that the tonic activity on the deltoid muscle has progressively decreasing frequency, and therefore the limbs exhibit vibratory tonic activity.

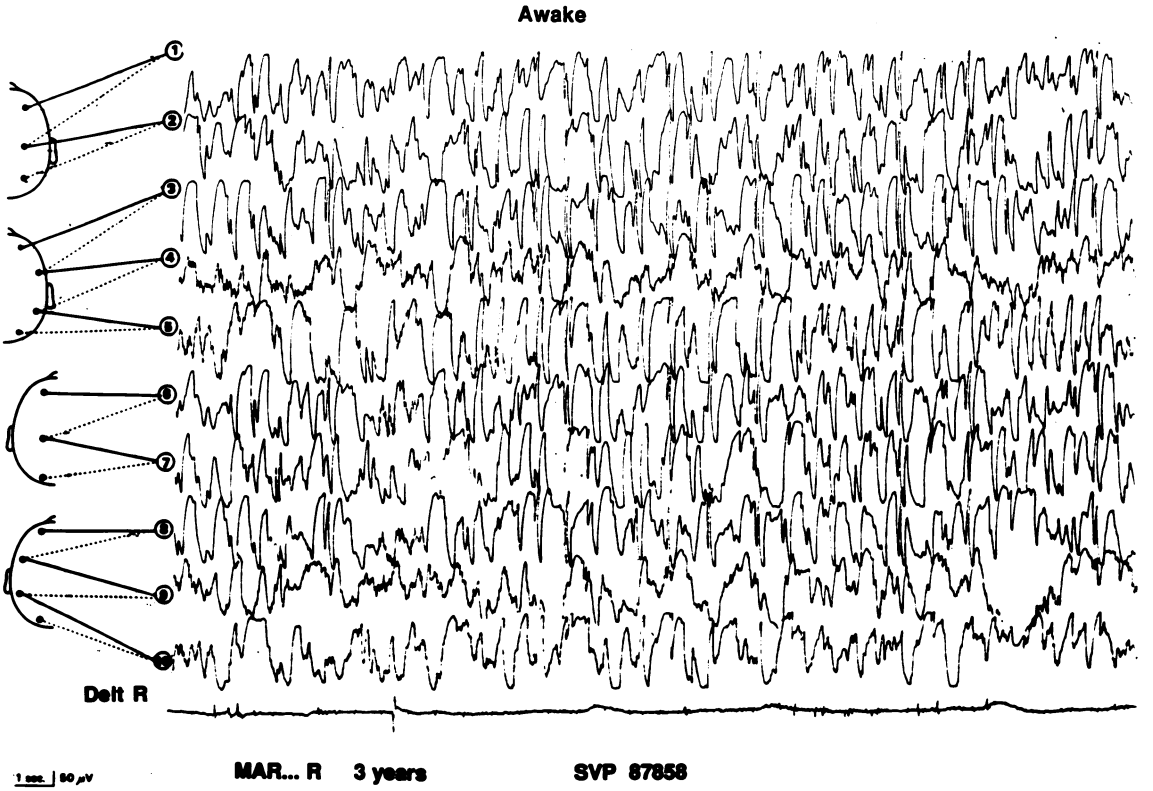

Fig. 2. EEG pattern A: Long sequences of generalized irregular spike and slow wave activity with disappearance of physiological rhythms.

epilepsy in adolescence (JME). The duration of various drug treatments was also determined, together with eventual drug-induced worsening of seizures.

Mental status was evaluated on the basis of intelligence quotient (IQ values) (available for 44 patients) and educational achievement for those patients with no available psychometric data. Patients were considered normal if IQ was over 80, moderately retarded if it was between 50 and 80, and severely retarded when it was under 50.

Five interictal EEG patterns could be identified: long sequences of generalized irregular spike and slow wave (SSW) activity with disappearance of physiological rhythms lasting several minutes of the whole recording (pattern A) (Fig. 2), short sequences of 3-Hz spike-waves (SW) with persistence of basic activity lasting 2–5 s (pattern B), short sequences of SSW activity predominating over the frontal areas lasting 2–5 s (pattern C), long sequences of SSW activity with frontal predominance lasting several minutes of the whole tracing (pattern D), and focal paroxysmal activity (pattern E).

These EEG patterns were distinguished according to whether they were identified either in the first year of the disorder or later in the course of the disease.

2.3. Data analysis

The first step of our study consisted of representing graphically (Bernard et al., 1987) distinct groups of patients based on all electroclinical features at our disposal, each group of patients being distinguished from the rest of the series because they shared several clinical and EEG features, and realized a different combination of

features than the rest of the series. A well-adapted method for this purpose is the geometric method of data analysis called Multiple Correspondence Analysis (MCA) (Benzécri and Benzécri, 1984; Greenacre, 1984; Leclerc, 1988; Crichton and Hinde, 1989; Greenacre, 1992; Benzécri, 1992). Each individual (here a patient) is represented in a multidimensional space based on the response to each modality (23 electroclinical variables in the present case), hence a 'cloud' of 72 points, where the distance between points reflects the similarities between individual profiles: the shorter the distance, the greater the similarity. In order to permit visualization, the cloud of points, which lies in a space with many dimensions, is projected onto subspaces of a small number of dimensions (here two) that account for most of the variance.

As a second step, we applied classical automatic classification methods to the cloud of patients, in order to identify significant clusters that would constitute homogeneous groups of patients. This permits determination of the variables or variable combinations that contribute most significantly to discriminate clusters.

We then attempted to test the stability of the clusters identified by the MCA method, including the features of the whole course of the disease. We thus performed four randomizations, each one drawing half the patients of the series, and we repeated the MCA on each sample. The remaining patients (not selected by the randomization) were then projected onto the graph produced by these MCAs. The stability of the clusters identified by these MCAs was tested by Wilcoxon test. The patients who did not remain in the same group on two randomizations were considered unclassifiable.

These methods were first applied to the clinical and EEG features collected throughout the whole follow-up period. In a second MCA, only items involving the first year of the disease were included, in order to determine whether distinct groups of patients could be identified from the onset of the seizure disorder, or if the different groups appeared only during the course of the disease.

In order to further explore the prognostic value of the initial clinical and EEG parameters, we performed a logistic regression, with features of unfavorable outcome (namely presence or absence of mental retardation at the end of the follow-up period) as variables to be explained, and the initial electroclinical parameters significantly related to this outcome (on univariate analysis), as explanatory variables.

3. Results

Seventy-two patients met the inclusion criteria. Follow-up ranged up to the age of 16 years (median 6.5). Duration of follow-up ranged up to 12 years (median 3) after the last seizure for the 43 patients who were seizure-free and up to 13 years (median 8) for 29 who continued seizing at the end of follow-up.

3.1. Variables collected throughout the seizure disorder

When applied to the overall clinical and EEG parameters, the MCA could identify three groups of patients, comprising respectively 39 (Group 1), 22 (Group 2) and 11 (Group 3) patients (Fig. 3). Following each of the four randomizations, we applied to the three groups and two by two, the Wilcoxon test which showed that the difference between these groups was highly significant ($P < 0.001$).

Only six patients (8%) were excluded by stability tests since they failed to appear in the same group on repeat randomizations. Three of these patients shared characteristics of Groups 1 and 2, and two others those of Groups 2 and 3, whereas a single patient shared the characteristics of Groups 1 and 3.

The remaining 66 patients were thus classified into Groups 1 (37 patients), 2 (18 patients) and 3 (11 patients).

The most contributive items for the classification were, in decreasing order of contribution: mental retardation, duration of the seizure disorder, long bursts of slow spike and waves (D EEG pattern), tonic seizures, absences, vibratory tonic seizures, episodes of tonic, absence or myoclonic status epilepticus, massive myoclonus, long lasting

bursts of irregular spike and slow wave activity (A EEG pattern), and age of onset of the seizure disorder (Table 1).

3.1.1. Group 1

The most contributive items consisted of lack of severe mental retardation on follow-up and cessation of seizures within the first 3 years of the disorder. This group comprised more boys (73%) than girls, with a high personal incidence of febrile convulsions (22%) or familial history of epilepsy (19%), the latter consisting of childhood or juvenile absence epilepsy (three cases), idiopathic generalized epilepsy with tonic clonic seizures (two cases), or epilepsy unclassifiable because of insufficient data (two cases) (Tables 2 and 3). Eight patients had had simple febrile convulsions between 17 and 40 months of life (mean 29), a mean 6.4 months before the first non febrile seizure. The first non febrile seizure occurred between 18 and 50 months of age (mean 35.2) (Fig. 4), and consisted of generalized tonic–clonic, myoclonic, or absence seizures, or a combination of the latter. In addition, 38% of the patients had 'classical tonic' seizures. Within 1–11 months (mean 3), the patients had very frequent seizures of several types. They were ataxic, but there was no other abnormality on neurological examination. IQ was measured in 19 patients during the first 2 years of the disorder, and it

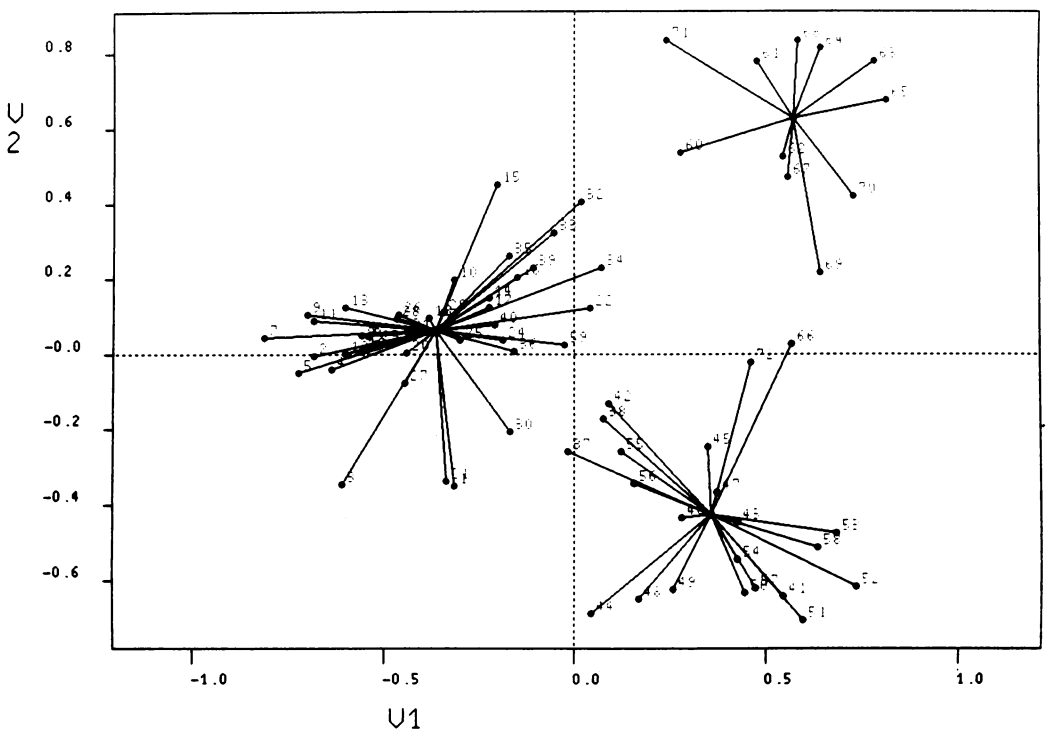

Fig. 3. MCA with clinical and EEG variables (72 individuals and 23 variables). This figure shows the graphic visualisation as given by the computer. Notice that there are three distinct groups identified by this method. Group 1 is on the left. Group 2 is on the lower right. Group 3 is on the upper right. Numbers represent individuals. Axis 1 and 2 comprise the most contributive variables (78.4% of the variance, axis 1: 54.6%, axis 2: 23.8%). The first horizontal 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 > duration of the seizure disorder over 3 years > vibratory tonic seizures > tonic status epilepticus > absences status epilepticus. The second, vertical axis V2 comprises in order of importance: Negative values: myoclonic status epilepticus > vibratory tonic seizures > A EEG pattern. Positive values: absence of massive myoclonus > age of onset of seizure disorder between 5 and 10 years > no drop attacks > no myoclonic status epilepticus.

Table 1
Various features that distinguish each given group from the two others[a]

Incidence of items in each group	Group 1	Group 2	Group 3
100%	No vibratory tonic seizures	**Disorder duration > 3 years**	**Absences**, no familial antecedents, no myoclonic status, no febrile convulsions
90–100%	**Frequent massive myoclonus**, no partial seizures, no absence status, no C or D EEG patterns	**Frequent massive myoclonus, drop attacks, tonic–clonic seizures**, no familial antecedents, no febrile convulsions, no C EEG pattern	**Classical tonic seizures, disorder duration > 3 years**, no A EEG pattern, no tonic status, no JME
80–90%	**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
70–80%	**Boys, tonic–clonic seizures, B EEG pattern**, no febrile convulsions	**Other tonic seizures, severe mental retardation, tonic–clonic seizures, age of onset 2–4 years**, no JME	

[a] The data are drawn from the first MCA study including characteristics from throughout the seizure disorder. Bold characters correspond to positive characteristics. JME, the recurrence of myoclonic seizures after the age of 10 years.

ranged from 73 to 125 (mean 91). Parents complained of severe hyperkinesia.

Episodes of myoclonic status were both rare (13.5%) and brief (less than 1 month). They occurred between 24 and 40 months of age, 2–6 months after the first seizure. In addition, four patients had episodes of absence or tonic–clonic status. No patient exhibited vibratory tonic seizures throughout the seizure disorder. The phase of frequent seizures was followed by a progressive or sudden decrease of seizure frequency. For the 36 patients (97%) who had stopped having seizures at the end of follow-up, the overall duration of the seizure disorder ranged from 1 to 63 months (mean 18). In 76% of the cases, cessation of seizures occurred within the first 2 years, whereas the seizure disorder lasted over 3 years in only 19% of the cases. Four of the 16 patients who were followed after the age of 10 years exhibited recurrence of massive myoclonus in adolescence as the only type of seizures.

Interictal EEG mainly showed short bursts of 3-Hz SW (B EEG pattern), both at onset (69%) and on follow-up (81%), whereas long bursts of irregular spikes and slow waves (A EEG pattern) were less frequent, both at onset (28%) and on follow-up (27%).

In 20 patients at the end of follow-up, mean IQ was 84 (range 51–146) and was under 70 in four patients. Cognitive outcome showed that patients mostly suffered from dysarthria and dyspraxia with poor manual dexterity.

The most frequently administered medications were valproate, benzodiazepines and ethosuximide. Carbamazepine was administered to 19 patients, eight of whom experienced worsening in seizure frequency or severity.

3.1.2. Group 2

The most contributive factors on MCA consisted of the persistence of seizures for over 3 years, severe mental retardation at the end of follow-up, the occurrence of myoclonic status for over 1 month, vibratory tonic seizures, and long bursts of irregular spikes and slow waves (A EEG pattern). This group also mostly comprised boys (83%) with a moderate incidence of familial antecedents of epilepsy (Tables 2 and 3). It was very similar to Group 1 in terms of age of onset and seizure types. The seizure disorder started between 27 and 53 months (mean 36) (Fig. 4), with massive myoclonus in most cases (94%), alone or in

combination with other types of generalized seizures (88%). Ten patients (55%) also had frequent 'classical tonic' seizures, an incidence twice higher than in Group 1. Cognitive characteristics were similar to those of Group 1. IQ measured in 17 patients during the first 2 years ranged from 63 to 133 (mean 84).

The EEG tracings mainly showed long bursts of irregular spikes and slow waves (A EEG pattern), both at onset (78%) and during the course of the disease (95%). Short bursts of spikes and slow waves (B EEG pattern) were also observed at onset (28%) and during follow-up (67%). From onset, the incidence of both EEG patterns was different from that of Group 1, the A EEG pattern being more frequent and the B EEG pattern less frequent in Group 2 than in Group 1 (Table 2).

The course was characterized by the occurrence of one or several episodes of myoclonic status. During these episodes, the patients experienced alteration of vigilance, loss of contact with the surrounding or somnolence. They were drooling with speech disorders ranging from dysarthria to mutism. They exhibited erratic myoclonus predominating in the face and extremities of the upper limbs, mainly the eyelids, mouth, tongue and fingers; they were ataxic with hypotonia and tremor, and walking was difficult or impossible. These episodes usually started insidiously, thus it was difficult in most instances to determine the precise date of onset, since the diagnosis was often retrospective when the patient was admitted to hospital for an increase of seizure frequency. Indeed, the parents had noticed that the child was less interactive than previously, but this had

Table 2
Characteristics of the three groups as defined by MCA. Initial electroclinical data (first year of seizure disorder)

Initial clinical patterns	Group 1	Group 2	Group 3
n	37	18	11
Sex	27 boys (73)	15 boys (83)	5 boys (45.5)
Familial antecedents of epilepsy	7 (19)	1 (5.5)	0 (0)
Age of onset (years)			
1–2	2 (5)	0 (0)	0 (0)
2–3	14 (38)	6 (33)	2 (18)
3–4	17 (46)	9 (50)	1 (9)
4–5	4 (11)	3 (17)	1 (9)
>5	0 (0)	0 (0)	7 (64)
Personal antecedents of febrile convulsions	8 (22)	2 (11)	0 (0)
Myoclonus			
Frequent	34 (92)	17 (94.5)	1 (9)
Rare	2 (5)	1 (5.5)	3 (27)
Absent	1 (3)	0 (0)	7 (64)
Drop attacks	31 (84)	16 (89)	3 (27)
Tonic clonic	29 (79)	17 (95)	6 (54)
Absences	23 (63)	16 (89)	11 (100)
Classical tonic seizures	14 (38)	10 (55)	10 (90)
Partial seizures	0 (0)	0 (0)	6 (54)
EEG patterns[a]			
n	32	14	7
A	9 (28)	11 (78)	0 (0)
B	22 (69)	4 (28)	2 (28)
C	2 (6)	0 (0)	1 (14)
D	1 (3)	3 (21)	4 (57)
E	1 (3)	0 (0)	3 (42)

[Table 2a] Initial EEG patterns are missing for 13 patients. Parenthesis indicate percentage.

Table 3
Follow-up clinical data of the three groups, as defined by MCA (outcome of seizure disorder)

Clinical patterns	Group 1	Group 2	Group 3
n	37	18	11
Vibratory tonic seizures	0 (0)	17 (95)	0 (0)
Myoclonic status			
None	32 (86)	1 (5.5)	11 (100)
<1 month	4 (11)	5 (27.5)	0 (0)
>1 month	1 (3)	12 (67)	0 (0)
Tonic status	0 (0)	8 (44.5)	2 (18)
Absence status	2 (5)	8 (44.5)	6 (54)
Tonic–clonic status	4 (11)	3 (16.5)	2 (18)
Juvenile myoclonic epilepsy			
Yes	4 (11)	1 (5.5)	0 (0)
No	12 (32)	15 (83.5)	8 (73)
Unknown[a]	21 (56)	2 (11)	3 (27)
Disorder duration			
<1 year	18 (49)	0 (0)	1 (9)
1–2	10 (27)	0 (0)	0 (0)
2–3	2 (5)	0 (0)	0 (0)
>3 years	7 (19)	18 (100)	10 (91)
Mental retardation			
IQ>80	21 (57)	1 (5.5)	0 (0)
IQ 80–50	15 (40)	2 (11)	7 (64)
IQ<50	1 (3)	15 (83.5)	4 (36)
EEG patterns			
A	10 (27)	17 (95)	1 (9)
B	30 (81)	12 (67)	2 (18)
C	3 (8)	1 (5.5)	4 (36)
D	1 (3)	5 (28)	9 (82)
E	4 (11)	6 (33)	5 (45)

[Table 3a] For patients followed until less than 10 years of age, it was not possible to determine whether they would exhibit JME (recurrence of myoclonic seizures after the age of 10 years) or not since this type of epilepsy rarely begins before this age.

started sometime earlier and they could not determine precisely when. The approximate age of worsening due to myoclonic status ranged from 33 to 83 months (mean 53), 1–60 months (mean 17.5) after the first seizure. There were one to 20 such episodes (mean 4) per patient, and the time course from the apparent onset of the first episode to the end of the last one ranged from 1 to 94 months (mean 22). Other types of seizures often occurred during these episodes, including absences, eyelid jerks, drop attacks, massive myoclonus and generalized tonic or tonic–clonic seizures. EEG showed lack of basic activity and diffuse and irregular spikes and slow waves similar to the A EEG pattern (Fig. 2) but persisting continuously throughout the episode of myoclonic status, in combination with erratic myoclonus recorded on electromyogram. In addition to myoclonic status, 44% of the patients suffered from other types of status, absence, tonic or tonic–clonic.

Following the episodes of myoclonic status, 95% of the patients remained with vibratory tonic seizures at the end of night sleep. This type of seizure occurred 15–91 months (mean 45) after the first seizure. For all patients of Group 2, the disorder lasted over 3 years, and 16/18 (88%) still had seizures at the end of follow-up, usually vibratory tonic seizures, the last two patients having had their last seizure 9 years after onset. At the end of follow-up, 94% of patients were mentally retarded, severely in 83%. Long lasting bursts of slow spike-waves (D EEG pattern) affected only 28% of the patients.

Psychometric evaluation was performed following the last myoclonic status in 14 patients and confirmed low intellectual functioning (IQ ranged from 88 to untestable, and was under 50 in 83% of patients). Most patients exhibited major speech disorders and dyspraxia. The patients also showed slowness, lack of initiative and perseverance.

The most prescribed medication consisted of benzodiazepines, valproate, carbamazepine and progabide. Eight of 17 patients treated with carbamazepine experienced worsening.

3.1.3. Group 3

The most contributive factors on MCA consisted of severe mental retardation at the end of follow-up, persistence of seizures for over 3 years, lack of massive myoclonus, onset after 5 years of age, and lack of myoclonic status. This group was distinct from the two previous ones from the very beginning since sex ratio was one, there was no familial history of epilepsy, or personal history of febrile convulsions, and the age of onset was distinctly later than for the two previous groups, ranging from 24 to 108 months (mean 54.5) (Fig. 4). First seizures were partial or absences, whereas myoclonus was both rare and affecting few patients (36%). During the course of the disease, all

the patients had absences and 90% had 'classical tonic' seizures, but none had vibratory tonic seizures. The time lag to occurrence of another type of seizures following the first one was 0–54 months, usually under 12 months, although it was up to 9 years for the occurrence of the first tonic seizures.

No patient suffered myoclonic status, but 54% exhibited absence status and 18% tonic status. The seizure disorder lasted over 3 years in 91% of patients. One patient who no longer had seizures at the end of follow-up had had his last seizure at 15 years, the others still had seizures at the end of follow-up. Mental deterioration occurred abruptly from the beginning of the disorder and was characterized by apathy, memory disorders, impaired visuomotor speed and perseverance. IQ was measured during the first 2 years in four patients and ranged from 53 to 80. At the end of follow-up, mental retardation affected all the patients (IQ ranged between 10 and 75). Nevertheless, these patients did not show major speech troubles.

The EEG tracings at onset mainly showed long bursts of slow spike waves (D EEG pattern) (57%) and focal abnormalities (E EEG pattern) (42%). During follow-up, 82% of patients showed long bursts of slow spike waves (D EEG pattern).

Various medications were administered to these patients, including carbamazepine, and no patient experienced worsening with this drug.

3.2. Variables collected for the first year

EEG tracings performed within the first year of the seizure disorder were available for 59 patients. When applied to the clinical and EEG parameters of the first year of the seizure disorder in these 59 patients for whom all data were available, MCA could only identify two groups of patients since Groups 1 and 2 could no longer be distinguished, whereas Group 3 was distinct from the first year of the disease. The most contributive features for the classification were, in decreasing order of contribution: age of onset, massive myoclonus, drop

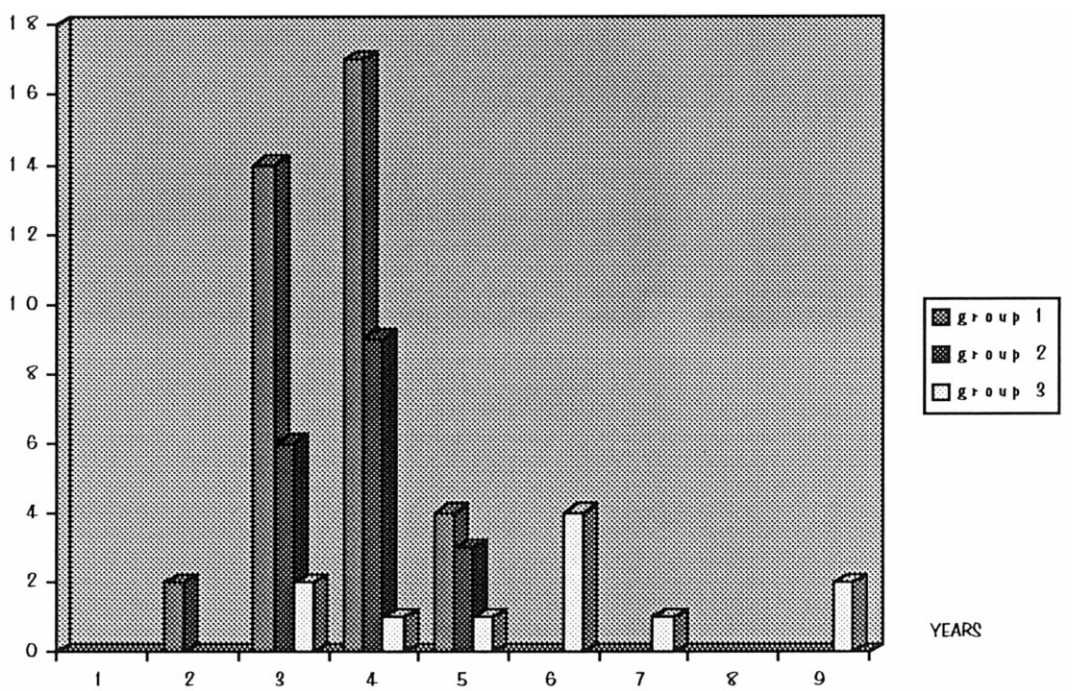

Fig. 4. Age of onset according to groups.

attacks, focal abnormalities on EEG (E EEG pattern), tonic seizures, absences, and long bursts of spike and slow waves (D EEG pattern).

During the first year of the disease, Group 3 was characterized by onset after the age of five, lack of myoclonus, focal abnormalities (E EEG pattern), long bursts of spike and slow waves (D EEG pattern) and tonic seizures. The combined Groups 1 and 2 were characterized by rare tonic and absences seizures, and presence of myoclonus. In addition, when applied to the first year parameters of the patients belonging exclusively to Groups 1 and 2, the MCA failed to distinguish these two groups.

The stability tests mentioned earlier confirmed that the patients belonged to either Group 3, or the combination of Groups 1 and 2.

3.3. Risk to develop mental retardation in the combined Groups 1 and 2

Mental retardation and persisting seizures are the two major features that prevent the patient from social integration. In Group 3, all patients suffered from mental retardation and persisting seizures, but this group was distinct from the two others from the onset, and prognosis could therefore be determined.

Regarding the rest of the series (including the three unclassified patients who shared characteristics of both Groups 1 and 2 on the initial MCA study), mental retardation affected 35 of the 58 (60%) patients, but since Groups 1 and 2 could not be distinguished at onset, prognosis was difficult to establish. For these 58 patients, both mental retardation and persisting seizures (over 3 years) were highly linked ($P < 0.001$). We thus decided to concentrate on the risk factors for mental retardation.

Univariate analysis of *initial electroclinical variables* showed that the lack of familial antecedents and of the B EEG pattern, and the presence of the tonic and absence seizures were all significantly related to the development of mental retardation. *Logistic regression* calculated on these four variables show that the highest probability to have mental retardation at the end of follow-up was for the combination of lack of familial epilepsy or type B EEG pattern, and presence of tonic and absence seizures ($P = 0.92$, CI: 0.61–0.99), and that the lowest risk was for the opposite combination: ($P = 0.01$, CI: 0.03–0.32). Confidence intervals (CI) of the calculated probabilities are large, as expected given the sample size and the number of possible patterns.

Regarding *follow-up variables* related to the development of mental retardation, *univariate analysis* showed significant links to the duration of epilepsy for over 3 years ($P < 0.001$), and occurrence of vibratory tonic seizures ($P < 0.001$) and myoclonic status ($P = 0.02$).

Thus, lack of familial antecedents and type B EEG pattern, and the presence of tonic and absence seizures was the combination that, throughout the disorder, exhibited the highest risk for mental retardation. During follow-up, it was the duration of epilepsy over 3 years, vibratory tonic seizures and occurrence of myoclonic status.

4. Discussion

This study provides the first statistical demonstration of the existence of discrete groups of patients sharing a combination of clinical and EEG characteristics, thus distinguishing and defining precisely well delineated epilepsy syndromes. It shows that for children with generalized epilepsy exhibiting several types of generalized seizures, three distinct groups can be demonstrated, of which only two are distinct from the beginning of the disorder.

4.1. Methodological issues

The study has the drawbacks of any retrospective clinical investigation, mainly the variable duration of follow-up and the quality of clinical observation. Follow-up may appear limited for seizure-free patients, but it is clearly established that in childhood epilepsy, recurrence of seizures after the last one usually occurs within the first year following the last fit (Shinnar et al., 1994). Therefore, a minimum 1 year after the last seizure seemed reasonable. Moreover, no patient in Groups 2 and 3 exhibited more than a few days of seizure freedom before relapse for the first 5 years of the disorder.

Many types of seizures could not be recorded or videotaped, and their type is therefore based on the description given by the surrounding. The conditions of observation were however homogeneous since patients were seen at the same epilepsy center from the onset of the seizure disorder.

EEGs were not recorded at predetermined dates but recording was decided according to the clinical condition, thus increasing the probability to record the full range of various EEG patterns for the patients who experienced an unfavorable course compared to those with favorable outcome. However, this was not the case, and patients of Group 3 that had the biggest number of EEG tracings differed significantly from those of Group 1 by the lack of one specific pattern, that of short bursts of 3-Hz spikes and slow waves (B EEG pattern), including at the onset of the disorder. Patients from all three groups, including Group 1, experienced some degree of worsening, indicating EEG recording during the course of the disease. In fact, when patients were repeatedly recorded in a given period, recordings were similar for one given patient. Therefore, the analysis of the data can be considered as stable.

The groups were not comparable in terms of medication, and this could be an issue since drugs may modify the clinical and EEG expression of some types of epilepsy in childhood (Doose et al., 1970). However, since Group 3 was distinct from the beginning of the seizure disorder, it is unlikely that medication could have contributed to determine its existence just by altering its course. Nevertheless, iatrogenic factors are likely to have altered the course within the combined Groups 1 and 2. Indeed, various antiepileptic drugs are known to eventually increase seizure frequency in specific epilepsy syndromes, particularly myoclonic epilepsies (Perruca et al., 1998). In this series also, half the patients with myoclonic epilepsy who received carbamazepine experienced an increase of seizure frequency.

The MCA method is based on the projection of a multidimensional cloud of points on a two-dimensional plane in order to make it interpretable, and it therefore reduces the range of visual information, but does not affect identification of variables that contribute most to distinguish each group from the other ones. In this study, the first two axes accounted for 78.4% of the information. By repeating the measures several times on randomized subgroups of the same set of patients, we could confirm the initial findings. Only six patients (8%) were not assigned to the same group on repeat measures. They were excluded from the analysis of the characteristics of each of the three groups, but the two patients who shared characteristics of Groups 1 and 2 were included for evaluation of the risk to develop mental retardation.

4.2. Nosological significance of the three groups

One group (Group 3) that mainly exhibited atypical absences and tonic seizures, long bursts of slow spike-waves and severe mental retardation, meets the main characteristics of Lennox–Gastaut syndrome (LGS). The age of onset was unusually late in this series compared to the mean of 2–6 years classically reported (ILAE, 1989). However, the classical series comprise 40% of patients for whom LGS followed infantile spasms in the first year of life. In addition, our series excluded symptomatic cases. In other epileptic encephalopathies such as infantile spasms, symptomatic cases begin earlier than cryptogenic ones (Dulac et al., 1994). These two reasons may account for the relatively late onset of cryptogenic LGS in our series. It is striking that in the present study one distinctive feature of these LGS patients was the frequent existence from the first year of the disorder of focal, clinical and EEG abnormalities, which suggests some unidentified brain lesion, likely therefore to be prenatal since there was no history of brain damage. Lack of myoclonus in the great majority of cases is remarkable.

Another group (Group 1) recovered from the seizure disorder, although a number of patients were left with moderate mental retardation. Massive myoclonus, short bursts of 3-Hz spike waves (B EEG pattern) and the high incidence of familial antecedents are major characteristics shared by myoclonic astatic epilepsy, an epilepsy supposed to be idiopathic and mainly due to genetic predis-

position (Doose et al., 1970). Most patients in this group belonged to the benign form of MAE that we have reported previously (Dulac et al., 1990). It could be called favorable MAE. The clinical pattern of this group was clearly distinct from that of benign myoclonic epilepsy of infancy (BMEI) since there were several types of seizures as opposed to only myoclonic seizures in BMEI, later age of onset and the occurrence of transient worsening of the clinical condition with daily drop attacks and/or the development of mental retardation.

In contrast with the previous, cryptogenic LGS group, favorable MAE exhibited no focal, clinical or EEG features. On the other hand, it is remarkable that one-third of these patients had tonic seizures, a feature classically considered as being a hallmark of LGS. Before this study, we have often been mislead in terms of prognosis and choice of medication by the occurrence of tonic seizures combined with spikes and slow waves, in patients who experienced favorable outcome.

The most difficult group to classify nosologically was Group 2, since it shares characteristics of both Groups 1 and 3. It comprises atypical absences, tonic seizures and long bursts of spikes and slow waves, and remains intractable with severe cognitive deficits (Kieffer-Renaux et al., 1997). In addition, it comprises massive myoclonus, myoclonic status and vibratory tonic seizures, and the long bursts of paroxysmal activity consist of irregular spikes and slow waves. This group has therefore the characteristics of the so-called myoclonic or idiopathic variants of Lennox–Gastaut syndrome (Boniver et al., 1987; Giovannardi Rossi et al., 1988).

However, not only is it distinct from Group 3, the LGS group, throughout the seizure disorder as shown by MCA, but it is also indistinguishable from Group 1 during the first year of the disease, during which it shares with the latter the early onset, massive myoclonus, normal cognitive functions, familial antecedents of epilepsy, brief bursts of 3-Hz spike waves, and lack of focal abnormalities. For these reasons, other authors consider it as being part of MAE with unfavorable outcome (Doose et al., 1970).

Therefore, Group 2 seems to start like Group 1 but for some reason it turns to a severe course after a few months. This turn is characterized by the occurrence of myoclonic status combined with vibratory tonic seizures, long bursts of irregular spikes and slow waves, and cognitive deterioration. The pattern at this point is therefore of an epileptic encephalopathy, in which the deterioration seems to be correlated with the so-called interictal activity resembling non-convulsive status epilepticus and lasting for several months or years (Beaumanoir, 1973).

Several authors have insisted that familial antecedents, myoclonic seizures and 3-Hz spike-wave activity are factors indicating genetic predisposition, as opposed to atypical absences, tonic seizures and 2-Hz spike wave activity indicating brain damage (Doose et al., 1970; Beaumanoir, 1973). According to the present series, at onset, when the pattern is clearly distinct from LGS, the risk factors for mental retardation are the characteristics shared by LGS (the presence of tonic and absence seizures and lack of familial antecedents or 3-Hz spike-wave activity) whereas later in the course of the disease, when the pattern shares some characteristics of LGS, the factors that contribute to severity are those that distinguish it from LGS (vibratory tonic seizures and myoclonic status).

Several reasons could account for the variable, including unfavorable outcome of a genetically determined idiopathic epilepsy. A whole range of genetic factors weighing differently in terms of susceptibility to treatment is claimed by Doose et al. (1970). This is unlikely because differences should appear from the onset of the disease, which is not the case. However, perhaps a larger population would show different subgroups at onset that do not appear in this small series. The existence of unidentified cortical lesions is another unlikely eventuality because since these patients lack a history of brain damage, such lesions would be congenital, and therefore should express themselves early in the course of the disease, which is the case for Group 3, the cryptogenic LGS.

Whatever the contribution of these factors, the most striking characteristic of Group 2 is that

worsening is delayed. In addition, the age of occurrence of this turn in the course of the disease, with appearance of myoclonic status (33–87 months, mean 53) is in the same range as in the age of onset of cryptogenic LGS (24–108, mean 55). Therefore, these two conditions seem to share some common age-related, therefore maturational factor in addition to, respectively genetic predisposition in case of MAE and focal or multifocal cryptogenic brain lesions in case of LGS. The combination of two etiologic factors could determine intractability in both instances. This hypothesis would account for the existence of cases unclassifiable between Groups 1 and 2 that would share genetic predisposition, and between Groups 2 and 3 that would share age-related hyperexcitability, the overall set appearing as if it was a biological continuum.

Since this additional factor is age-related, it is most likely linked to maturation. The cerebral cortex is indeed known to undergo rapid maturation in childhood, particularly the premotor areas of the frontal lobes, as shown by functional imaging (Chiron et al., 1992). Animal models have shown that maturation is characterized by transient overexpression of *N*-methyl-D-aspartate receptors, and this contributes to increase excitability and therefore paroxysmal activity (Wasterlain and Shiraska, 1994).

In conclusion, it is possible to validate statistically the nosological distinction between discrete epilepsy syndromes. Among a set of patients exhibiting non symptomatic epilepsy beginning in childhood and comprising several types of generalized seizures excluding epileptic spasms, the method used permitted identification of three distinct groups corresponding respectively to LGS and to favorable and unfavorable cases of MAE. The unfavorable cases of MAE had the same pattern as the so-called myoclonic variant of LGS. They shared at onset the characteristics of the favorable cases of MAE, and during the course of the disorder, a number of those of LGS. Clinical and EEG risk factors for mental retardation and/or intractability could be identified both at onset and during the course of the disease.

The hypothesis that seems to fit best with these findings would be that MAE results from genetic predisposition as suggested by Doose, whereas LGS would be due to cortical brain lesions, undetectable in cryptogenic cases. In addition to being genetically determined, unfavorable cases of MAE, would share with LGS age-related cortical hyperexcitability linked to maturation phenomena. Such a hypothesis could account for the clinical and EEG pattern, including the types of seizures, cognitive deficits and intractability. It would also account for the impression of a continuum (Aicardi, 1995).

These findings should contribute to optimize treatment and stimulate molecular genetic research in idiopathic generalized epilepsy. Indeed, one of the most puzzling findings is that the MAE cases with unfavorable outcome have at onset the characteristics of idiopathic epilepsy. Only a prospective study with a homogeneous treatment algorithm is likely to determine the respective roles played by genetic background, iatrogenic and age-related features, and at which stage of the disorder each of the three groups identified in the study could be recognized.

Acknowledgements

We are indebted to Virginie Kieffer and Isabelle Jambaqué who performed the neuropsychological assessment, including psychometric evaluation; Jacqueline MacAleeze, Henri Rouanet, Brigitte le Roux and Bernard Bru who contributed to the mathematical studies; Drs A.L. Johnson and Catherine Chiron who critically reviewed the manuscript.

References

Aicardi, J., 1995. Myoclonic epilepsies difficult to classifyas either Lennox–Gastaut or myoclonic astatic epilepsy. In: Wallace, S. (Ed.), Epilepsy in Children. Chapman and Hall, London, pp. 271–273.

Beaumanoir, A., 1973. Les spasmes infantiles avec hypsarythmie. In: Lugaresi, E., Pazzaglia, P., Tassinari, C.A. (Eds.), Evolution and Prognosis of Epilepsies. Aulo Gaggi, Bologna.

Benzécri, J.P., 1992. Handbook of Correspondence Analysis. Dekker, New York.

Benzécri, F., Benzécri, J.P., 1984. Analyse de données: exposé élémentaire. Dunod, Paris.

Bernard, J.M., Baldy, R., Rouanet, H. The language for interrogating data LID, INRIA Symposium on data analysis and informatics. North Holland, 1987.

Boniver, C., Dravet, C., Bureau, M., Roger, J., 1987. Idiopathic Lennox–Gastaut Syndrome. In: Wolf, P., Dam, M., Janz, D., Dreifuss, F. (Eds.), Advances in Epileptology, vol. 16. Raven Press, New York.

Chiron, C., Raynaud, C., Mazière, B., Zilbovicius, M., Laflamme, L., Masure, M.C., Dulac, O., Bourguignon, M., Syrota, A., 1992. Changes in regional cerebral blood flow during brain maturation in children and adolescents. J. Nucl. Med. 33, 696–703.

Crichton, N.J., Hinde, J.P., 1989. Correspondence analysis as a screening method for indicators for clinical diagnosis. Stat. Med. 8, 1357–1362.

Doose, H., Gerken, H., Leonhardt, R., Voelzke, E., Voelz, C., 1970. Centrencephalic myoclonic-astatic petit mal. Clinical and genetic investigations. Neuropaediatrie 2, 59–78.

Doose, H., Lunau, H., Castiglione, E., Waltz, S., 1998. Severe idiopathic generalized epilepsy of infancy with generalized tonic–clonic seizures. Neuropediatrics 29, 229–238.

Dulac, O., Plouin, P., Chiron, C., 1990. Forme 'bénigne' d'épilepsie myoclonique chez l'enfant. Neurophysiol. Clin. 20, 115–129.

Dulac, O., Chugani, H., Dalla Bernardina, B., 1994. Infantile Spasms and West Syndrome. Saunders, London.

Giovannardi Rossi, P., Gobbi, G., Melideo, G., Parmeggiani, A., Tullini, A., Santucci, M., 1988. Myoclonic manifestations in the Lennox–Gastaut syndrome and other childhood epilepsies. In: Niedermeyer, E., Degen, R. (Eds.), The Lennox–Gastaut Syndrome. Alan R. Liss, New York, pp. 137–158.

Greenacre, M., 1984. Theory and Applications of Correspondence Analysis. Academic Press, London.

Greenacre, M., 1992. Correspondence analysis in medical research. Stat. Methods Med. Res. 1, 97–118.

Commission on Classification and Terminology of the International League Against Epilepsy, 1989. Proposal for Revised Classification of Epilepsies and Epileptic Syndromes. Epilepsia 30, 389–399.

Kieffer-Renaux, V., Jambaqué, I., Kaminska, A., Dulac, O., 1997. Evolution neuropsychologique des enfants avec syndromes de Lennox–Gastaut et de Doose. ANAE 42, 84–88.

Leclerc, A., 1988. Correspondence analysis: one logistic modeling complementary use in the analysis of health survey among nurses. Stat. Med. 7, 983–995.

Perruca, E., Gram, L., Avanzini, G., Dulac, O., 1998. Antiepileptic drugs as a cause of worsening seizures. Epilepsia 39, 5–17.

Shinnar, S., Berg, A.T., Moshé, S.L., Kang, H., O'Dell, C., Alemany, M., Goldensohn, E.S., Hauser, W.A., 1994. Discontinuing antiepileptic drugs in children with epilepsy: a prospective study. Ann. Neurol. 35, 534–545.

Wasterlain, C., Shirasaka, Y., 1994. Seizures, brain damage and brain development. Brain Dev. 16, 279–295.