PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2015) **57**, 1143–1148 doi: 10.1111/ped.12705

Original Article

Prognostic factors of drug-resistant epilepsy in childhood: An Italian study

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Abstract

Background: Epilepsy is drug resistant in 30–40% of cases. We studied, retrospectively, the prognostic factors of drug resistance (DR) during a 15 year period, in an Italian sample of patients with childhood epilepsy.

Methods: A total of 117 patients were divided into two groups: one with DR, and the other without DR. The two groups were compared at the following time points: epilepsy onset (T0), and at 2, 5, 8 and 10 years after seizure onset (T2, T5, T8 and T10, respectively) using Fisher's exact test and randomization test. Multiple logistic regression analysis was then used to identify the most reliable predictive model of DR.

Results: Positive neurological examination at onset, symptomatic/probable symptomatic etiology, lack of response to the first drug, seizure clustering during follow up, intelligence quotient ≤ 70, altered neuropsychological examination at onset, and presence of cerebral lesions were predominant in cases of DR. The most reliable combinations of predictors of DR included partial or no response to the first drug, presence of seizure clustering during follow up, altered neurological examination at onset, and long latency between epilepsy onset and first drug at T2; partial or absent response to the first drug and positive magnetic resonance imaging (MRI) at T5; positive MRI and absence of generalized seizures at T8; and positive MRI at T10. DR also sometimes appeared after discontinuation of an effective therapy.

Conclusions: Predictive factors of DR can be recognized in a large number of patients with epilepsy at disease onset, although the current possibility of predicting epilepsy outcome remains limited. In the long term, evidence of cerebral lesions appears to become the most significant prognostic factor.

Key words anti-epileptic drug, drug resistance, epileptic seizure, outcome, prognostic factor.

Epilepsy is a chronic neurological disorder characterized by recurrent seizures. Seizures are caused by epileptic discharges due to enhancing and inhibiting factors.[1] In most cases, epilepsy has a favorable course: approximately 60–70% of diagnosed patients may experience remission after adequate treatment with anti-epileptic drugs (AED), as monotherapy or in combination.[2] After ineffective treatment with a first AED, seizures disappear only in 14% of patients after treatment with a second or third drug; 30–40% of patients with epilepsy do not respond to any adequate anti-epileptic treatment, and 30–40% of newly diagnosed patients do not achieve satisfactory seizure control.[2–4] In a minority of subjects in whom seizures are not controlled with known pharmacological therapy, it is possible to control seizures with a new generation of drugs, which entered the market in the last decade.[5]

The definition of drug resistance (DR) is widely debated. In 2009, the International League Against Epilepsy (ILAE) proposed that epilepsy be defined as drug resistant when "a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" occurs.[6]

The recurrence of drug-resistant epilepsy is considerable: of 525 subjects, with age varying from 9 to 93 years old and newly diagnosed with epilepsy, 37% had drug-resistant seizures after 13 years of treatment.[7] Furthermore, patients taking a first AED with no improvement have a lower probability rate (11%) of future therapy success in comparison with patients who failed the treatment because of drug intolerance (41–55%).[7]

Around 60% of drug-resistant epilepsy is associated with focal cortical lesions due to cortical dysplasia, hippocampal sclerosis, phakomatoses, tumors, and outcome of post-hemorrhagic and post-inflammatory damage. The remaining 40% of drug-resistant epilepsy can be considered idiopathic or without identifiable etiology (probable symptomatic).[8,9] In the literature, lack of response to the first drug, presence of symptomatic – or so presumed – epilepsy, high frequency of seizures at onset, seizure clusters, abnormalities observed on neurological examination and on electroencephalogram (EEG) are predictive factors of DR.[10–21]

The aim of this 15 year retrospective study was to assess, for the first time in an Italian population, a broad set of predictive factors of DR in subjects with epilepsy onset in childhood.

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Received 24 March 2015; revised 18 April 2015; accepted 7 May 2015.

Methods

The work was carried out retrospectively using the data obtained from 15 years of medical records. Patients had given, at the time of clinical evaluation, informed consent for the processing of personal data; ethics approval was also obtained. We studied 117 cases involving patients of the Child Neurology and Psychiatry Service at the Neurological Clinic of the University of Bologna, but who had come from all over Italy. This is a referral clinic for neurological diseases including adulthood and childhood epilepsy. We enrolled in the study all consecutive patients affected by any type of idiopathic, symptomatic, or probable symptomatic epilepsy, newly diagnosed or already drug treated, observed from 1995 to 2010, with an age range from 1 to 18 years. We also enrolled subjects with mental retardation of any degree. We excluded patients affected by rolandic epilepsy and occipital epilepsy (Panayiotopoulos variant) because they were not treated due to the known benignity of these two conditions, and subjects without ascertained therapy compliance. The examined subjects included 62 male and 55 female patients, who all had epilepsy with partial or generalized seizures with follow up ≥ 2 years. Mean age at first observation was 3 years 3 months, while that at last observation was 9 years 10 months; mean duration of observational follow up from the first to the last observation was 7 years (median duration, 5 years 8 months). Wake and sleep EEG and neuroimaging were performed in all patients. We divided the case series into two groups: the first included patients with drug-resistant epilepsy, the second included patients without drug-resistant epilepsy. Following the ILAE 2009 definition, we considered as drug resistant those cases in which at least two, well tolerated, appropriately chosen and utilized drugs failed.

Assessment was carried out using five time points in the follow up, namely epilepsy onset (T0), and 2, 5, 8 and 10 years from seizure onset (T2, T5, T8 and T10, respectively). Initially, anamnestic, clinical and instrumental parameters were compared one by one using Fisher's exact test in patients with and without DR. These parameters included gender, family history of epilepsy, prematurity (if present), pre-, peri- and postnatal complications, presence of neonatal convulsions, psychomotor development, presence of febrile convulsions (FC), age at epilepsy onset (<6 years or ≥ 6 years), type of seizure and frequency at onset, neurological examination at epilepsy onset, presence of cerebral palsy (CP), EEG at epilepsy onset (presence or absence of paroxysmal epileptic abnormalities, including slow and sharp waves), cerebral magnetic resonance imaging (MRI), neuropsychological test at epilepsy onset (in patients for whom neuropsychological evaluation data were not available due to their young age, we considered the progress of psychomotor development), intelligence quotient (IQ), psychiatric comorbidity, first drug administered, response to the first drug, cognitive/behavioral regression (if present), presence of seizure clusters during the course, and change in seizure type during follow up. We used the randomization test to compare cases with and without DR with respect to the time elapsed between seizure onset and treatment with the first drug. Multiple logistic regression analysis was then used to identify the most reliable predictive model of DR, namely the combination of independent variables better enabling the prediction of DR appearance at T2, T5, T8 and T10, respectively. To this end, we selected the following variables: family history of epilepsy, age at onset, cerebral MRI, neurological examination at onset (normal; minor neurological signs; or severely altered), IQ (normal, >84; borderline, 71–84; mild retardation, 50/55–70; moderate retardation, 35/40–50/55, and severe/profound retardation, $<35/40$),[22] type of seizure at onset (partial or generalized), response to the first drug (seizure disappearance; relief with seizure reduction $>50\%$; persistence or reduction of seizures $\leq 50\%$), frequency of seizures at onset (pluri-daily, pluri-weekly, pluri-monthly, ≤ 1 seizure per month), latency period between seizure and initiation of therapy, and presence of seizure clusters during follow up. Finally, we assessed the progress of epilepsy after suspension of therapy that had been successful in controlling seizures up to that point.

Results

The case set decreased in number during follow up given that some patients dropped out of the study (34 at T5, 29 at T8, and 17 at T10). We correlated such withdrawal with the disappearance of seizures and suspension of drug therapy in 30% of cases, geographical distance in 20% of cases, and unspecified cause in the remaining subjects. Moreover, one patient died. At T2, prevalence of DR was 65.8%; at T5, 61.4%; at T8, 57.4%; and at T10, 62.2%.

With regard to the etiologic diagnosis, we observed a significant prevalence of symptomatic and probable symptomatic forms, which made the case set extremely selective. The most frequent cerebral lesions detected on MRI were heterogeneous brain malformations (14/117, 12.0%), periventricular leukomalacia (12/117, 10.3%), cortical and subcortical atrophy (9/117, 7.7%), and cortical atrophy (9/117, 7.7%). By evaluating these variables one by one on Fisher's exact test (Tables 1–5), we observed a significant prevalence of DR throughout the study in patients with altered neurologic examination at onset (T2, $P < 0.0001$; T5, $P < 0.01$; T8, $P < 0.001$; T10, $P < 0.05$) and in symptomatic/probable symptomatic cases (T2, $P < 0.0001$; T5, $P < 0.05$; T8, $P < 0.05$; T10, $P < 0.05$). As for the other variables listed in the previous section, significant correlation was not constant throughout the study: a significant prevalence of DR appeared at T2, T5 and T8 but not at T10 in patients who did not respond positively to the first drug; in those patients who had clusters during epilepsy evolution; and in those with IQ ≤ 70. In subjects with altered neuropsychological examination at onset, DR prevalence was significant at every time point of the study except T5. DR prevalence was significant in patients with cerebral lesions on MRI at T2 ($P < 0.01$) and at T8 ($P < 0.01$), almost significant at T10 ($P = 0.05$), but not at T5. At T2 and T5 only, we also observed a significant prevalence of DR in patients who had frequent seizures at onset, in those with change in seizure type during follow up, and in patients with EEG paroxysmal epileptic abnormalities at onset. We observed a change in seizure type during follow up in 16.2% of cases at T2, 18.1% at T5, 14.8% at T8, and 16.2% at T10. Only at T2 was DR prevalence significant in patients with delayed psychomotor development. Only at T8 was DR prevalence significant in epilepsy patients with partial seizures compared with those with generalized

Table 1 Subject characteristics and psychomotor development: Correlation with DR

Variables	T2 (n = 117), n (%)		T5 (n = 83), n (%)		T8 (n = 54), n (%)		T10 (n = 37), n (%)	
	DR (n = 77)	No DR (n = 40)	DR (n = 51)	No DR (n = 32)	DR (n = 31)	No DR (n = 23)	DR (n = 22)	No DR (n = 15)
Male	33 (42.9)	29 (72.5)	21 (41.2)	18 (56.3)	14 (45.2)	11 (47.8)	11 (50.0)	6 (40.0)
	$P < 0.01$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
Family history of epilepsy	37 (48.1)	28 (70.0)	23 (45.1)	20 (62.5)	14 (45.2)	13 (56.5)	12 (54.5)	7 (46.7)
	$P < 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
Prematurity	16 (20.8)	5 (12.5)	10 (19.6)	6 (18.8)	7 (22.6)	3 (13.0)	6 (27.3)	3 (20.0)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
Perinatal complications	33 (42.9)	14 (35.0)	17 (33.3)	19 (59.4)	14 (45.2)	11 (47.8)	9 (40.9)	8 (53.3)
	$P > 0.05$		$P < 0.05$		$P > 0.05$		$P > 0.05$	
Neonatal convulsions	7 (9.1)	4 (10.0)	5 (9.8)	3 (9.4)	4 (12.9)	1 (4.3)	3 (13.6)	1 (6.7)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
Psychomotor delay	55 (71.4)	14 (35.0)	36 (70.6)	16 (50.0)	22 (71.0)	10 (43.5)	12 (54.5)	8 (53.3)
	$P < 0.001$		$P > 0.05$		$P > 0.05$		$P > 0.05$	

DR, drug resistance.

Table 2 Epilepsy parameters and cerebral lesions on MRI: Correlation with DR

Variables	T2 (n = 117), n (%)		T5 (n = 83), n (%)		T8 (n = 54), n (%)		T10 (n = 37), n (%)	
	DR (n = 77)	No DR (n = 40)	DR (n = 51)	No DR (n = 32)	DR (n = 31)	No DR (n = 23)	DR (n = 22)	No DR (n = 15)
Symptomatic or probable symptomatic cases	72 (93.5)	24 (60.0)	46 (90.2)	23 (71.9)	29 (93.5)	16 (69.6)	21 (95.5)	10 (66.7)
	$P < 0.0001$		$P < 0.05$		$P < 0.05$		$P < 0.05$	
Febrile convulsions	13 (16.9)	5 (12.5)	7 (13.7)	8 (25.0)	4 (12.9)	7 (30.4)	5 (22.7)	3 (20.0)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
Epilepsy onset <6 years of age	62 (80.5)	27 (67.5)	38 (74.5)	28 (87.5)	27 (87.1)	17 (73.9)	20 (90.9)	10 (66.7)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
Seizure type at onset: partial (vs generalized)	42 (54.5)	15 (37.5)	30 (58.8)	13 (40.6)	22 (71.0)	8 (34.8)	15 (68.2)	6 (40.0)
	$P > 0.05$		$P > 0.05$		$P < 0.05$		$P > 0.05$	
Seizure clusters	36 (46.8)	4 (10.0)	23 (45.1)	4 (12.5)	12 (38.7)	1 (4.3)	7 (31.8)	1 (6.7)
	$P < 0.0001$		$P < 0.01$		$P < 0.01$		$P > 0.05$	
Positive cerebral MRI	48 (62.3)	12 (30.0)	30 (58.8)	12 (37.5)	21 (67.7)	6 (26.1)	15 (68.2)	5 (33.3)
	$P < 0.01$		$P > 0.05$		$P < 0.01$		$P = 0.05$	

DR, drug resistance; MRI, magnetic resonance imaging.

Table 3 CP and psychiatric/neurological parameters: Correlation with DR

Variables	T2 (n = 117), n (%)		T5 (n = 83), n (%)		T8 (n = 54), n (%)		T10 (n = 37), n (%)	
	DR (n = 77)	No DR (n = 40)	DR (n = 51)	No DR (n = 32)	DR (n = 31)	No DR (n = 23)	DR (n = 22)	No DR (n = 15)
CP comorbidity	17 (22.1)	5 (12.5)	11 (21.6)	7 (21.9)	7 (22.6)	2 (8.7)	4 (18.2)	2 (13.3)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
Psychiatric comorbidity	10 (13.0)	12 (30.0)	7 (13.7)	9 (28.1)	5 (16.1)	7 (30.4)	5 (22.7)	5 (33.3)
	$P < 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
Cognitive–behavioral regression	26 (33.8)	11 (27.5)	12 (23.5)	9 (28.1)	5 (16.1)	2 (8.7)	4 (18.2)	2 (13.3)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
Change in seizure type	18 (23.4)	1 (2.5)	13 (25.5)	2 (6.3)	7 (22.6)	1 (4.3)	5 (22.7)	1 (6.7)
	$P < 0.01$		$P < 0.05$		$P > 0.05$		$P > 0.05$	
IQ ≤ 70	61 (79.2)	14 (35.0)	40 (78.4)	17 (53.1)	26 (83.9)	12 (52.2)	16 (72.7)	7 (46.7)
	$P < 0.00001$		$P < 0.05$		$P < 0.05$		$P > 0.05$	
Neuropsychological pathological examination	66 (85.7)	24 (60.0)	43 (84.3)	21 (65.6)	28 (90.3)	14 (60.9)	20 (90.9)	8 (53.3)
	$P < 0.01$		$P > 0.05$		$P < 0.05$		$P < 0.05$	

CP, cerebral palsy; DR, drug resistance; IQ, intelligence quotient.

Table 4 Seizure frequency and pathologic–neurologic and EEG parameters: Correlation with DR

Variables	T2 (n = 117), n (%)		T5 (n = 83), n (%)		T8 (n = 54), n (%)		T10 (n = 37), n (%)	
	DR (n = 77)	No DR (n = 40)	DR (n = 51)	No DR (n = 32)	DR (n = 31)	No DR (n = 23)	DR (n = 22)	No DR (n = 15)
Seizure frequency ≥ 1/week at onset	58 (75.3)	12 (30.0)	38 (74.5)	10 (31.3)	21 (67.7)	10 (43.5)	15 (68.2)	7 (46.7)
	$P < 0.00001$		$P < 0.001$		$P > 0.05$		$P > 0.05$	
Pathologic neurological examination at onset	70 (90.9)	22 (55.0)	46 (90.2)	21 (65.6)	30 (96.8)	13 (56.5)	20 (90.9)	9 (60.0)
	$P < 0.0001$		$P < 0.01$		$P < 0.001$		$P < 0.05$	
Pathologic EEG at onset	69 (89.6)	28 (70.0)	45 (88.2)	21 (65.6)	28 (90.3)	16 (69.6)	20 (90.9)	13 (86.7)
	$P < 0.05$		$P < 0.05$		$P > 0.05$		$P > 0.05$	

DR, drug resistance; EEG, electroencephalogram.

Table 5 Drug response and type of first drug: Correlation with DR

Variables	T2 (n = 117), n (%)		T5 (n = 83), n (%)		T8 (n = 54), n (%)		T10 (n = 37), n (%)	
	DR (n = 77)	No DR (n = 40)	DR (n = 51)	No DR (n = 32)	DR (n = 31)	No DR (n = 23)	DR (n = 22)	No DR (n = 15)
Lack of response to first drug	60 (77.9)	11 (27.5)	38 (74.5)	12 (37.5)	22 (71.0)	9 (39.1)	13 (59.1)	6 (40.0)
	$P < 0.000001$		$P < 0.01$		$P < 0.05$		$P > 0.05$	
	DR (n = 22)	No DR (n = 10)	DR (n = 13)	No DR (n = 11)	DR (n = 8)	No DR (n = 6)	DR (n = 4)	No DR (n = 4)
VPA (vs CBZ) utilized as first drug for partial seizures	11 (50.0)	6 (60.0)	8 (61.5)	7 (63.6)	6 (75.0)	4 (66.7)	3 (75.0)	1 (25.0)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
	DR (n = 26)	No DR (n = 8)	DR (n = 19)	No DR (n = 9)	DR (n = 15)	No DR (n = 5)	DR (n = 10)	No DR (n = 3)
VPA (vs PB) utilized as first drug for partial seizures	11 (42.3)	6 (75.0)	8 (42.1)	7 (77.8)	6 (40.0)	4 (80.0)	3 (30.0)	1 (33.3)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
	DR (n = 26)	No DR (n = 6)	DR (n = 16)	No DR (n = 6)	DR (n = 11)	No DR (n = 3)	DR (n = 8)	No DR (n = 5)
CBZ (vs PB) utilized as first drug for partial seizures	11 (42.3)	4 (66.7)	5 (31.3)	4 (66.7)	2 (18.2)	2 (66.7)	1 (12.5)	3 (60.0)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	
	DR (n = 29)	No DR (n = 23)	DR (n = 19)	No DR (n = 17)	DR (n = 8)	No DR (n = 14)	DR (n = 6)	No DR (n = 9)
VPA (vs PB) utilized as first drug for generalized seizures	21 (72.4)	15 (65.2)	13 (68.4)	11 (64.7)	6 (75.0)	8 (57.1)	3 (50.0)	4 (44.4)
	$P > 0.05$		$P > 0.05$		$P > 0.05$		$P > 0.05$	

DR, drug resistance; CBZ, carbamazepine; PB, phenobarbital; VPA, valproic acid.

seizures. Absence of DR was significant only at T2 in male subjects; in patients with a family history of epilepsy; and in those with psychiatric comorbidity; and only at T5 in patients with perinatal stress. Finally, no significant correlation was found between DR and prematurity, positive history of neonatal convulsions and FC, epilepsy onset under 6 years of age, CP comorbidity, cognitive/behavioral regression, and type of drug given at disease onset (Tables 1–5). As for the latter variables, the most utilized drugs were phenobarbital (PB), valproic acid (VPA) and carbamazepine (CBZ). In relation to latency between epilepsy onset and treatment with the first drug, only one significant difference in mean time ($P < 0.05$, randomization test) was observed at T2, between subjects with DR (4.0 months) and those without DR (2.1 months).

On multiple logistic regression analysis the most reliable DR predictive model was characterized by the combination of the following variables: at T2, partial or absent response to the first drug, presence of seizure clusters during the course, slightly or severely altered neurological examination at onset, and long latency between epilepsy onset and treatment with the first drug; at T5, partial or absent response to the first drug and positive cerebral MRI; at T8, positive cerebral MRI and absence of generalized seizures; and at T10, positive cerebral MRI.

Finally, 12/83 patients (14.5%) at T5, 9/54 (16.7%) at T8, and 9/37 (24.3%) at T10 became drug resistant after suspension of therapy (as recommended by a specialist) that had been effective up to that point.

Discussion

In the literature, the definition and complex physiopathogenesis of DR, the latter resulting from the interaction of several factors, are widely discussed.[10–21] According to Hauser, in theory all epilepsies should be considered as resistant to therapy because the action of AED is only palliative, and does not influence the causal pathobiology of the epilepsy.[23] Cascino suggested a more operational definition at the clinical level by proposing as a DR marker the persistence of seizures over the years, even with appropriate mono/polytherapy and at the maximum tolerated doses.[24] Finally, Schachter connected the concept of DR with the notion of quality of life: a subject with DR is incapable of maintaining a lifestyle appropriate to his/her possibilities due to seizure persistence, the side-effects of AED or other psychosocial problems.[25] With regard to DR pathogenesis, theories concerning target and drug transporters have received great attention in the last 15 years. More recently, the hypothesis of intrinsic severity has suggested the existence of neurobiological factors as contributing to both the severity of epilepsy and drug refractoriness.[26] Although neurobiological mechanisms of DR are still unclear, some researchers propose that those factors correlated with disease severity are also the cause of DR.[26–28]

The present study – the first of this kind to be carried out in Italy – is characterized by a large sample of patients with epilepsy and prolonged follow up, performed by a team of experts in the Neurological Clinic of the University of Bologna. Although there is a risk of selection bias, nonetheless it also confirms and deepens what is described in the literature on the strict correlation between DR and variables including presence of abnormalities at neurological examination at onset, symptomatic/probable symptomatic epilepsy, lack of response to the first drug, IQ $\leq$ 70, altered neuropsychological examination at onset, and presence of lesions on MRI.[10,11,13,14]

Altered neurological examination at onset and symptomatic/probable symptomatic etiology may represent major negative prognostic factors. The data thus showed a significant correlation with DR at every time point of the study.

The lack of positive response to the first drug in the present sample had a more significant correlation with prognosis than in other studies.[14,20] We agree with Sillanpää and Schmidt[16] that the appearance of seizure clusters during the course of epilepsy may contribute to unfavorable evolution. Also, EEG showing paroxysmal epileptic abnormalities at onset may represent an unfavorable sign, according to Okuma and Kumashiro.[13]

We confirm also the importance of age at epilepsy onset as a factor in prognosis. Arts *et al.* reported a better outcome in patients with age $<$ 6 years, as in the present patients.[19] With regard to the elapsed time between seizure onset and treatment with the first drug, while for Okuma and Kumashiro the interval should be $<$1 year in order to facilitate good outcome,[13] in the present sample it was found to be $<$2 months on average.

It is important to note, however, that the number of patients gradually decreased during follow up, due to reasons given in the previous section; therefore, it is not surprising that some variables lost significance at T10. In addition, the altered-at-onset neuropsychological examination and presence of alterations on MRI appear to be important predictive factors of DR because these were significant at T2, T8 and T10 (at T10 near significant for MRI).

A total of 12/83 patients (14.5%) at T5, 9/54 (16.7%) at T8, and 9/37 (24.3%) at T10 became drug resistant after the suspension of therapy that had been effective up to that point. Moreover, it is not possible to ascribe the reappearance of drug-resistant seizures to therapy interruption, because in some of these patients relapse occurred many years after drug suspension (4.8% at T5, 7.4% at T8, 10.8% at T10). And, given that in such cases it was not possible to determine whether seizures would have reappeared without suspension of treatment, we did not investigate this aspect further.

Analysis of the type of the first drugs administered at onset showed extensive use of PB, VPA and CBZ. This may be because most of the present patients had seizure onset in the first half of the 1990s, when few new drugs were available for children. Correct diagnosis and pharmacological choice at onset are significant variables because false DR is linked to inadequate diagnosis or therapy choice.

The present study has some limitations including its retrospective nature, the number of cases coming from a center specializing in epilepsy, and, above all, the fact that many patients had their first diagnosis at other centers. For these reasons, the recurrence of DR in the present sample was significantly higher compared with the literature on patients with epilepsy (65.8% at T2, $P < 0.00000001$; 61.4% at T5, $P < 0.00000001$; 57.4% at T8, $P < 0.0001$; 62.2% at T10, $P < 0.0001$; binomial test). The accuracy of diagnosis may have influenced the interpretation of real or apparent changes observed during follow up in 16.2% of patients at T2, in 18.1% at T5, in 14.8% at T8 and in 16.2% at T10, as predictive factors of DR. In some patients, however, who had changes in their condition, it is evident that the initial diagnosis, later adapted due to such changes, was based on the symptoms and clinical data; for others it is unclear from the available information whether this change was actual or the consequence of an initial diagnostic and/or therapeutic error.

Conclusions

Different predictive models of DR were identified in the form of varying combinations that predicted DR depending on the time point of the study: at T2, partial or absent response to first drug,

presence of seizure clusters during the course, slightly or severely altered neurological examination at onset, and long latency between epilepsy onset and treatment with the first drug; at T5, partial or absent response to first drug and positive cerebral MRI; at T8, positive cerebral MRI and absence of generalized seizures; and at T10, positive cerebral MRI.

Cerebral lesions on MRI in childhood appear to be increasingly important during follow up: although variables linked to prompt and appropriate pharmacological choice seem to have relatively more impact in the short term, in the long term, evidence of cerebral lesions becomes the most significant prognostic factor.

Several important points identified in the present Italian study and which confirm and deepen the literature are as follows: first, the relevance of correct diagnosis and appropriate drug treatment for epilepsy; second, the need for thorough consideration of the development of epilepsy in childhood, which may offer predictive factors for a large number of patients at disease onset (although the current possibility of predicting epilepsy outcome remains limited); third, the increasing importance during follow up of cerebral lesions on MRI in childhood (although variables linked to prompt and appropriate pharmacological choice seem to have relatively more impact in the short term, in the long term, evidence of cerebral lesions seems to become the most significant prognostic factor); and finally, the confirmed usefulness of the concept of false DR, which is due to diagnostic and/or therapeutic error or to patient/family non-compliance with a prescribed treatment that may complicate epilepsy course and prognosis.

Acknowledgments

We thank Dr Cecilia Baroncini for help with English-language editing and Mr Massimo Armaroli for technical assistance. The authors declare no conflicts of interest.

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