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Prognostic factors in epileptic encephalopathies at onset in the first 2 years of life: The experience of a tertiary healthcare center in Italy

Giuditta Pellino [a,*], Francesca Chiavarino [a], Elisa Fiumana [a], Antonella Boni [b], Angelo Russo [b], Raffaella Faggioli [a]

[a] Section of Pediatrics, Department of Medical Sciences, University of Ferrara, University Hospital Arcispedale Sant'Anna, Ferrara, Italy
[b] IRCCS Istituto delle Scienze Neurologiche di Bologna, Pediatric Neurology Unit, Bologna, Italy

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ABSTRACT

Introduction: The aim of this retrospective cohort study was to identify some prognostic factors in anamnestic/clinical/instrumental data at the onset of epileptic encephalopathy (EE), for multiple outcome measures.
Methods: We recruited patients diagnosed as affected by EE at Sant'Anna University Hospital, with onset in the first 24 months of life, with follow-up lasting longer than 3 years.
Results: At the end of the follow-up, 6 patients (14%) died within 2 years of age; 20 patient (49%) had a drug-resistant epilepsy (DRE); 9 patients (22%) had a language development delay (LDD); 12 patients (30%) had an autism spectrum disorder (ASD); 20 patients (49%) had a global psychomotor impairment (GPI); 9 patients (22%) needed palliative care; and nobody had a normal psychomotor development. Preexisting developmental delay predicts death ($p = 0.009$), and in survivors, it is associated with a GPI ($p < 0.001$); patients with normal neurological examination at the onset of EE only develop a LDD ($p = 0.020$). Neuroimaging structural alterations are associated with DRE ($p = 0.012$) and with a GPI ($p = 0.013$). The history of perinatal risk factors predicts the worst prognosis (death: $p = 0.035$, GPI: $p = 0.015$, and access to palliative care: $p = 0.007$). The absence of early response to treatment is correlated to a poor long-term prognosis (GPI, $p = 0.019$; DRE, $p = 0.001$). The multivariate analysis confirms that a normal development at onset predicts the most favorable prognosis, both in terms of survival and cognitive outcome (OR [odds ratio] = 0.1). An early response to treatment is a protective factor for DRE (OR = 0.1). A perinatal pathology is confirmed as an independent prognostic factor of severe comorbidities (access to palliative care: OR = 10.4).
Significance: This study was conducted to recognize possible prognostic factors among onset data of patients with EE, considering multiple outcome measures. This study design represents an innovative element compared to available papers, which were centered on isolated endpoints of prognosis, such as the prediction of neurocognitive development impairment or drug resistance.
The data obtained from the study confirm that EEs prognosis is generally, but not universally, poor. Structural etiology and/or lack of response to antiepileptic drug (AED) within three months are main risk factors for DRE. Normal development at the onset of EEs and early response to treatment are the main positive prognostic factors.

1. Introduction

Epileptic encephalopathies (EEs) are defined as a group of conditions in which cognitive, sensory, and/or motor functions deteriorate as a consequence of epileptic activity, which consists of frequent seizures and/or interictal paroxysmal activity, beyond what might be expected from the underlying pathology alone (e.g., cortical malformation) [1,2]. In the position paper of the ILAE (International League Against Epilepsy) Commission for Classification and Terminology of 2017, Scheffer et al. introduced the definition of "developmental encephalopathy" because many of these severe genetic disorders also have developmental consequences, arising directly from the effect of genetic mutation, in addition to the frequent epileptic activity. In many instances where a genetic mutation of major effect is identified, the terms "developmental and epileptic encephalopathy" may be subsumed by using the gene name together with the word encephalopathy (e.g., STXBP1 encephalopathy) [3].

There are several descriptive studies on EEs, especially focused on the etiology and on the clinical-electroencephalographic (EEG) features of the syndromes [4–6]. On the other hand, literature is lacking in publications about prognostic factors.

Papers published are focused particularly on West or Lennox–Gastaut syndromes, EEs selected for their numerous eligible sample, and for their well-known electroclinical patterns. Jeavons et al. [7], in

* Corresponding author at: Section of Pediatrics, Department of Medical Sciences, University of Ferrara, University Hospital Arcispedale Sant'Anna, Via Aldo Moro, 8, Cona, FE 44124, Italy.
E-mail address: pllgtt@unife.it (G. Pellino).

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a key study conducted on the natural history of the West syndrome published in 1973, identified acquired etiology and latency between the onset of seizures and the beginning of the therapy as the most important prognostic factors for the neurological outcome: structural forms and therapeutic delay are in fact associated with worsening conditions. Aicardi et al. [8] in 1994, in another study about West syndrome, defined the absence of neurological normality and/or the finding of other types of seizures before the onset of spasms as negative prognostic factors. More recently, in order to identify risk factors of cognitive impairment, Van Rijckevorsel et al. [9] in 2006 suggested that the absence of early remission of seizures is related in West syndrome to the development of autism spectrum disorders; in Lennox–Gastaut, the factors associated with cognitive regression are a high frequency of seizures, traumatic brain injury due to falling seizures, severe epileptiform interictal activity during sleep, and multidrug therapy. Conversely, there are numerous studies focused on the prognostic factors of drug resistance, although taking into consideration not only EEs but also all the epileptic syndromes with pediatric onset [10,11]. Recruiting a population with epilepsy onset within the first two years of life, with drug resistance in 2/3 of patients, Yildiz et al. [12] in 2017 showed by multivariate statistical analysis that the predictors of drug resistance are history of status epilepticus, developmental delay at onset, and EEG pattern of multifocal epileptiform discharges. In this retrospective study, we evaluated 41 patients affected by EEs with onset in the first 24 months of life, who were recruited in order to recognize possible clinical prognostic factors for multiple outcome measures (survival, antiepileptic drug (AED) resistance, access to palliative care, global psychomotor impairment, autism spectrum disorder, specific language delay).

2. Materials and methods

A retrospective cohort study was carried out at Sant'Anna University Hospital, a tertiary hospital in Italy. The database of Neurologic Pediatric Unit was accessed to retrieve all consecutive records of patients diagnosed as affected by an EE, with onset in the first 24 months of life, presented from 1 January 1990 to 31 December 2013. We included patients with at least a three-year long follow-up. Currently used computerized archives and medical records were reviewed to collect the following data for each patient: date of birth, age at the onset of EE (months), dates of first and last access to our pediatric neurology center, family history of epilepsy or febrile seizure, perinatal risk factors (hypoxia, sepsis), history of neonatal seizures, association with structural epilepsy, neurological examination at presentation, syndromic diagnosis of EE, neuroimaging at onset, time within response to treatment (if applicable), and prognosis (death, drug resistance, access to palliative care, global psychomotor impairment, autism spectrum disorder, language developmental delay). We defined EE as an epileptic disorders that appear in the first two years of life, with age-specific clinical and EEG (ictal and interictal epileptic discharges) characteristics, recognized by the ILAE, as follows: early infantile EE (Ohtahara syndrome), early myoclonic encephalopathy, epilepsy of infancy with migrating focal seizures, infantile spasms (West syndrome), severe myoclonic epilepsy in infancy (Dravet syndrome), myoclonic–atonic epilepsy (Doose syndrome), Lennox–Gastaut syndrome, EE with continuous spike-and-wave during sleep, and Landau–Kleffner syndrome. Age at onset, seizure type(s) according to the semiologies described in the medical records and EEG ictal and interictal patterns were used to perform the classification. Electroencephalographic interpretations were done independently by 2 certified epileptologists with at least 5-year experience in EEG, and in case of disagreement, the interpretation was finalized after a joint meeting. Developmental milestones were used to classify development as normal or delayed. Neuroimaging findings (ultrasound, CT [computed tomography], and MRI [magnetic resonance imaging] brain) were classified within the following three groups: negative findings, findings with presence of structural lesion, and findings with presence of noncausative abnormalities (hypoplasia of the corpus callosum, white matter signal abnormalities, posterior fossa abnormalities). We considered early response to treatment in case of remission of seizures and of specific EEG pattern within 3 months from the beginning of antiepileptic therapy. Drug-resistant epilepsy is defined as failure of two or more AEDs with seizure frequency of more than one every 6 months in the years immediately before final follow-up. We have selected as possible prognostic factors: age at onset of EE, family history of epilepsy/febrile seizure, perinatal risk factor, neonatal seizures, neurologic

Table 1
Correlation between proposed prognostic factors and the considered outcome measures. Median and interquartile ranges have been reported for continuous variable "age at onset"; the Wilcoxon–Mann–Whitney test for continuous variables and the Fisher test for categorical variables were used to compare outcomes. We indicated in bold statistically significant results ($p \leq 0.05$).

		Death (age ≤ 2 years old), n (%)	AED resistance, n (%)	Access to palliative care, n (%)	Global psychomotor impairment, n (%)	Autism spectrum disorder, n (%)	Language developmental delay, n (%)
Age at onset	Month	2.5 [1.5–3.5]	4.75 [2–6.75]	6 [3.5–7.5]	3.5 [1.5–6]	5.25 [2.25–7]	5 [2.5–6.5]
	p-Value	**0.0351**	0.3548	0.6262	0.0776	0.6459	0.1040
Family history of epilepsy/febrile seizures	Yes (n = 11)	2 (18.2)	3 (30.0)	1 (9.1)	3 (27.3)	3 (27.3)	5 (45.5)
	No (n = 30)	4 (13.3)	17 (65.4)	8 (27.6)	17 (56.7)	9 (30.0)	4 (13.3)
	p-Value	0.651	0.073	0.399	0.159	1.000	**0.042**
Perinatal risk factor	Yes (n = 11)	4 (36.4)	5 (71.4)	6 (54.6)	9 (81.8)	1 (9.1)	1 (9.1)
	No (n = 30)	2 (6.7)	15 (51.7)	3 (19.3)	11 (36.7)	11 (36.7)	8 (26.7)
	p-Value	**0.035**	0.426	**0.007**	**0.015**	0.128	0.401
Normal development at the onset	Yes (n = 21)	0 (0.0)	10 (47.6)	1 (5.0)	4 (19.1)	9 (42.9)	9 (38.1)
	No (n = 20)	6 (30.0)	10 (66.7)	8 (40.0)	16 (80.0)	3 (15.0)	1 (5.0)
	p-Value	**0.009**	0.320	**0.020**	<**0.001**	0.085	**0.020**
Neuroimaging at the onset	Negative (n = 6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)	3 (50.0)
	Structural lesion (n = 23)	4 (17.4)	13 (68.4)	7 (30.4)	15 (65.2)	5 (21.7)	3 (13.0)
	Noncausative abnormalities (n = 12)	2 (16.7)	7 (63.6)	2 (18.2)	5 (41.7)	4 (33.3)	3 (25.0)
	p-Value	0.702	**0.012**	0.330	**0.013**	0.400	0.128
Neonatal seizure	Yes (n = 7)	2 (28.6)	5 (83.3)	2 (28.6)	6 (85.7)	1 (14.3)	0 (0.0)
	No (n = 34)	4 (11.8)	15 (50.0)	7 (12.2)	14 (41.2)	11 (32.4)	9 (26.5)
	p-Value	0.268	0.196	0.645	**0.045**	0.651	0.315
Early response to treatment	Yes (n = 14)	0 (0.0)	3 (21.4)	1 (7.1)	3 (21.4)	4 (28.6)	7 (50.0)
	No (n = 25)	6 (24.0)	16 (80.0)	7 (29.2)	16 (64.0)	7 (28.0)	2 (8.0)
	p-Value	0.071	**0.001**	0.216	**0.019**	1.000	**0.005**

Table 2
Logistic regression models were used. We indicated in bold statistically significant results ($p \leq 0.05$).

	Prognostic factor	p-Value	Odds ratio (95% CI)
Drug resistance	Neuroimaging positive for structional lesion	0.403	1.8 (0.46–6.73)
	Early response to treatment	**0.008**	0.1 (0.02–0.53)
Access to palliative care	Perinatal risk factor	**0.006**	10.4 (1.93–56.04)
	Normal neurological examination	0.133	0.2 (0.01–1.74)
Global psychomotor delay	Neuroimaging positive for structional lesion	0.546	1.9 (0.23–15.47)
	Early response to treatment	**0.016**	0.1 (0.01–0.62)
	Neuroimaging positive for structional lesion	0.452	1.9 (0.36–10.0)
	Early response to treatment	0.225	0.3 (0.04–2.15)
Language developmental delay	Family history of epilepsy/febrile seizure	0.093	5.8 (0.74–45.09)
	Normal neurological examination	0.095	8.1 (0.69–94.68)
	Early response to treatment	**0.031**	9.6 (1.22–74.99)

examination at the onset, neuroimaging at onset, early response to treatment. The following indicators were considered as outcome measures: survival ≥2 years of life, drug-resistant epilepsy, access to palliative care, global psychomotor impairment, autism spectrum disorder, and language developmental delay.

2.1. Statistical analysis

The categorical variables have been described by absolute and percentage frequencies, and median and interquartile ranges have been reported for continuous variables. The Wilcoxon–Mann–Whitney test for continuous variables and the Fisher test for categorical variables were used to compare outcomes. A value of $p \leq 0.05$ was considered statistically significant. To perform the multivariate statistical analysis, logistic regression models were used.

3. Results

Forty-one patients (24 males and 17 females) meet the inclusion criteria listed above.

The median age at onset of EE is 5 months [2.5–6.6 months]. The median age at the end of follow-up is 9.7 years [4.8–14.5 years]. Median follow-up duration is 10.2 years [4.7–16.2 years]. Family history of epilepsy/febrile seizures was found in 11 (26.8%) patients. Perinatal risk factors were present in 11 (26.8%) patients. A pathological neurological examination at the onset was found in 20 (48.8%) patients. At presentation, neuroimaging was negative in 6 (14.6%) patients, abnormal for structural lesion in 23 (56.1%) patients, and positive for noncausative abnormalities in 12 (29.3%) patients. Seven (17.0%) patients have a history of neonatal seizure. According to syndromic classification of EE, we recognized West syndrome in 24/41 patients (58.5%), Ohtahara syndrome in 7/41 (17.1%), early myoclonic epilepsy in 3/41 (7.3%), Dravet

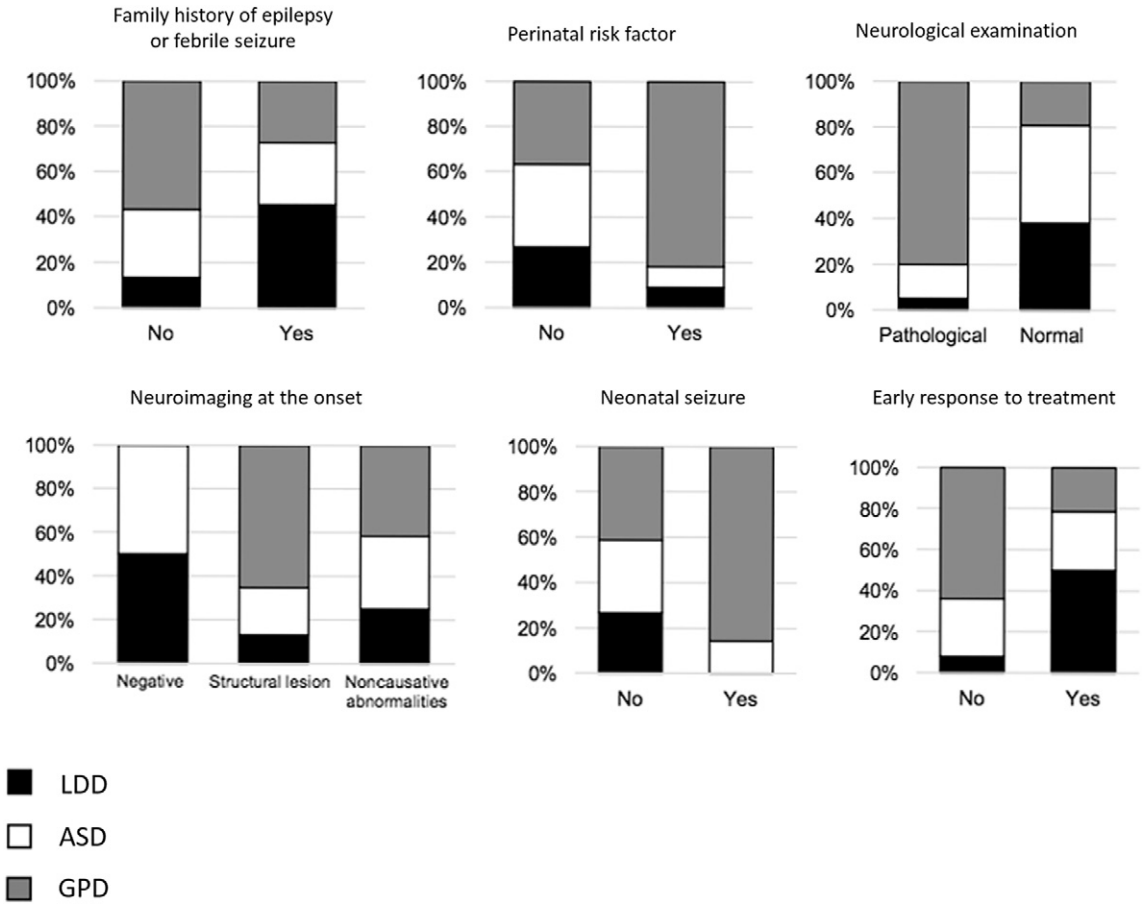

Fig. 1. Distribution of neurocognitive outcome for analyzed prognostic factors.

syndrome in 2/41 (4.9%), EE with continuous spike-and-wave during sleep in 2/41 (4.9%), Lennox–Gastaut syndrome in 1/41 (2.4%), and epilepsy of infancy with migrating focal seizures in 1/41 (2.4%). In 18 (43.9%) patients, structural epilepsy was associated with EE. In 14 (34.1%) patients, an early response to treatment was found. At the end of the follow-up, 6 patients died within 2 years of age; 20 patients had a drug-resistant epilepsy; 9 patients had a language developmental delay; 12 patients had an autism spectrum disorder; 20 patients had a global psychomotor impairment; 9 patients had access to palliative care; and nobody had a normal psychomotor development. A statistical analysis highlights significant associations between the proposed prognostic factors and the considered outcome measures (Table 1). In particular, a pathological neurological examination at presentation predicts death ($p = 0.009$), and in survivors, it is associated with a global psychomotor impairment at the end of follow-up ($p < 0.001$); patients with a normal neurological examination only develop a language developmental delay ($p = 0.020$). Neuroimaging structural alterations at the onset of EE are associated with drug resistance ($p = 0.012$) and with global psychomotor impairment ($p = 0.013$). The presence of perinatal risk factors predicts the worst prognosis as for survival (death, $p = 0.035$) and as for neurological/physical outcome (global psychomotor impairment, $p = 0.015$; access to palliative care, $p = 0.007$). The absence of early response to treatment is correlated with a poor long-term prognosis (global psychomotor impairment, $p = 0.019$; drug resistance, $p = 0.001$). The presence of family history of epilepsy/febrile seizure, a normal development at presentation, and an early response to treatment are predictive of language developmental delay. At the limit of significance ($p = 0.08$) is the association between a neurological normality at onset of EE and the diagnosis of autism spectrum disorder during the follow-up. In the multivariate logistic regression analysis (Table 2), the strongest predictive factors were as follows: for drug resistance, the early response to treatment with odds ratio (OR) = 0.1 (0.02–0.53); for the access to palliative care, the presence of perinatal diseases with OR = 0.4 (1.93–56.04); for the presence of language developmental delay, the early response to treatment with OR = 9.6 (1.22–74.99); and a normal neurological examination results as a protective factor versus the global psychomotor impairment with an OR = 0.1 (0.01–0.62). We also presented in Fig. 1 the distribution of outcome measures for each variable considered at the onset.

4. Discussion

Epileptic encephalopathies are a group of epilepsies occurring most frequently during neonatal period and infancy, in which epileptic seizures, epileptiform abnormalities, or both are believed to contribute to the progressive cognitive and/or behavioral deterioration of the subject [13]. Epileptic activity begins in a critical phase for the organization of cognitive networks, compromising not only the functions already learned, but also the age-related development of new acquisitions. Consequently, a stop or a regression of neurodevelopment occurs, which can be global or limited to specific functions such as language. Various authors described clinical and EEG characteristics of patients affected by EEs, but literature is lacking in studies designed to identify prognostic factors. Our study was conducted on 41 patients affected by EEs, to recognize possible prognostic factors among onset patients' data, considering multiple outcome measures (survival, drug resistance, access to palliative care, global psychomotor impairment, autism spectrum disorder, language developmental delay). This study design represents an innovative element compared to previous available studies, which were centered on isolated endpoints of prognosis, such as the prediction of neurocognitive development impairment or drug resistance. For example, Berg et al., in a prospective cohort study in 2012 conducted on pediatric patients with epilepsy, had already identified the association between alteration of neurological examination at onset (hemiparesis, tetraparesis, diplegia) and worse cognitive outcome [14]. Also, our results show that neurological development before the onset of EE represents a determining prognostic factor, as for survival and as for neuroevolutive state. In particular, a preexisting developmental delay at onset perfectly predicts death, and in survivors, it is associated with a global psychomotor impairment at the end of follow-up; instead, a normal neurological examination is correlated with a language developmental delay, which represents the best outcome in long-term prognosis of our population. Structural etiology has been presented as a major prognostic factor for drug resistance in many other studies on pediatric epilepsy [15–17]; also in our population, neuroimaging structural abnormalities are associated with drug resistance and global impairment of neurodevelopment. Perinatal disease, analyzed in numerous previous publications, had been identified only as a predictor of drug resistance [18]. Our study highlighted that in patients with EE, perinatal diseases (hypoxia, sepsis) predict the worst prognosis (death, global psychomotor delay, and access to palliative care). Lack of response to AED within three months is correlated with a severe long-term prognosis (global psychomotor impairment; drug resistance). Similar data are currently available only for West syndrome [19,20]. Our proposal based on reaching prognostic factors among onset clinical characteristics, excluding genotype information, could appear anachronistic in this current historical moment. In fact, genetic testing has a leading role into the diagnostic management of patients affected by EE, representing itself a predictive factor of disease's course. However, we have to consider the absence of a clear genotype–phenotype correlation, especially without neurophysiologic studies, and the latency between genetic response and clinical timing practice.

The data obtained from the study confirm that EEs' prognosis is generally, but not universally, poor. Structural etiology and/or lack of response to AED within three months are main risk factors for drug-resistant epilepsy. Normal development at the onset of EEs and early response to treatment are the main positive prognostic factors.

The weaknesses of this study are the retrospective drawing of the work and the limited number of the sample. Multicentric studies would allow the experimenters to consider further variables.

Statement of ethics

The study was complied with the principles cited in the Declaration of Helsinki. In consideration of retrospective design, we did not seek ethical committee approval, because all data analyzed were collected as part of routine diagnosis and treatment and patients were diagnosed and treated according to national guidelines and agreements.

Author contributions

Dr. Giuditta Pellino identified the research questions and drafted the manuscript; Dr. Francesca Chiavarino and Angelo Russo collected data and critically reviewed the manuscript; Dr. Elisa Fiumana and Dr. Antonella Boni performed statistical analysis and critically reviewed the manuscript; Dr. Raffaella Faggioli coinitiated the submission of this manuscript and performed the first critical review of the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors have no financial relationships relevant to this article and no conflicts of interest to disclose.

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