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**Research** Paper

# The burden of epilepsy on long-term outcome of genetic developmental and epileptic encephalopathies: A single tertiary center longitudinal retrospective cohort study

Mario Mastrangelo<sup>a, b, \*, 1</sup>, Filippo Manti<sup>b, c, 1</sup>, Giacomina Ricciardi<sup>c</sup>, Rossella Bove<sup>c</sup>, Carlo Greco<sup>c</sup>, Manuela Tolve<sup>c,d</sup>, Francesco Pisani<sup>b,c</sup>

<sup>a</sup> Department of Women/Child Health and Urological Science, Sapienza University of Rome, Rome, Italy

<sup>b</sup> Unit of Child Neurology and Psychiatry, Azienda Ospedaliero Universitaria Policlinico Umberto, Rome, Italy

Unit of Child Neurology and Psychiatry, Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy

<sup>d</sup> Department of Experimental Medicine, Sapienza University of Rome, Italy

ARTICLE INFO ABSTRACT Keywords: Background: This retrospective cohort analysis highlighted neurodevelopmental outcome predictors of genetic Epilepsy developmental and epileptic encephalopathies (DEE). Outcome Patients and Methods: Patients' demographic, clinical and molecular genetics data were collected. All patients Genetic epilepsies underwent clinical, developmental, and neuropsychological assessments. Neurodevelopmental disorders children *Results*: We recruited 100 participants (53 males, 47 females) with a mean follow-up lasting  $10.46 \pm 8.37$  years. Age at epilepsy-onset was predictive of poor adaptive and cognitive functions (VABS-II score, r = 0.350, p =0.001; BRIEF control subscale, r = -0.253; p = 0.031). Duration of epilepsy correlated negatively with IQ (r = -0.234, p = 0.019) and VABS-II score (r = -0.367, p = -00.001). Correlations were found between delayed/lacking EEG maturation/organization and IQ (r = 0.587, p = 0.001), VABS-II score (r = 0.658, p = 0.001), BRIEF-MI and BRIEF-GEC scores (r = -0.375, p = 0.001; r = -0.236, p = 0.033), ASEBA anxiety (r = -0.220, p = 0.047) and ADHD (r = -0.233, p = 0.035) scores. The number of antiseizure medications (ASMs) correlated with IQ (r = -0.414, p = 0.001), VABS-II (r = -0.496, p = 0.001), VABS-II (r = -0.496), p = 0.001), p = 0.001), p = 0.001), p = 0.001, p = 0.001), p = 0.001), p = 0.001, p = 0.001), p = 0.001), p = 0.001), p = 0.001, p = 0.001), p= 0.001), and BRIEF-MI (r = 0.294, p = 0.012) scores; while age at the beginning of therapy with ASEBA anxiety score (r = 0.272, p = 0.013). The occurrence of status epilepticus was associated with worse adaptive performances. The linear regression analysis model showed that delayed/lacking EEG maturation/organization had a significant influence on the IQ (R2 = 0.252, p < 0.001) and the BRIEF-GEC variability (R2 = 0.042, p = 0.036). The delayed/lacking EEG maturation/organization and the duration of epilepsy also had a significant influence on the VABS-II score (R2 = 0.455, p = 0.005).Conclusions: Age at seizure-onset, EEG maturation/organization, duration of epilepsy, occurrence of status epilepticus, age at the introduction and number of ASMs used are reliable predictors of long-term outcomes in patients with genetic DEE.

## 1. Background

The term "developmental and epileptic encephalopathies" (DEE) identifies those conditions in which epileptic seizures and neurodevelopmental disorders impacting cognitive, social, and behavioral functioning may coexist and occur as the consequence of a common underlying etiology (i.e., developmental encephalopathy) or/and the direct effect on the development of recurring seizures and frequent EEG epileptiform activity (i.e., epileptic encephalopathy) [1]. The cumulative incidence of DEE was more than 1 in 2000 live births in some

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<sup>\*</sup> Corresponding author at: Dipartimento Materno-Infantile e Scienze Urologiche, Sapienza-Università di Roma, Via dei Sabelli 108 00185, Roma, Italy. E-mail address: mario.mastrangelo@uniroma1.it (M. Mastrangelo).

<sup>&</sup>lt;sup>1</sup> These authors contributed equally to the paper.

studies, while in a more recently reported cohort it was 169/100,000 children [2–5]. A monogenic disease is diagnosed in up to 50 % of the cases, and about 400 chromosomal imbalances have been associated with phenotypes, including epilepsy and developmental delay or intellectual disabilities (ID) with different degrees of severity [4,6,7].

The impact of the epilepsy phenotypes and the neurodevelopmental impairment in the long-term outcome of patients with DEE has been infrequently analyzed. There are no longitudinal observational studies, no reliable biomarker predictors, and only a few published retrospective longitudinal data about single gene related disorders [5].

This single-center retrospective cohort analysis aimed to investigate the main clinical predictors of the neurodevelopmental and psychiatric outcome in genetically confirmed DEE.

#### 2. Patients and methods

Consecutive patients with a molecular genetic confirmed DEE referred to our Institution between 1997 and 2021 were considered eligible for the study (Supplementary Table 1, Fig. 1). All the eligible patients were mostly followed up by the authors MM, FM, GR, RB, CG and FP except for a few patients with a more prolonged epilepsy history who were under the care of other physicians during the onset phase of their illness.

Exclusion criteria included patients with DEE without a molecular genetic diagnosis and patients with identified non-genetic etiologies.

Medical records were retrospectively reviewed, and anonymized data were collected in a digital database, including demographic information, perinatal history, developmental milestones, onset, and evolution of seizures during the follow-up, length of the follow-up, predominant seizure types, occurrence of status epilepticus, age at the beginning of drug therapy and number of used lifetime antiseizure medications (ASMs). Response to ASMs was considered as a) full when seizure freedom or seizure reduction between 50 and 75 % was achieved; b) partial in case of seizure reduction between 25 and 50 %; c) lacking when seizure reduction was lower than 25 %). Furthermore, co-occurrence and severity of neurodevelopmental disorders, duration of epilepsy, age at molecular genetics diagnosis, and diagnostic delay (i.e., temporal span between the onset of symptoms and the molecular-genetic diagnosis) were considered.

Seizure freedom was defined according to ILAE criteria [8].

The EEG maturation/organization (e.g., consistency with the physiological age-related EEG structure), the presence of specific EEG pathological patterns at onset and during the follow-up (e.g., suppression burst, hypsarrhythmia, etc.), the distribution of the EEG abnormalities (scored as focal/multifocal or focal secondarily generalized/diffuse abnormalities), were also annotated data. [9–11].

EEG maturation/organization was qualitatively evaluated according to the age-related features of 21 criteria from the literature (Fig. 2). [10] It was reported as a dichotomic variable (adequate for age versus not adequate for age) and inserted in an ad-hoc data sheet (Fig. 2) resulting from clinical judgments and case-by-case discussions involving 6

authors (MM, FM, GR, RB, CG, and FP).

Neuroimaging and genetic features were also reviewed and collected (Supplementary Table 1).

Seizure types and epilepsy syndromes were classified according to the 2017 ILAE Commission for Classification and Terminology taxonomy [12,13].

Co-occurrent neurodevelopmental and psychiatric disorders were defined according to DSM-5 criteria [14].

Developmental profile was evaluated via DQ (Developmental Quotient) within Griffiths Scales of Child Development, Third Edition (Griffiths III) for children < 2 years and 6 months [15]. Global developmental delay was defined in patients under 6 years with impairment in two or more developmental domains [14].

Intellectual development was assessed using the IQ (Intelligence Quotient) score that was measured via specific age-related scales: a) Wechsler Preschool and Primary Scale of Intelligence-III edition (WPPSI-III) for children 2 years and six months-7 years and 2 months [16]; b) Wechsler intelligence scale for children III edition (WISC-III), and IV edition (WISC-IV) for children 6–16 years and 11 months [17,18]; d) Wechsler adult intelligence scale IV edition (WAIS-IV) for adults  $\geq$  17 years [19]; c) Leiter International Performance Scale – Third Edition (Leiter-3) for non-verbal children, adolescent and adult patients[20]. Patients older than 6 years with IQ < 70 were deemed with intellectual disability [14].

Executive functions were assessed by the Behavior Rating Inventory of Executive Function (BRIEF, preschool, children, adolescent, and adult versions) [21,22,23]. The questionnaire measures different aspects of executive function (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organise, Organisation of Materials, and Monitor). These scales combine to form two indexes [Behavior Regulation Index (BRI) and the Metacognition Index (MI)] and one composite summary score (Global Executive Composite, GEC) [21,22,23]. BRIEF T-scores greater than 65 were considered clinically significant for executive dysfunction [21-23]. Adaptive functioning was assessed as a standardized measure employing the Vineland Adaptive Behavior Scale- Second Edition (VABS-II) through a semi-structured parent interview [24]. The VABS-II consists of 11 subdomains grouped into four domain composites (Communication, Daily Living Skills, Socialization, and Motor Skills), with the domain composites used to derive the adaptive behavior composite [24]. VABS-II standard scores have a mean of 100 (standard deviation (SD)  $\pm$  15), with lower scores associated with greater impairment [24]. Emotional and behavioral profile was assessed by the Achenbach System of Empirically Based Assessments (ASEBA, Child Behavior Checklist (CBCL) for children 18 months-5 years and children 6-18 years, or the Adult Self Report) [25,26].

Each test mentioned above was performed during the follow-ups according to clinical needs and at the last clinical evaluation. The scores of the tests performed during the last follow-up were considered for the evaluation of long-term outcomes in patients who underwent multiple developmental assessments.

Genetic diagnoses were obtained through different methods



Fig. 1. Composition of the cohort: A) Age at the enrollment. B) Neurodevelopmental and psychiatric outcomes in patients with DEE in the herein-reported cohort.



**Fig. 2.** A) Comparison of neuropsychological profiles (mean values) between patients with delayed/lacking EEG maturation (EEG-) and the ones having adequately organized traces (EEG + ). B) Datasheet for the clinical judgment formulated about EEG maturation/organization across the different age ranges. LEGEND: AFA = Adequate for age; NAFA = Not adequate for age.

according to clinical suspects. Gene variants were classified according to the American College of Medical Genetics criteria [27].

All statistical analyses were conducted using IBM SPSS Statistics version 23.0 (SPSS Inc., Chicago, Illinois, USA). Normality was assessed with the Kolmogorov-Smirnov test. Correlation analyses were estimated by Spearman's correlation coefficient.

Comparisons were performed by independent sample *t*-test for continuous variables. The dimensional effect of clinical variables on outcome was evaluated by multivariate linear regression analysis. Four different regression analyses were performed to identify the variables that best predicted the clinical outcome. A stepwise method was applied with full IQ, VABS-II composite scores, BRIEF Global Executive Composite (GEC) score, and ASEBA Internalizing scale as dependent variables and age at the beginning of ASMs, duration of epilepsy, the number of ASMs, and delayed/lacking EEG maturation/organization as independent variables. A p-value < 0.05 represented statistical significance for all tests.

Written consent was obtained for all participants. The study was approved by the Ethics Committee of our Institution.

## 3. Results

## 3.1. Cohort composition and etiological diagnoses

Table 1, Fig. 1, and Suppl. 1 summarize the main demographic, clinical, and molecular genetic data of the 100 patients included in the study.

The mean duration of the clinical follow-up was  $10.46 \pm 8.37$  years (range 6 months-50 years). Thirty-four patients were followed up for less than 5 years, 22 patients between 5 and 10 years, and 44 participants for more than 10 years.

The presence of a neurodevelopmental disorder was assessed before the onset of epileptic seizures in 56 patients.

The mean age at the molecular genetic diagnosis was 6.95  $\pm$  5.52 years (age range 1 month-20 years) with a mean diagnostic delay of 4.22  $\pm$  4.94 years. These parameters were partially mediated by a cohort effect due to the progress of molecular genetics techniques over the analyzed wide time frame.

Monogenic diseases were present in 82 patients, while copy number variants were detected in 18 patients. (Table 2, Suppl. 1).

The most frequent diagnoses were represented by Angelman (n = 7), Rett (n = 6) and Fragile-X syndromes (n = 6).

Most of the single pathogenic variants involved genes encoding for regulators of the cellular cycle (26 patients) or modulators of synaptic transmission and cellular trafficking (26 patients); in comparison, channelopathies and inborn metabolism errors accounted for 14 and 10 patients (Table 2, Suppl. 1).

MRI was available for all participants, with 33 patients presenting neuroradiological abnormalities consistent with the etiological diagnosis, and only 3 patients had malformations with assessed epileptogenic potentials. In 8 patients, biochemical markers suggestive of the etiological diagnosis were detected (Suppl. 1).

## 3.2. Epilepsy phenotype

A well-codified epileptic syndrome was recognizable in 24 patients. The most frequent were Lennox-Gastaut (10 patients), Myoclonic-Atonic (6 patients), and Dravet (3 patients) syndromes. An evolution from Infantile Spasms to Lennox Gastaut syndrome was observed in 3 cases.

Focal epilepsies were mildly predominant, while a delayed EEG maturation/organization was observed in half of the cases (Table 1).

Response to ASMs was poor in most, and 66 participants were treated with more than two drugs (range 2–19) during their epilepsy history. Twenty-six patients had achieved complete seizure freedom at the last evaluation. The mean age at the achievement of seizure freedom was  $7.93 \pm 6.44$  years.

## 3.3. Developmental outcome

Table 1 and Suppl. 1 summarize the distribution of neurodevelopment and psychiatric disorders in the whole cohort.

Intellectual disabilities with different degrees of severity were assessed in more than 2/3 of patients (Table 1). Eighty-five patients and their parents completed the VABS-II, BRIEF questionnaire, and ASEBA scale.

Sixty-six patients were beyond normal cut-off value for clinically relevant symptoms on the composite score of the VABS-II (score = 42.80  $\pm$  16.18, range 20–70), while 83.5 % (71/85) presented executive dysfunction scores at the Global Executive Composite (GEC) of the BRIEF questionnaire (score = 78.62  $\pm$  9.65, range 65–105). Eight patients with GDD or mild ID fell within the borderline range (range 70–76) on the composite score of the VABS-II scale. Fourteen patients had normal or borderline cognitive scores with concurrent normal adaptive abilities. Among patients that were followed up for more than ten years, adaptive functions were more preserved in children than in adults (VABS-II Communication: 56.88  $\pm$  29.73 vs 39.11  $\pm$  18.44, p = 0.036; VABS-II Socialization: 58.12  $\pm$  27.81 vs 39.74  $\pm$  16.15, p = 0.019; VABS-II ABC: 53.01  $\pm$  28.25 vs 36.84  $\pm$  17.60, p = 0.044).".

#### Table 1

Demographic data and clinical features of all the recruited patients

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		PSYCHOSIS	2 patients

Legend. DDE = developmental and epileptic encephalopathies; ID = intellectual disability; ADHD = attention deficit hyperactivity disorder; LD = language disorder, ASD = autism spectrum disorder; DCD = developmental coordination disorder; LE. DI. = learning disorders; GAD = generalized anxiety disorder, DQ = developmental quotient, IQ = Intelligence Quotient.

Thirty-four patients revealed positive symptoms on at least one ASEBA subscale. In the group of participants who completed the ASEBA checklist, the overall agreement between psychiatric diagnosis assessed according to DSM-5 criteria and parent/self-reported data was 93 %.

Significant correlations were found between IQ scores and duration of epilepsy, delayed/lacking EEG maturation/organization, and the number of ASMs (Table 3). The VABS-II composite scores were correlated with the age at the epilepsy onset, the duration of epilepsy, the delayed/lacking EEG maturation/organization, and the number of ASMs (Table 3). The age at the epilepsy onset correlated with the BRIEF control subscale (r = -0.253; p = 0.031), the number of ASMs with the BRIEF Metacognition Index (MI) scores (r = 0.294, p = 0.012), while the delayed/lacking EEG maturation/organization with the BRIEF-MI and GEC scores (Table 3). Higher scores at BRIEF were negatively correlated with IQ scores [Inhibit (r = -0.219, p = 0.048); shift (r = -0.378, p <0.001); Initiate r = -0.448, p < 0.001); Plan/Organise (r = -0.302, p =0.006); Working Memory (r = -0.246, p = 0.026); Organization of Materials (r = -0.260, p = 0.026); Control (r = -0.351, p = 0.002); Behavior Regulation Index (r = -0.233, p = 0.048); Metacognition Index (r = -0.430, p < 0.001); Global Executive Composite (r = -0.401, p < 0.001).

The Anxiety and ADHD subscales of the ASEBA test were correlated with the delayed/lacking EEG maturation/organization (r = -0.220 and r = 0.233) (Table 3).

Finally, Internalizing and Anxiety subscales (respectively, r = 0.265, p = 0.016; r = 0.272, p = 0.013) correlated with the age at the beginning of ASM therapy.

Lower IQ/DQ was observed in the group with generalized epilepsy (n = 25) compared to those with focal epilepsy ( $39.60 \pm 17.54$  vs.  $49.48 \pm 21.94$ , p = 0.027).

Patients with delayed/lacking EEG maturation/organization (n = 50) performed significantly worse than those having adequately organized background EEG activity (n = 50) regarding the IQ, VABS-II composite score, BRIEF-Shift/Initiate/Control/MI/GEC subscales, and ASEBA-ADHD subscale (Table 3).

No significant differences in cognitive, adaptive, and emotional profiles were assessed between patients carrying focal interictal EEG abnormalities and those with generalized EEG discharges at the onset of epilepsy. No relevant differences in the same outcome measures were found in the comparison between patients who received the diagnosis of epilepsy before the diagnosis of neurodevelopmental disorders and patients in which the diagnosis of neurodevelopmental disorders preceded the onset of epilepsy (*t*-test: IQ/DQ =  $51.59 \pm 24.48 \text{ vs } 43.41 \pm 17.79$ , p = 0.066; VABS-II ABC =  $55.69 \pm 27.49 \text{ vs } 49.38 \pm 20.89$ , p = 0.251; BRIEF GEC =  $71.84 \pm 13.03 \text{ vs } 76.44 \pm 14.27$ , p = 0.136).

Patients who experienced status epilepticus had lower scores at the VABS-II compared to the others (communication scale =  $45.03 \pm 23.18$  vs  $56.29 \pm 24.43$ , p = 0.043; daily living scale =  $43.53 \pm 25.34$  vs  $56.74 \pm 23.48$ , p = 0.025, and composite score =  $44.10 \pm 24.04$  vs  $55.84 \pm 23.13$ , p = 0.036).

Four different regression analyses were performed to identify the clinical features that best predicted clinical outcomes. A stepwise method was applied with full IQ, BRIEF Global Executive Composite (GEC), VABS-II Adaptive Behaviour Composite (ABC), and ASEBA Internalizing scale scores as dependent variables, and the age at seizure onset, age at treatment onset, the occurrence of status epilepticus, duration of epilepsy, delayed/lacking EEG maturation/organization, predominant seizure types, and the number of used antiseizure medications as independent variables.

The delayed/lacking EEG maturation/organization was significantly correlated with the IQ ( $R^2 = 0.252$ , p < 0.001) and the BRIEF GEC variability ( $R^2 = 0.042$ , p = 0.036). Furthermore, the delayed/lacking EEG maturation/organization and the duration of epilepsy were significantly correlated with the VABS-II ABC score ( $R^2 = 0.455$ , p = 0.005). Lastly, the age at treatment onset contributed to ASEBA Internalizing score variability ( $R^2 = 0.058$ , p = 0.030). The Variance Inflation Factor (VIF) was computed for any potential predictor to assess correlation

## Table 2

Pathogenic variants detected in the clinical sample.

Disease cluster	ID	Gene/Disease	Genotype and Genetic Aberration	Disease cluster	ID	Gene/Disease	Genotype and Genetic Aberration
Cell cycle regulation and	1	UNC80	c.[1513C > T];[ 3899del]/p. [Arg505Ter];[Ala1300ProfsTer26]	Copy Number Variation and	51	Trisomy 21	47,XX,+21
signal	2	CDKL5/Rett	c.[587C > T];[=]/p.[Ser196Leu];[=]	chromosome	52	Angelman	abnormal methylation of
transduction disorder :		syndrome CDKL5	c.[551 T > A];[=]/ p.[Leu184His];[=]	disorders	53	syndrome Angelman syndrome	15q11 - q13 maternal PWS-AS region deletion [15q11.2–11.3 deletion]
	4	CDKL5	c.[146-?_320+?del]; [=]		54	Angelman syndrome	uniparental disomy of chromosome 15011-013
	5	CDKL5/Rett syndrome	c.[125A > G];[=]/p.[Lys42Arg];[=]		55	Angelman syndrome	15q11-q13 deletion
	6	KMT2E	c.[2434delT];[=]/p.[Ser812Leufs*9];		56	Angelman	uniparental disomy of
	7	MECP2/Rett	c.[445C > G];[=]/p.[Pro152Arg];[=]		57	Angelman	uniparental disomy of
	8	MECP2/Rett	Xq28 [chrX:153,101,077–153,713,921] x2		58	Angelman	15q11.2-q13 deletion
	9	MECP2/Rett	c.[803delG];[=]/p.[Val288Ter];[=]	Inborn error of metabolism	59	ADSL	c.[65C > T]; [340 T > C]/p. [Ala22Val]:[Tvr114His]
	10	MECP2/Rett syndrome	c.[979_1216del1239ins24];[=]	incurbonsin	60	ALDH5A1/4- hydroxybutyric	c.[278G > T]; [526G > A]/ p.[Cys93Phe];[Gly176Arg]
	11	NF1/ Neurofibromatosis	c.[7846C > T];[=]/p.[Arg2616Ter];[=]		61	DHPR	c.[547delG];[547delG]; [=]/p.[Val183LeufsTer7]; [Val183LeufsTer7]
	12	NPRL3	c.[1270C > T];[=]/p.[Arg424Ter];[=]		62	DHPR	c.[41 T > C];[41 T > C]/p.
	13	NPRL3	c.[1215G > C];[=]/p.[Gln405His];[=]		63	GAMT	c.[491dup];[460-3C > G]/ p [Val165ArgfsTer26]:[2]
:		NPRL3	c.[1270C > T];[=]/p.[Arg424Ter ];[=]		64	PAH/ Phenylketonuria	c.[1222C > T];[1222C > T]/p.[Arg408Trp]; [Arg408Trp]
	15	PTEN	c.[1003C > T];[=]/p.[Arg335Ter];[=]		65	PAH/ Phenvlketonuria	c.[781C > T];[1315 + 1G > A]/p.[Arg261Ter]:[?]
	16	PTEN/Cowden syndrome	c.[424C > T];[=]/p.[Arg142Trp];[=]		66	PAH/ Phenylketonuria	c.[653G > T];[1222C > T]/ p.[Gly218Val]; [Arg408Trp]
	17	FOXG1	c.[946del];[=]/p.[Leu316CysfsTer10]; [=]		67	PNPO	c.[347G > A];[347G > A]/ p.[Arg114Gln];[=]
	18	FOXG1	c.[969delC];[=]/p.[Ser323ArgfsTer3]; [=]		68	LHON	m.14484 T > C/p.Met64Val
	19	CAMK2	c.[416C > T];[=]/p.[Pro139Leu];[=]	Synaptopathies and Trafficking disease	69	FMR1/Fragile X syndrome	c128GGC[>200]
	20	CHD2	c.[561del];[=]/p.[Lys188AsnfsTer61]; [=]		70	FMR1/Fragile X syndrome	c128GGC[>200]
	21	CHD2	c.[1562C > A];[=]/p.[Ser521Ter];[=]		71	FMR1/Fragile X syndrome	c128GGC[>200]
	22	CHD2	c.[2698C > G];[=]/p.[Arg900Gly];[=]		72	FMR1/Fragile X syndrome	c128GGC[>200]
	23	HECTD4	c.[4903C > T];[11992G > A]/p. [Arg1635Trp];[Val3998Met]		73	FMR1/Fragile X syndrome	c128GGC[>200]
	24	HECTD4	c.[4903C > T];[11992G > A]/p. [Arg1635Trp];[Val3998Met]		74	FMR1/Fragile X syndrome	c128GGC[>200]
	25	PHF21A	c.[1027C > T];[=]/p.[Gln343Ter];[=]		75	DNM1	c.[993-2A > G];[=]
Channelonathios	26	PIGQ	c.[1A > G];[=]/p.[?];[=]		76	GRIN1	c.[1643G > A];[=]/p. [Arg548Gln];[=] a [2502C > T]:[-1/p
Channelopathies	27	KONH1 /	[Tyr1483ThrfsTer27];[=]		70	CDIN2A	[Arg865Cys];[=]
	20	Zimmermann	c.[1054C > G],[=]/p.[Leu552vai],[=]		78	GRINZA	[Cys87Ter]; [=]
	29	KCNH1/ Zimmermann	c.[1405G > A];[=]/p.[Gly469Arg];[=]		79	GRIN2A	c.[261C > A];[=]/p. [Cys87Ter];[=]
	30	KCNMA1	c.[2855A > G];[=]/p.[Asn952Ser];[=]		80	GRIN2A	c.[1784dup];[=]/p.
	31	KCNMA1	c.[2855A > G];[=]/p.[Asn952Ser];[=]		81	IQSEC2	c.[854del];[0]/p.
Channelopathies	32	KCNQ2	c.[629G > C];[=]/p.[Arg210Pro];[=]	Synaptopathies and Trafficking disease	82	IQSEC2	c.[4110_41111del];[=]/p. [Tvr1371GlnfsTer151·[-]
	33	KCTD7	c.[533C > T];[533C > T]/ p. [Ala178Val];[Ala178Val]		83	PRRT2	16p11.2 deletion [gene deletion]

(continued on next page)

Disease cluster	ID	Gene/Disease	Genotype and Genetic Aberration	Disease cluster	ID	Gene/Disease	Genotype and Genetic Aberration
	34	SCN1A	c.[4814A > T];[=]/p.[Asn1605Ile];[=]		84	PRRT2	c.[649dup];[=]/p. [Arg217ProfsTer8]:[=]
	35	SCN1A	c.[4907G > A];[=]/p.[Arg1636Gln];		85	PRRT2	c.[649dupC];[=]/p. [Arg217ProfsTer8]:[-]
	36	SCN1A	c.[431 T > C];[=]/ p.[Phe144Ser];[=]		86	SHANK3	c.[3637dupC];[=]/p. [His1213ProfsTer83];[=] + EBF3: c.[379_383 del]; [=]/p.[Tyr127SerfsTer38]; [=]
	37	SCN2A	c.[408G > A];[=]/p.[Met135Ile];[=]		87	STPXBP1	c.[1652C > A];[=]/p. [Arg551Hys];[=]
	38	SCN2A	c.[781 G > A];[=]/p.[Val261Met];[=]		88	STXBP1	c.[316_318del];[=]/p. [Phe106del];[=]
	39	SCN8A	c.[3563G > A];[=]/p.[Arg1188Gln]; [=]		89	SYNGAP1	c.[1352 T > A];[=]/p. [Leu451Gln];[=]
	40	GABRB3	c.[146A > G];[=]/p.[Asp49Gly];[=]		90	SYNGAP1	c.[1167del];[=]/p. [Gly391AlafsTer129];[=]
Copy Number Variation and chromosome	41	15q13.3 microdeletion syndrome	15q13.1q13.3 [Chr15:28958779–32446830]x1		91	SYNGAP1	c.[3706C > T];[=]/p. [Gln1236Ter];[=]
disorders	42	15q15.2q15.3 microduplication	15q15.2q15.3 [chr15:43166300-43688916]x3		92	PACS1	c.[607C > T];[=]/p. [Arg203Trp]:[=]
	43	16p11.2 microdeletion syndrome	16p11.2 [Chr16:29609368–30188030] x1		93	PRICKLE1	c.[820G > A];[820G > A]/ p.[Ala274Thr]; [Ala274Thr]
	44	16p11.2 microduplication syndrome	16p11.2 [Chr16:29591078–30172575] x3		94	TRAPPC9	c.[2851-2A > C];[=]/p. [Thr951TyrfsTer17];[=]
	45	22q11.2del∕ DiGeorge syndrome	22q11.2 deletion	Transportopathies	95	ATP1A3	c.[2324C > G];[=]/p. [Pro775Arg];[=]
	46	2p13.3p12 deletion	2p13.3p12 [Chr2:71046480–76510194]x1		96	SLC2A1/GLUT1 deficiency syndrome	c.631C > T(;)=/p. Pro211Ser(;)=
	47	2q24 deletion syndrome	2q24.3q31.1 [Chr2:164375953–170535670]x1		97	SLC2A1/GLUT1 deficiency syndrome	c.[470dup];[=]/p. [Thr158HisfsTer79];[=]
	48	Distal 10q trisomy syndrome	10q26.11q26.3 duplication		98	SLC2A1	c.[940G > A];[=]/p. [Gly314Ser];[=]
	49	Xq28 syndrome	Xq28[chrX:153,566,595–153,626,738] x2; Xq28 [chrX:153,629,413–153,783,168]x3; Xq28[chrX:153,815,416–154,929,486] x2		99	SLC2A1	c.[998G > A];[=]/p. [Arg333Gln];[=]
	50	Xq28 microduplication syndrome	Xq28 microduplication		100	SLC13A5	c.[15_19delGAGCT];[=]/p. [SerCysfsTer134];[=]

among independent variables. All predictor variables had VIF < 3, suggesting the absence of relevant multicollinearity.

## 4. Discussion

The clinical portrait of the reported cohort strengthened some data that emerged in the recent literature of DEE: different etiologies, the predominance of focal seizures, the occurrence of status epilepticus in more than 30 % of patients, drug resistance as the main hallmark and trend to the resolution of epilepsy over time in up to one-fourth of the cases [5,28].

This study highlighted that six seizure-related variables might significantly influence the mental development, neurocognitive, emotional, and behavioral functioning in patients with genetic DEE. Namely, age at seizure-onset, EEG maturation/organization, duration of epilepsy, the occurrence of status epilepticus, age at the introduction of ASMs and the number of ASMs used.

Earlier age at seizure onset was less significantly correlated with lower IQ than with worst VABS-II scores (that depended on the whole contribution of intellectual functioning, executive functions, and the presence of a psychiatric disorder). Other previous studies had evidenced stronger correlations between this clinical predictor and lower IQ scores in patients with less severe idiopathic and uncomplicated

epilepsies [29,30]. These combined data might suggest that a more compromised adaptive functioning might represent a more relevant outcome marker in DEEs than in epilepsies with no associated developmental impairment. Early age at seizure onset has already been highlighted as a predictor of poor developmental functioning in cohorts of patients with Tuberous Sclerosis Complex or infantile spasms of varying etiologies but also in more heterogeneous cohorts, including severe drug-resistant epilepsies [31-34]. The analysis of our cohort suggests that an early seizures onset might interfere with the emergence of inhibitory control abilities in a significant proportion of patients, confirming that executive functions represent a vulnerable cognitive domain in children with epilepsy since their impairment has been reported in 25-66 % of the patients [35-39]. The main reason for this vulnerability is probably represented by the lack of functional specialization of the cortical and subcortical networks involving the mesial prefrontal, temporo-parietal cortices, and other extra-frontal areas in the earlier ages [39,40,41]. Furthermore, recent experimental studies in brain slices of mice neocortex provided data confirming that early life seizures result in permanent changes in cortical network dynamics persisting into adulthood [40]. In these studies, pentylenetetrazol (PTZ)induced seizures resulted in a higher spontaneous network activity (called "Up states" and mirroring neuronal hyper-excitability) when the epileptogenic stimulus was administered in earlier developmental stages

#### Table 3

Spearman r correlations between clinical predictors, and neuropsychological performance.

IO         r = 0.132         r = 0.234         r = 0.537         r = 0.014*         r = 0.033         r = 0.139           BRUEF         p = 0.131         p = 0.019*         p < 0.001**		Age at the onset of epilepsy (months)	Duration of epilepsy (months)	Delayed/lacking EEG maturation	N° of antiseizure medications	Age at the beginning of drug therapy	Occurrence of status epilepticus
RURF $p = 0.0131$ $p = 0.019^{\circ}$ $p < 0.001^{\circ \circ}$ $p = 0.0031^{\circ \circ}$ $p = 0.003$ $p = 0.0031^{\circ \circ}$ Inhibit $r = 0.042$ $r = 0.010$ $r = 0.229$ $r = 0.058$ $r = 0.011$ $r = 0.058$ Shif $r = 0.151$ $r = 0.229$ $r = 0.022$ $r = 0.011$ $r = 0.044$ $r = 0.035$ Emotional Control $r = 0.013$ $r = 0.028$ $r = 0.011$ $r = 0.048$ $r = 0.012$ $r = 0.012$ $r = 0.012$ $r = 0.013$ $r = 0.018$ Behavior Regulation $r = 0.035$ $r = 0.013$ $r = 0.013$ $r = 0.017$ $r = 0.013$ $r = 0.013$ $r = 0.013$ $r = 0.013$ $r = 0.018$	10	r = 0.152	r = -0.234	r = 0.587	r = -0.414	r = 0.053	r = -0.138
BRUEFiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiii<i<i<i<i<i<i<i<i<i<i<i<i<i<i	-4	p = 0.131	$p = 0.019^*$	p < 0.001**	$p < 0.001^{**}$	p = 0.603	p = 0.170
Inhibitr = 0.042r = 0.010r = 0.239r = 0.050r = 0.714r = 0.058Sintr = 0.131r = 0.247r = 0.036r = 0.111r = -0.048r = 0.034Emotional Controlr = 0.013r = 0.025p = 0.0099*p = 0.522p = 0.669p = 0.773Emotional Controlr = 0.031r = 0.013r = 0.128r = 0.121r = 0.126p = 0.673Behavior Regulationr = 0.038r = 0.138r = 0.022p = 0.668p = 0.674Initizr = 0.037r = 0.132r = 0.024p = 0.616p = 0.484p = 0.364Initizr = 0.207r = 0.137r = 0.010*p = 0.149p = 0.216Working Memoryr = 0.021r = 0.013r = 0.010*p = 0.129p = 0.439Plan/Organiser = 0.012r = 0.013r = 0.010*p = 0.229p = 0.439Plan/Organiser = 0.016r = 0.029p = 0.229p = 0.439p = 0.127Plan/Organiser = 0.016r = 0.030r = 0.137r = 0.012*p = 0.029p = 0.326Organization ofr = 0.016r = 0.030*p = 0.022*r = 0.127p = 0.037Metradayp = 0.065p = 0.017*r = 0.136r = 0.137r = 0.136r = 0.127Metradayp = 0.069p = 0.127r = 0.137r = 0.136r = 0.137r = 0.137Metradayp = 0.069p = 0.012*p = 0.012*p = 0.012*p = 0.013*p = 0.013*Metradayp = 0.069p = 0.012*p = 0.012*<	BRIEF	r	I	I	I	r	r
shiftp = 0.705p = 0.929p = 0.038'p = 0.580p = 0.71p = 0.607Shiftr = 0.131r = 0.011r = 0.014r = 0.018p = 0.322p = 0.669p = 0.73Endotand Lottelr = 0.013r = 0.018'r = 0.012r = 0.124r = 0.018p = 0.874Behavior Regularr = 0.088r = 0.133r = 0.131r = 0.060r = 0.083r = 0.134Indexp = 0.457p = 0.262p = 0.616p = 0.484p = 0.344Inditater = 0.071r = 0.171r = 0.147r = 0.010p = 0.161p = 0.783p = 0.271p = 0.013p = 0.013p = 0.171r = 0.147Varing Morrowp = 0.073p = 0.216p = 0.043p = 0.013p = 0.011r = 0.017p = 0.732p = 0.033r = 0.137r = 0.013p = 0.043p = 0.142p = 0.012P = 0.733p = 0.031r = 0.013r = 0.013p = 0.026p = 0.012p = 0.037P = 0.212p = 0.033r = 0.127p = 0.012p = 0.026p = 0.012p = 0.012Matrialisp = 0.089p = 0.012p = 0.026p = 0.012p = 0.012p = 0.012Matrialisp = 0.031p = 0.031r = 0.037p = 0.012p = 0.012p = 0.012Matrialisp = 0.012p = 0.012p = 0.012p = 0.012p = 0.012p = 0.012Matrialisp = 0.012r = 0.013r = 0.013p = 0.012p = 0.012p = 0.012Matrialisp = 0.012p	Inhibit	r = -0.042	r = -0.010	r = -0.229	r = 0.062	r = 0.041	r = 0.058
Shift $r = 0.151$ $r = 0.277$ $r = 0.287$ $r = 0.011$ $r = -0.669$ $r = 0.034$ Enoriand $r = 0.013$ $r = 0.045$ $r = 0.021$ $r = 0.124$ $r = 0.021$ $r = 0.026$ Behavior Regulation $r = 0.085$ $r = 0.322$ $P = 0.652$ $P = 0.674$ Behavior Regulation $r = 0.087$ $P = 0.022$ $P = 0.052$ $P = 0.026$ $P = 0.074$ Indica $r = 0.087$ $P = 0.222$ $P = 0.022$ $P = 0.052$ $P = 0.034$ $P = 0.034$ Indita $r = 0.207$ $r = 0.137$ $r = 0.010^{\circ}$ $P = 0.149$ $P = 0.374$ Parto Signa $r = 0.037$ $r = 0.017^{\circ}$ $P = 0.010^{\circ}$ $P = 0.210$ $P = 0.010^{\circ}$ Parto Signa $r = 0.033$ $r = 0.017^{\circ}$ $P = 0.029$ $P = 0.239$ $P = 0.210$ Parto Signa $r = 0.013$ $r = 0.013^{\circ}$ $P = 0.029$ $P = 0.259$ $P = 0.439$ Parto Signa $r = 0.016$ $r = 0.013^{\circ}$ $P = 0.029$ $P = 0.259$ $P = 0.259$ Parto Signa $r = 0.016^{\circ}$ $P = 0.028^{\circ}$ $P = 0.028^{\circ}$ $P = 0.029$ $P = 0.259$ Parto Signa $r = 0.016^{\circ}$ $P = 0.037^{\circ}$ $P = 0.012^{\circ}$ $P = 0.019^{\circ}$ $P = 0.271$ Parto Signa $r = 0.016^{\circ}$ $P = 0.013^{\circ}$ $P = 0.013^{\circ}$ $P = 0.013^{\circ}$ $P = 0.013^{\circ}$ Composite $P = 0.016^{\circ}$ $P = 0.037^{\circ}$ $P = 0.013^{\circ}$ $P = 0.013^{\circ}$ $P = 0.013^{\circ}$ Composite $P = 0.016^{\circ}$ $P = 0.037^{\circ}$ $P = 0.013^{\circ}$		p = 0.705	p = 0.929	p = 0.038*	p = 0.580	p = 0.714	p = 0.607
p = 0.177p = 0.025"p = 0.009"p = 0.322p = 0.669p = 0.763Emotional Cartonir = 0.013r = 0.013r = 0.012r = 0.013r = 0.013P = 0.955P = 0.681P = 0.821P = 0.660r = 0.083r = 0.133P = 0.978P = 0.242P = 0.616P = 0.874P = 0.364IndicatP = 0.477P = 0.249P = 0.161P = 0.171r = 0.134P = 0.078P = 0.272P < 0.011"	Shift	r = -0.151	r = 0.247	r = -0.286	r = 0.111	r = -0.048	r = 0.034
Emotional Control $r = 0.013$ $r = 0.045$ $r = 0.018$ $r = 0.026$ $r = 0.0263$ $r = 0.087$ Behavior Regulation $r = 0.087$ $r = 0.133$ $r = 0.137$ $r = 0.060$ $r = 0.083$ $r = 0.087$ Index $p = 0.047$ $p = 0.012$ $p = 0.016$ $p = 0.0263$ $p = 0.0263$ $r = 0.037$ Initia $r = 0.207$ $r = 0.129$ $r = 0.017$ $r = 0.010^{110}$ $p = 0.147$ $r = 0.017$ $r = 0.037$ Working Memory $r = 0.027$ $r = 0.027$ $p = 0.010^{110}$ $p = 0.012^{110}$ $p = 0.012^{110}$ $p = 0.017^{110}$ $r = 0.037$ Plan/Organize $r = -0.137$ $r = -0.173$ $r = 0.264^{110}$ $p = 0.026^{110}$ $p = 0.026^{110}$ $p = 0.027^{110}$ $p = 0.027^{110}$ Organization of $r = 0.018$ $r = 0.018^{110}$ $p = 0.017^{110}$ $p = 0.017^{110}$ $p = 0.017^{110}$ $p = 0.017^{110}$ Control $r = 0.033$ $r = 0.020$ $p = 0.026^{110}$ $p = 0.017^{110}$ $p = 0.017^{110}$ $p = 0.017^{110}$ Control $r = 0.031^{110}$ $r = 0.031^{110}$ $p = 0.017^{110}$ $p = 0.018^{110}$ $p = 0.021^{110}$ Materials $p = 0.000^{1110}$ $p = 0.017^{110}$ $p = 0.017^{110}$ $p = 0.018^{110}$ $p = 0.021^{110}$ Control $r = 0.018^{110}$ $r = 0.017^{110}$ $r = 0.018^{110}$ $p = 0.017^{110}$ $p = 0.018^{110}$ Control $r = 0.013^{110}$ $r = 0.013^{110}$ $r = 0.021^{110}$ $p = 0.018^{110}$ $p = 0.018^{110}$ Control $r = 0.013^$		p = 0.177	p = 0.025*	p = 0.009**	p = 0.322	p = 0.669	p = 0.763
p = 0.905p = 0.688p = 0.282p = 0.865p = 0.874Behavior Regulationr = 0.088r = 0.137r = 0.060r = 0.083r = 0.108Indexp = 0.457p = 0.222p = 0.249p = 0.616p = 0.484p = 0.364Initiater = 0.078p = 0.277p = 0.011**p = 0.010*p = 0.147r = 0.330r = 0.147r = 0.331r = 0.078p = 0.216p = 0.078p = 0.216p = 0.078p = 0.216p = 0.078p = 0.231r = 0.078p = 0.221p = 0.078p = 0.231r = 0.177r = 0.246r = 0.013r = 0.127p = 0.032p = 0.321p = 0.031p = 0.031*p = 0.012*p = 0.062*p = 0.55*Metacognition Indexr = 0.361r = 0.374r = 0.033*r = 0.031*p = 0.012*p = 0.024*p = 0.024*p = 0.024*p = 0.024*p = 0.024* <t< td=""><td>Emotional Control</td><td>r = 0.013</td><td>r = 0.045</td><td>r = -0.118</td><td>r = 0.021</td><td>r = 0.124</td><td>r = 0.018</td></t<>	Emotional Control	r = 0.013	r = 0.045	r = -0.118	r = 0.021	r = 0.124	r = 0.018
Behavior Regulation $r = -0.088$ $r = 0.133$ $r = -0.137$ $r = 0.081$ $r = 0.084$ $r = 0.084$ $r = 0.084$ $r = 0.084$ Initiat $r = -0.207$ $r = 0.017*$ $r = 0.010*$ $r = -0.171$ $r = 0.147$ Working Memory $r = -0.130$ $r = -0.010*$ $r = -0.073$ $r = -0.073$ $r = -0.071$ $r = 0.087$ Plan/Organise $r = -0.137$ $r = 0.017*$ $r = 0.069$ $p = 0.226$ $r = 0.037$ Organization of $r = 0.016$ $r = 0.017$ $r = 0.017$ $r = 0.017$ $r = 0.017$ Organization of $r = 0.016$ $r = 0.017$ $r = 0.035$ $r = 0.216$ $r = 0.228$ Organization of $r = 0.016$ $p = 0.024$ $p = 0.071*$ $p = 0.073$ Metacognition Intex $p = 0.021*$ $p = 0.088$ $p = 0.021*$ $p = 0.052$ $p = 0.554$ Global Excertive $r = 0.187$ $p = 0.037*$ $p = 0.012*$ $p = 0.053$ $r = 0.285$ Metacognition Intex $p = 0.037*$ $p = 0.037*$ $p = 0.012*$ $p = 0.564$		p = 0.905	p = 0.688	p = 0.282	p = 0.852	p = 0.265	p = 0.874
Index $p = 0.457$ $p = 0.262$ $p = 0.249$ $p = 0.516$ $p = 0.484$ $p = 0.364$ Initiate $p = 0.078$ $p = 0.277$ $p = 0.010^{14}$ $p = 0.010^{14}$ $p = 0.149$ $p = 0.216$ Working Memory $r = 0.032$ $r = 0.033$ $r = 0.010^{14}$ $p = 0.013^{14}$ $r = 0.043$ $r = 0.047$ Plan/Organise $r = 0.137$ $r = 0.120$ $p = 0.629$ $p = 0.259$ $p = 0.439$ Plan/Organise $r = 0.016$ $r = 0.060$ $r = 0.120$ $p = 0.026^{14}$ $p = 0.029$ $p = 0.256$ Organization of $r = 0.016$ $r = 0.060$ $r = -0.137$ $r = 0.026^{14}$ $p = 0.073$ $r = 0.211$ Materials $p = 0.086$ $p = 0.012$ $p = 0.073$ $r = 0.018^{14}$ $r = 0.228$ Materials $p = 0.069$ $p = 0.072$ $p = 0.003^{1+7}$ $p = 0.018^{14}$ $r = 0.228$ Metacognition Index $r = -0.010$ $r = 0.217$ $p = 0.013^{1+7}$ $p = 0.032^{1+7}$ $r = 0.018^{1+7}$ $p = 0.053$ Metacognition Index $r = -0.102$ $r = 0.017^{14}$ $p = 0.013^{1+7}$ $p = 0.033^{1+7}$ $r = 0.012^{1+7}$ $p = 0.053$ Composite $p = 0.001^{1+7}$ $p = 0.031^{1+7}$ Composite $p = 0.001^{1+7}$ $p = 0.018^{1+7}$ $p = 0.011^{1+7}$ $p = 0.013^{1+7}$ $p = 0.012^{1+7}$ $p = 0.053$ Metacognition Index $r = 0.162$ $r = 0.187$ $r = 0.187$ $r = 0.047^{1+7}$ $p = 0.0012^{1+7}$ <td>Behavior Regulation</td> <td>r = -0.088</td> <td>r = 0.133</td> <td>r = -0.137</td> <td>r = 0.060</td> <td>r = 0.083</td> <td>r = 0.108</td>	Behavior Regulation	r = -0.088	r = 0.133	r = -0.137	r = 0.060	r = 0.083	r = 0.108
	Index	p = 0.457	p = 0.262	p = 0.249	p = 0.616	p = 0.484	p = 0.364
p = 0.078p = 0.277p < 0.001*p = 0.101*p = 0.149p = 0.216Working Memoryp = 0.363p = 0.769p = 0.010p = 0.049r = 0.071r = 0.037Plan/Organiser = 0.137r = 0.167r = 0.029p = 0.529p = 0.439Plan/Organiser = 0.016r = 0.016r = 0.017r = 0.026p = 0.029p = 0.221Organization ofr = 0.016r = 0.060r = -0.137r = 0.035r = 0.15r = 0.120Materialsp = 0.969p = 0.021p = 0.021p = 0.071p = 0.011p = 0.073Controlr = 0.031*p = 0.038p = 0.032*r = 0.407r = -0.168r = 0.228Metacognition Indexr = 0.018*p = 0.032*p = 0.001**p = 0.012*p = 0.629p = 0.654Global Executiver = -0.102r = 0.137r = -0.294r = -0.063r = 0.053r = 0.053Metacognition Indexr = 0.372p = 0.03**p = 0.012*p = 0.063*r = 0.053r = 0.053Compositer = 0.361p = 0.03*p = 0.03**p = 0.012*p = 0.03*p = 0.03*p = 0.03*Ording Ising Skillsr = 0.355r = 0.371r = 0.464r = 0.152r = 0.287r = 0.287Po .001**p = 0.001**p < 0.001**	Initiate	r = -0.207	r = 0.129	r = -0.417	r = 0.300	r = -0.171	r = 0.147
Working Memory $r = 0.012$ $r = 0.033$ $r = 0.013$ $r = 0.071$ $r = 0.087$ Plan/Organise $r = 0.137$ $r = 0.187$ $r = 0.173$ $r = 0.036$ $p = 0.529$ $p = 0.420$ Organization of $r = 0.016$ $r = 0.006$ $p = 0.120$ $p = 0.026$ $p = 0.929$ $p = 0.221$ Organization of $r = 0.016$ $r = 0.016$ $r = 0.016^{+}$ $p = 0.929$ $p = 0.221$ Materials $p = 0.896$ $p = 0.615$ $p = 0.127$ $r = 0.026^{+}$ $r = 0.015^{+}$ $r = 0.211$ Materials $p = 0.896$ $p = 0.615$ $p = 0.342$ $r = 0.407$ $r = 0.168$ $r = 0.228$ $p = 0.031^{+}$ $p = 0.031^{+}$ $p = 0.031^{+}$ $p = 0.031^{+}$ $p = 0.318$ $r = 0.375$ $r = 0.294$ $r = 0.006^{+}$ $p = 0.031^{+}$ $p = 0.031^{+}$ $p = 0.031^{+}$ $p = 0.031^{+}$ $p = 0.361$ $r = 0.375$ $r = 0.221$ $r = 0.363$ $r = 0.53$ $p = 0.031^{+}$ $p = 0.012^{+}$ $p = 0.031^{+}$ $p = 0.031^{+}$ $p = 0.031^{+}$ $p = 0.03^{+}$ $p = 0.53$ $p = 0.53$ $p = 0.400$ $p = 0.72$ $p = 0.031^{+}$ $p = 0.012^{+}$ $p = 0.032^{+}$ $p = 0.53$ $p = 0.53$ $commanication$ $r = 0.355$ $r = 0.374$ $r = 0.470$ $r = 0.235$ $r = 0.251$ $commanication$ $r = 0.355$ $r = 0.379$ $r = 0.644$ $r = 0.162$ $r = 0.231$ $r = 0.261$ $r = 0.011^{+}$ $p = 0.001^{++}$ $p < 0.001^{++}$ $p < 0.001^{++}$ $p = 0.001^{++}$ $p $		p = 0.078	p = 0.277	p < 0.001**	p = 0.010*	p = 0.149	p = 0.216
$n_{1}$ $p = 0.363$ $p = 0.769$ $p = 0.210$ $p = 0.699$ $p = 0.529$ $p = 0.439$ Plan/Organise $r = 0.137$ $r = 0.017$ $r = 0.010$ $r = 0.010$ $r = 0.017$ $p = 0.221$ $p = 0.093$ $p = 0.026^{\circ}$ $p = 0.929$ $p = 0.256$ Organization of $r = 0.016$ $r = 0.060$ $r = -0.137$ $r = 0.035$ $r = 0.112$ Materials $p = 0.896$ $p = 0.615$ $p = 0.724$ $p = 0.073$ $r = 0.211$ Control $r = -0.233$ $r = 0.201$ $r = -0.342$ $r = 0.407$ $r = -0.168$ $r = 0.228$ Control $r = -0.323$ $r = 0.221$ $p = 0.002^{**}$ $p = 0.012^{**}$ $p = 0.052$ $p = 0.652$ Metacognition Index $r = -0.100$ $r = 0.137$ $r = 0.294$ $r = -0.168$ $r = 0.053$ Metacognition Index $r = -0.102$ $r = 0.177$ $p = 0.012^{**}$ $p = 0.053$ $r = 0.654$ Global Executive $r = 0.117$ $p = 0.031^{**}$ $p = 0.031^{**}$ $p = 0.031^{**}$ $p = 0.053$ $r = 0.590$ Composite $p = 0.361$ $p = 0.03^{**}$ $p < 0.001^{**}$ $p < 0.001^{**}$ $p = 0.033^{**}$ $p = 0.020^{**}$ Daily Living Skills $r = 0.355$ $r = 0.379$ $r = 0.644$ $r = 0.470^{**}$ $r = 0.235$ $r = 0.294$ Daily Living Skills $r = 0.367$ $r = 0.563$ $r = -0.644$ $r = 0.185$ $r = 0.020^{**}$ Daily Living Skills $r = 0.367$ $r = 0.0563$ $r = -0.646$ $r = 0.222$ $r = 0.026^{**}$ Dail	Working Memory	r = -0.102	r = -0.033	r = -0.140	r = 0.043	r = -0.071	r = 0.087
$\begin{split} & \text{Plan}(Organise & r = -0.137 & r = 0.187 & r = -0.173 & r = 0.246 & r = -0.010 & r = 0.127 \\ & p = 0.021 & p = 0.003 & p = 0.120 & p = 0.025 & p = 0.929 & p = 0.226 \\ & \text{Organization of} & r = 0.016 & r = 0.060 & r = -0.137 & r = -0.035 & r = 0.155 & r = 0.211 \\ & \text{Mattrials} & p = 0.896 & p = 0.615 & p = 0.249 & p = 0.771 & p = 0.191 & p = 0.073 \\ & \text{Control} & r = -0.233 & r = 0.201 & r = -0.342 & r = 0.407 & r = -0.168 & r = 0.228 \\ & p = 0.031^* & p = 0.088 & p = 0.003^{**} & p < 0.001^{**} & p = 0.012^* & p = 0.052 & p = 0.654 \\ & p = 0.031^* & p = 0.088 & p = 0.003^{**} & p < 0.001^{**} & p = 0.052 & p = 0.654 \\ & p = 0.400 & p = 0.272 & p = 0.001^{**} & p = 0.012^* & p = 0.962 & p = 0.654 \\ & \text{Composite} & p = 0.361 & p = 0.187 & p = 0.033^* & p = 0.146 & p = 0.153 & p = 0.539 \\ & \text{Composite} & p = 0.361 & p = 0.187 & p = 0.033^* & p = 0.146 & p = 0.153 & p = 0.539 \\ & \text{Composite} & p = 0.001^{**} & p = 0.003^{**} & p < 0.001^{**} & p < 0.001^{**} & p = 0.030^* & p = 0.201^* \\ & p = 0.001^{**} & p = 0.003^{**} & p < 0.001^{**} & p = 0.001^{**} & p = 0.020^* \\ & \text{Communication} & r = 0.355 & r = -0.311 & r = 0.646 & r = -0.470 & r = 0.215 & r = -0.287 \\ & p = 0.001^{**} & p = 0.001^{**} & p < 0.001^{**} & p < 0.001^{**} & p = 0.001^{**} & p = 0.000^{**} \\ & p = 0.001^{**} & p < 0.001^{**} & p < 0.001^{**} & p < 0.001^{**} & p = 0.001^{**} & p = 0.007^{**} \\ & p = 0.001^{**} & p = 0.001^{**} & p < 0.001^{**} & p = 0.001^{**} & p = 0.007^{**} \\ & p = 0.001^{**} & p = 0.001^{**} & p < 0.001^{**} & p = 0.001^{**} & p = 0.007^{**} \\ & p = 0.001^{**} & p = 0.001^{**} & p < 0.001^{**} & p < 0.001^{**} & p < 0.001^{**} & p = 0.002^{*} \\ & p = 0.001^{**} & p = 0.001^{**} & p < 0.001^{**} & p < 0.001^{**} & p = 0.001^{*} & p = 0.007^{**} \\ & p = 0.001^{**} & p = 0.001^{**} & p < 0.001^{**} & p < 0.001^{**} & p = 0.047^{*} & p = 0.077 \\ & p = 0.001^{**} & p = 0.001^{**} & p < 0.001^{**} & p < 0.001^{**} & p = 0.017 & r = 0.231 \\ & p = 0.001^{**} & p = 0.001^{**} & p < 0.001^{**} & p < 0.001^{**} & p = $		p = 0.363	p = 0.769	p = 0.210	p = 0.699	p = 0.529	p = 0.439
$^{\circ}$ $p = 0.221$ $p = 0.033$ $p = 0.120$ $p = 0.026^{*}$ $p = 0.929$ $p = 0.256$ Organization $r = 0.0161$ $r = 0.0137$ $r = 0.031$ $r = 0.115$ $r = 0.211$ Materials $p = 0.089$ $p = 0.011$ $p = 0.071$ $p = 0.191$ $p = 0.073$ Control $r = -0.233$ $r = 0.211$ $r = -0.467$ $r = -0.168$ $r = 0.228$ Metacognition Index $r = -0.001$ $r = 0.031^{*}$ $p = 0.001^{**}$ $p = 0.011^{**}$ $p = 0.052$ Metacognition Index $r = -0.100$ $r = 0.177$ $p = 0.011^{**}$ $p = 0.052$ $p = 0.654$ Global Executive $r = -0.132$ $r = 0.177$ $p = 0.012^{**}$ $p = 0.033^{**}$ $p = 0.554$ Composite $p = 0.361$ $p = 0.187$ $p = 0.033^{**}$ $p = 0.033^{**}$ $p = 0.030^{**}$ Material $r = 0.355$ $r = 0.177$ $p = 0.001^{**}$ $p = 0.033^{**}$ $p = 0.020^{**}$ Composite $p = 0.001^{**}$ $p = 0.001^{**}$ $p < 0.001^{**}$ $p = 0.033^{**}$ $p = 0.020^{**}$ Daily Living Skills $r = 0.355$ $r = 0.379$ $r = 0.644$ $r = 0.477$ $r = 0.235$ $r = 0.287$ Daily Living Skills $r = 0.355$ $r = 0.361$ $r = 0.553$ $r = 0.464$ $r = 0.185$ $r = 0.179$ Daily Living Skills $r = 0.355$ $r = -0.367$ $r = 0.563$ $r = 0.196$ $p = 0.007^{**}$ Socialization $r = 0.355$ $r = -0.367$ $r = 0.058$ $r = -0.196$ $r = 0.260$ <tr <tr="">Daily Living Skills&lt;</tr>	Plan/Organise	r = -0.137	r = 0.187	r = -0.173	r = 0.246	r = -0.010	r = 0.127
$\begin{array}{llllllllllllllllllllllllllllllllllll$	0	p = 0.221	p = 0.093	p = 0.120	p = 0.026*	p = 0.929	p = 0.256
	Organization of	r = 0.016	r = 0.060	r = -0.137	r = -0.035	r = 0.155	r = 0.211
Control $r = 0.253$ $r = 0.211$ $r = 0.342$ $r = 0.407$ $r = 0.168$ $r = 0.228$ Metacognition Index $r = 0.100$ $r = 0.130$ $r = 0.0375$ $r = 0.294$ $r = 0.006$ $r = 0.053$ $p = 0.400$ $p = 0.272$ $p = 0.001^{**}$ $p = 0.962$ $p = 0.654$ Global Executive $r = 0.12$ $r = 0.147$ $r = 0.236$ $r = 0.162$ $r = 0.053$ $r = 0.053$ Composite $p = 0.361$ $p = 0.187$ $p = 0.033^*$ $p = 0.166$ $r = 0.0.255$ $r = -0.251$ Communication $r = 0.355$ $r = -0.314$ $r = 0.646$ $r = -0.470$ $r = 0.235$ $r = -0.227$ Communication $r = 0.345$ $r = 0.379$ $r = 0.646$ $r = 0.470$ $r = 0.235$ $r = -0.227$ Socialization $r = 0.345$ $r = 0.379$ $r = 0.001^{**}$ $p =$	Materials	p = 0.896	p = 0.615	p = 0.249	p = 0.771	p = 0.191	p = 0.073
p = 0.031*p = 0.088p = 0.003**p < 0.01**p = 0.154p = 0.052Metacognition Indexr = 0.100r = 0.130r = -0.375r = 0.294r = -0.006r = 0.053Global Executiver = -0.102r = 0.147r = -0.236r = 0.162r = 0.053r = 0.069Compositep = 0.361p = 0.187p = 0.03*p = 0.142r = 0.053r = 0.059VABS-IICommunicationr = 0.355r = -0.314r = 0.646r = -0.470r = 0.235r = -0.221Daily Living Skillsr = 0.345r = -0.379r = 0.644r = -0.510r = 0.215r = -0.287Daily Living Skillsr = 0.345r = -0.361r = 0.663r = -0.464r = 0.185r = -0.179Daily Living Skillsr = 0.335r = -0.361r = 0.663r = -0.464r = 0.185r = -0.179Daily Living Skillsr = 0.335r = -0.361r = 0.663r = -0.464r = 0.185r = -0.179Daily Living Skillsr = 0.335r = -0.361r = 0.663r = -0.464r = 0.185r = -0.179Dailyp = 0.001**p < 0.001**p < 0.001**p < 0.001**p = 0.089p = 0.009Adaptive Behaviourr = 0.350r = -0.167r = 0.464r = 0.185r = 0.179De = 0.001**p = 0.001**p < 0.001**p < 0.001**p = 0.089p = 0.019Adaptive Behaviourr = 0.350r = -0.167r = 0.464r = 0.185r = 0.019De = 0.001**p = 0.001**p < 0.001**p =	Control	r = -0.253	r = 0.201	r = -0.342	r = 0.407	r = -0.168	r = 0.228
Metacognition Indexr = 0.100r = 0.130r = 0.375r = 0.294r = -0.006r = 0.053p = 0.400p = 0.272p = 0.001**p = 0.012*p = 0.962p = 0.654Global Executiver = 0.102r = 0.147r = -0.236r = 0.162r = 0.053r = 0.069Compositep = 0.361p = 0.187p = 0.033*p = 0.146p = 0.153p = 0.539VABS-IICommunicationr = 0.355r = -0.314r = 0.646r = -0.470r = 0.235r = -0.287Daily Living Skillsr = 0.345r = -0.379r = 0.644r = -0.510r = 0.215r = -0.287Daily Living Skillsr = 0.335r = -0.361r = 0.663r = -0.464r = 0.185r = -0.179Daily Living Skillsr = 0.350r = -0.367r = 0.658r = -0.464r = 0.185r = -0.179Do 1001**p = 0.001**p < 0.001**		p = 0.031*	p = 0.088	p = 0.003**	p < 0.001**	p = 0.154	p = 0.052
and the second part of the second	Metacognition Index	r = -0.100	r = 0.130	r = -0.375	r = 0.294	r = -0.006	r = 0.053
Global Executive $r = 0.102$ $r = 0.147$ $r = 0.236$ $r = 0.162$ $r = 0.053$ $r = 0.069$ Composite $p = 0.361$ $p = 0.187$ $p = 0.033^*$ $p = 0.146$ $p = 0.153$ $p = 0.539$ VABS-IICommunication $r = 0.355$ $r = -0.314$ $r = 0.646$ $r = -0.470$ $r = 0.235$ $r = -0.251$ Daily Living Skills $r = 0.345$ $r = -0.379$ $r = 0.644$ $r = -0.510$ $r = 0.215$ $r = -0.287$ Socialization $r = 0.335$ $r = -0.361$ $r < 0.001^{**}$ $p < 0.001^{**}$ $p < 0.001^{**}$ $p = 0.047^*$ $p = 0.007^{**}$ Socialization $r = 0.335$ $r = -0.361$ $r < 0.563$ $r = -0.464$ $r = 0.185$ $r = -0.287$ Adaptive Behaviour $r = 0.335$ $r = -0.367$ $r = 0.658$ $r = -0.496$ $r = 0.222$ $r = -0.260$ Composite $p = 0.001^{**}$ $p < 0.001^{**}$ $p < 0.001^{**}$ $p < 0.001^{**}$ $p = 0.001^{**}$ $p = 0.016^{**}$ ASEBA $r = 0.182$ $r = -0.116$ $r = 0.047$ $r = -0.131$ $r = 0.265$ $r = 0.014$ Aster $r = 0.395$ $p = 0.447$ $p = 0.277$ $p = 0.833$ $p = 0.301$ $p = 0.377$ $p = 0.028$ $p = 0.377$ $p = 0.234$ $p = 0.031$ $p = 0.337$ $p = 0.407^{*}$ $p = 0.399$ $p = 0.331$ Externalizing problems $r = 0.452$ $r = -0.028$ $r = -0.121$ $r = 0.224$ $p = 0.301$ $p = 0.377$ $p = 0.101$ $p = 0.337$ $p = 0.477$ $p = 0.333$ $p = 0.37$		p = 0.400	p = 0.272	p = 0.001 **	p = 0.012*	p = 0.962	p = 0.654
Composite VABS-II $p = 0.361$ $p = 0.187$ $p = 0.033^{*}$ $p = 0.146$ $p = 0.153$ $p = 0.539$ Communication $r = 0.355$ $r = -0.314$ $r = 0.646$ $r = -0.470$ $r = 0.235$ $r = -0.251$ Daily Living Skills $r = 0.345$ $r = -0.379$ $r = 0.644$ $r = -0.510$ $r = 0.215$ $r = -0.287$ Daily Living Skills $r = 0.345$ $r = -0.379$ $r = 0.601^{**}$ $p < 0.001^{**}$ $p < 0.001^{**}$ $p = 0.007^{**}$ Socialization $r = 0.335$ $r = -0.361$ $r = 0.563$ $r = -0.464$ $r = 0.185$ $r = -0.179$ Socialization $r = 0.335$ $r = -0.361$ $r = 0.563$ $r = -0.464$ $r = 0.089$ $p = 0.007^{**}$ Adaptive Behaviour $r = 0.350$ $r = -0.367$ $r = 0.658$ $r = -0.496$ $r = 0.222$ $r = -0.260$ Composite $p = 0.001^{**}$ $p < 0.001^{**}$ $p < 0.001^{**}$ $p < 0.001^{**}$ $p = 0.089$ $p = 0.099$ Adaptive Behaviour $r = 0.321$ $r = 0.047$ $p = 0.001^{**}$ $p = 0.015^{**}$ $r = -0.221$ $r = 0.022$ $r = -0.220$ Composite $p = 0.001^{**}$ $p = 0.301$ $p = 0.672$ $p = 0.234$ $p = 0.016^{**}$ $p = 0.898$ Externalizing problems $r = -0.95$ $r = -0.016$ $r = 0.022$ $r = 0.033$ $p = 0.833$ $p = 0.833$ $p = 0.898$ Externalizing problems $r = 0.945$ $r = -0.037$ $p = 0.833$ $p = 0.833$ $p = 0.898$ $p = 0.301$ $p = 0.393$ Depressive problems	Global Executive	r = -0.102	r = 0.147	r = -0.236	r = 0.162	r = 0.053	r = 0.069
VABS-Irrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr <td>Composite</td> <td>p = 0.361</td> <td>p = 0.187</td> <td>p = 0.033*</td> <td>p = 0.146</td> <td>p = 0.153</td> <td>p = 0.539</td>	Composite	p = 0.361	p = 0.187	p = 0.033*	p = 0.146	p = 0.153	p = 0.539
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	VABS-II	r	r	I	r	I	r
p = 0.001**p = 0.003**p < 0.001**p < 0.001**p = 0.030*p = 0.020*Daily Living Skillsr = 0.345r = -0.379r = 0.644r = -0.510r = 0.215r = -0.287p = 0.001**p < 0.001**	Communication	r = 0.355	r = -0.314	r = 0.646	r = -0.470	r = 0.235	r = -0.251
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		p = 0.001**	p = 0.003**	p < 0.001**	p < 0.001**	p = 0.030*	p = 0.020*
p = 0.001**p < 0.001**p < 0.001**p < 0.001**p = 0.007**p = 0.007**Socializationr = 0.335r = -0.361r = 0.563r = -0.464r = 0.185r = -0.179p = 0.002**p = 0.001**p < 0.001**	Daily Living Skills	r = 0.345	r = -0.379	r = 0.644	r = -0.510	r = 0.215	r = -0.287
Socializationr = 0.335r = -0.361r = 0.563r = -0.464r = 0.185r = -0.179 $Adaptive Behaviourr = 0.350r = -0.367r = 0.001**p < 0.001^{**}p = 0.001^{**}p = 0.0099Adaptive Behaviourr = 0.350r = -0.367r = 0.658r = -0.496r = 0.222r = -0.260Compositep = 0.001^{**}p = 0.898p = 0.001^{**}p = 0.898Externalizing problemsr = -0.95r = -0.085r = -0.121r = 0.024r = 0.020r = 0.093p = 0.708p = 0.377p = 0.047^{*}p = 0.698p = 0.301p = 0.933Depressive problemsr = -0.028r = -0.181r = 0.049$ r = 0.017r = 0.231 $p = 0.667$ $p = 0.802$ $p = 0.767$ $p = 0.9$	, ,	p = 0.001**	$p < 0.001^{**}$	p < 0.001**	p < 0.001**	p = 0.047*	p = 0.007**
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Socialization	r = 0.335	r = -0.361	r = 0.563	r = -0.464	r = 0.185	r = -0.179
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problems $p = 0.070$ $p = 0.938$ $p = 0.233$ $p = 0.496$ $p = 0.452$ $p = 0.515$	Oppositional defiant	r = -0.223	r = 0.010	r = -0.148	r = 0.085	r = -0.094	r = 0.081
	problems	p = 0.070	p = 0.938	p = 0.233	p = 0.496	p = 0.452	p = 0.515

Legend: IQ = Intellective quotient; BRIEF = Behaviour Rating Inventory of Executive Function; VABS-II = Vineland Adaptive Behaviour Scales-II edition. ASEBA = Achenbach System of Empirically Based Assessment. \*=p < 0.05; \*\*=p < 0.01.

and when it had a more prolonged duration [39]. Less significant effects were correlated with the frequency of seizures [39].

Prolonged duration of epilepsy was associated with the impairment of the cognitive and adaptive functions, as shown by our cohort's IQ and the VABS-II composite scores [27,34,36] A recent study on an Italian cohort of 48 patients with STXBP1-DEE, in which developmental trajectories were not negatively influenced by epilepsy duration, suggested that etiologies play additional and not easily quantifiable roles in determining differences in outcome severity [41].

A high frequency of behavioral problems and psychiatric symptoms was observed in the proportion of our patients followed up for more than 10 years. Specifically, it has been observed that a predominance of anxiety disorders among internalizing disorders and ADHD among the externalizing disorders without difference between patients with focal or generalized seizures. Emotional dysregulation disorder and behavioral disorders (e.g., impulsivity) were mainly observed in patients with more severe executive dysfunctions and lower ratings in VABS-II domains. These results were consistent with previous studies that had also assessed psychiatric symptoms before the epilepsy onset in up to 45 % of the pediatric patients and this could be probably due to a common neurobiological root of neurologic and psychiatric symptoms [42–44].

The occurrence of status epilepticus was related to lower performances at the VABS-II in our cohort. The diffuse or selective neuronal loss might partially explain this relationship through excitotoxicity cascades occurring during the SE, resulting in the impairment of cognitive and executive functioning networks [45,46]. However, patients with lower IQ and educational degrees have an increased risk of developing episodes of status epilepticus and this supports the predominant role played by the etiologies on the resulting cognitive functioning (the core of the concept of DEE itself) [44,45,47]. In fact, these patients usually have more severe brain dysfunction that produces a greater propensity to status epilepticus [46]. The lack of an organized background EEG activity seems to be strictly associated with a delayed brain maturation, even if it may be a complex matter of discussion whether this disorganization is the effect of epilepsy itself or is the result of the alteration of the synaptogenesis, myelination, and functional/behavioral development due to the underlying etiologies [48,49]. In our study, EEG dysmaturity and disorganization were associated with more severe cognitive, emotional, and adaptive impairments. The analysis of the BRIEF subscales highlighted that dysfunctions of Initiate, Shift, and Working Memory were more frequently impaired than Organization of Materials and Monitoring.

Interictal EEG abnormalities mirror dynamic events consisting of a synchronous discharge of neurons producing high-frequency oscillations and a succession of action potentials that disrupt the ongoing neural activity [50]. Early life interictal spikes at the EEG induced an ineffective new cell formation and decreased cell counts in the hippocampus of mice models with a subsequent deficient long-term potentiation (LTP) causing long-standing cognitive impairment [51]. Consolidated experimental data and several clinical studies showed several relationships between interictal EEG abnormalities and the worst developmental and neuropsychological long-term outcomes [52]. Our study suggested that differences in the type and the spatial distribution of the EEG abnormalities might have no different impacts in determining the severity of the developmental impairment and the long-term neurocognitive outcome. These data confirmed that the age at the occurrence of interictal EEG abnormalities might influence the severity of developmental impairment more than the morphology and localization of the EEG abnormalities.

The use of a higher number of ASMs and the need for therapy at earlier ages are commonly related to a poorer response to treatment and represented significant predictors of negative neurodevelopmental outcomes in our cohort [53,54]. These patients are likely to have a more severe brain dysfunction resulting in greater seizure propensity, resistance to therapy, and the worst outcome [52,53]. Recent studies suggested that the number of ASMs required to define drug resistance may differ according to the predominant seizure types [53]. These also support the hypothesis that the relationship between drug resistance and the neurodevelopmental outcome might vary according to the different epileptic syndromes [52,53]. The development of novel tailored therapeutic strategies impacting both epilepsy and neurocognitive, neurodevelopmental, and psychiatric comorbidities will represent a hot topic for future research [55]. Interesting perspectives were provided by recent studies on mice models evidencing the positive modulation of the opioid Sigma1 receptor induced by fenfluramine (resulting in antiepileptogenic effects on GABAergic signaling and in reduced cognitive decline, executive functions impairment, mood dysfunctions and hyperactivity in Dravet and Lennox-Gastaut syndromes) or the restoration of GABAA receptors expression and functioning in CDKL5 deficiency after the administration pregnenolone-methyl-ether (with positive implications on convulsivity, cognitive performances and autism-like features) [56,57].

The impairment of adaptive functioning in the studied cohort was more significant and transversal than IQ influence. These results might be correlated with the different methodologies for patient testing (parental semi-structured interview versus direct assessment); however, the high proportion of patients with incomplete or lacking seizure control and the wider variety of functions explored by VABS-II may play an important role. Uncontrolled and persistent seizures may have impacted adaptive functions because of different environmental or clinical/neurophysiological factors (e.g., more restrictions imposed by parents and more social isolation resulting in reduced opportunities to achieve age-appropriate independent living skills, effects of medications, exposure to persistent interictal abnormal brain activity) [58].

The strength of this study is represented by the extensive protocol used for cognitive, neuropsychological, and psychiatric evaluation of a cohort of patients with genetically identified DEE. The combination of tests, including direct assessments, semi-structured interviews, and parent/self-reported checklists, may support more reliable predictions of developmental outcomes. Moreover, different studies supported the use of all the administered tests in cohorts of patients with intellectual disability and developmental impairment even if some scores (i.e. VABS scores) are difficult to be measured in the most severe cases because of a floor effect [59–64]. Another strength point is the long duration of the mean follow-up, especially compared to similar earlier studies [31–43].

The main limitation of this study included its retrospective nature that might have reduced the reliability of the identified predictors of outcome (i.e. therapeutic prescription by different physicians, with potential different clinical approach and, furthermore, patient's or caregiver's compliance might have modified the influence of the number of ASMs over the years). The different genetic etiologies of the analyzed cohort probably constituted a bias towards the correct interpretation of the impact of etiologies on the clinical outcome. Conversely, the etiological groups within this cohort were too small to allow significant predictions based on molecular genetics defects. A similar bias was represented by excluding patients with DEE without a confirmed molecular genetic diagnosis. Other correlated limitations included lacking info on the predictive role of epileptic syndromes and epileptogenic lesions detectable with neuroimaging (Suppl. Table 1). A further limit included the lack of evaluation of the changes involving neurodevelopmental parameters over time that might have provided additional information about the natural history of DEEs and eventual agerelated peculiarities of the analyzed predictors of outcome.

### 5. Concluding remarks

A complete characterization of clinical factors and neuropsychological deficits, which may increase the risk of maladaptive sequelae in patients with epilepsy, is crucial to providing timely intervention referrals for intervention, decreasing comorbid psychopathology, and increasing the quality of life. The present study highlighted six variables that can be used as predictors of the neurologic, neurodevelopmental, behavioral, and psychiatric outcomes of pediatric-onset epileptic and developmental encephalopathies, supporting early identification of those patients at higher risk. These predictors might suggest useful criteria to identify the clusters of patients in which a more aggressive and earlier antiseizure treatment may impact the global neurodevelopmental and neuropsychological outcome more deeply. The distinction between the relevance of epilepsy, mirrored by these predictors, and the role played by the underlying genetic defects in determining global neurodevelopmental functioning remains hard to disentangle. The study of etiologies' role is feasible in single rare monogenic diseases but only in restricted cohorts with probable subsequent scarcely statistically significant results. Data about the influence of etiologies in the global setting of long-term neurodevelopmental outcomes in DEEs may acquire epidemiological relevance within international tools promoting large longitudinal observational data collections (e.g., collaborative studies, web-based patient registries studying natural history and other clinical aspects).

### CRediT authorship contribution statement

Mario Mastrangelo: Writing – review & editing, Writing – original draft, Methodology, Investigation, Conceptualization. Filippo Manti: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. Giacomina Ricciardi: Methodology, Formal analysis, Data curation. Rossella Bove: Software, Resources, Methodology, Formal analysis, Data curation. Carlo Greco: Methodology, Funding acquisition, Formal analysis. Manuela Tolve: Formal analysis, Data curation. Francesco Pisani: Writing – review & editing, Validation, Supervision, Investigation.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2024.109670.

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