Epilepsy & Behavior 92 (2019) 283–289

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Clinical and electroencephalographic correlates of psychiatric features in children with frontal lobe epilepsy

Chiara Ticci [a,1], Teresa Luongo [a,1], Giulia Valvo [b], Anna Rita Ferrari [c], Paola Brovedani [c], Gabriele Masi [c], Simona Pellacani [c], Federico Sicca [c,*]

[a] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[b] Child and Adolescent Neuropsychiatric Unit, Azienda USL Toscana Sudest, Grosseto, Italy
[c] Department of Developmental Neuroscience, IRCCS Stella Maris Foundation, Pisa, Italy

ARTICLE INFO

Article history:
Received 6 September 2018
Revised 4 January 2019
Accepted 4 January 2019
Available online 4 February 2019

Keywords:
Frontal lobe
Epilepsy
EEG
Psychopathology

ABSTRACT

Background and objective: Frontal lobe epilepsy (FLE) is often associated with psychiatric features, although the factors predisposing to the concurrence of these conditions have yet to be determined, especially in younger children. We aimed at defining possible clinical and electroencephalography (EEG) features that may enhance the psychiatric risk in pediatric FLE.
Method: We performed a structured psychiatric assessment of 59 children with FLE, using both categorical and dimensional approaches, correlated psychopathology with epilepsy data, and cognitive development.
Results: About 1/3 of patients with FLE displayed intellectual disability (ID), and more than 2/3 displayed psychiatric disorders, including depression, disruptive behaviors, anxiety, and bipolar/psychotic disorders. Psychiatric dimensions such as impulse control problems, attentional deficits, social problems, and aggressive behaviors were frequent features of FLE. Intellectual disability was associated with an earlier onset of psychiatric disorders and more frequent disruptive behavior disorders and aggressiveness. Long-standing epilepsy and bilateral or anterior frontal EEG abnormalities also increased the risk of psychopathology. Finally, right-hemisphere lesions were associated with disruptive behavior disorders, fast EEG rhythms with attention/memory problems, and phases of seizure remission with impulse control problems.
Conclusions: Clinical and EEG markers of increased psychopathological risk may help in defining consistent at-risk subgroups within FLE and improving early diagnosis, prognosis, and treatment. Categorical and dimensional approaches to psychiatric diagnosis may generate new research hypotheses and support the investigation of the complex pathophysiological bases shared by different neurodevelopmental disturbances.

1. Introduction

Epilepsy is associated with psychiatric symptoms in 25–50% of adults [1] and 26–44% of children and adolescents [2–4]. These rates are significantly higher than those reported in the general pediatric population (7%) [5]. Among the focal forms, frontal lobe epilepsy (FLE) is associated with the highest risk of psychiatric features because of the pivotal role of the frontal lobe in regulating executive functions, behavior, and mood [6]. Although the relation between epilepsy and psychiatric disorders can be complex and a close causal relationship remains highly questionable [7,8], aberrant epileptic networks within the frontal lobe may likely interfere with brain functions, resulting in cognitive, behavioral, and affective problems. Indeed, FLE in adults frequently cooccurs with anxiety [9], mood [10], and personality disorders [11,12]. Less information is available in the literature on the psychiatric features of FLE in youth, since studies include small groups of children [13,14] or have investigated only specific neuropsychological profiles [14–16]. The work from Zhang and colleagues has focused specifically on the occurrence of ADHD (attention-deficit hyperactivity disorder) in children with FLE and normal neurological and cognitive profiles [17]. The authors found a higher incidence of ADHD compared with that in the general population, without clear-cut correlation with epilepsy features (age at onset, family history, seizure type and control, ictal electroencephalography (EEG) except for an increased risk of ADHD in children with abnormal discharges in the most recent EEG recording. The study from Braakman and colleagues is particularly informative on the cognitive, neuropsychological, and behavioral skills of youth with FLE [18]. Through intelligence tests, extensive neuropsychological assessments, and behavioral questionnaires (Teacher Rating Form—TRF and Child Behavior Checklist—CBCL), the authors investigated

* Corresponding author at: Epilepsy and Clinical Neurophysiology Laboratory, Department of Developmental Neuroscience, IRCCS Stella Maris Foundation, Viale del Tirreno 331, Calambrone, 56128 Pisa, Italy.
E-mail address: fsicca@fsm.unipi.it (F. Sicca).
[1] CT and TL contributed equally.

https://doi.org/10.1016/j.yebeh.2019.01.008
1525-5050/

the performance of 71 children, aged 6–16 years, with FLE. They found lower performance on intellectual and neuropsychological tests in affected children compared with reference values, with significantly poorer mental calculation skills in patients with higher seizure activity. On the other hand, they found no significant correlation between behavioral problems (attention problems, anxiety, internalizing behaviors) and epilepsy factors. A possible reason for the absence of a clear correlation between behavioral problems and epilepsy in previous literature might be related to the lack of a self-report psychopathological information and more structured psychiatric measures, which may have limited the reliability of the psychiatric information. Parent-report and self-report measures are indeed complementary, and possible inconsistencies between them may further increase our understanding of psychopathology. Literature findings based on parent-reported behavioral assessments in FLE are indeed often inconsistent, as some studies report higher frequencies of "externalizing problems" [19,20], while others find more severe "internalizing problems" [18,21].

Although there is support for the hypothesis that FLE predisposes to psychopathology since childhood, the factors increasing the risk of psychiatric problems in FLE are still poorly understood. Using a comprehensive psychopathological assessment, we have therefore explored, in a large sample of children with FLE, the psychiatric features and the clinical and EEG correlates, expecting to define consistent at-risk subgroups within the heterogeneous clinical domain of FLE, thus improving early diagnosis, prognosis, and treatment.

2. Methods

2.1. Patients

The study was approved by the local ethics committee. All caregivers signed an informed consent form. The sample included patients referred to our tertiary epilepsy center (IRCCS Stella Maris Foundation, Pisa) between January 1995 and December 2015, with conditions fitting the diagnosis of FLE. We enrolled individuals with either epilepsy due to structural brain lesions or forms with unknown etiology displaying normal brain MRI. Children with progressive brain disorders were not included in the study. We excluded from our sample the patients with frontal seizures thought to be a result of spreading to the frontal lobe from other foci, based on both clinical semiology and the main localization of the interictal EEG abnormalities. Severe intellectual disability (ID) and autism spectrum disorders, possible confounding factors for a reliable, structured psychiatric assessment, were also considered as exclusion criteria for recruitment.

2.2. Clinical, MRI, and EEG data

We reviewed all clinical, EEG, and neuroimaging data for each subject with FLE. Following previous studies [18], we stratified patients for statistics according to the following: age at seizure onset (young: ≤ 5 years; old: >5 years); seizures frequency (low: ≤1/week; high: >1/week); typical duration of seizures (short: ≤1 min; long: >1 min); duration of epilepsy (short: ≤5 years; long: >5 years). We used the term "controlled epilepsy" for patients with a seizure-free period lasting more than 2 years. We also collected information about the daytime occurrence of seizures (during sleep, wakefulness, or both), and antiepileptic therapy (mono- or polytherapy).

We obtained digital video-EEG-polygraphic recordings in all patients, according to the 10–20 International System, and when available, we also reviewed the long-term video-EEG monitoring. Paroxysms were classified according to their predominant location within the frontal lobe, in anterior (Fp2-F4 and Fp1-F3; Fp2-F8 and Fp1-F7; Fz-Cz), posterior (F8-T4 and F7-T3; F4-C4 and F3-C3), and in left-sided, right-sided, or bilateral. In the condition of activity propagation, the term predominant location referred to the site where the interictal abnormalities appeared more clearly focal. We analyzed, in addition, whether interictal paroxysms involved only the frontal lobe, or if they were also multifocal or diffuse, and if they occurred only on awake, during sleep, or in both conditions. We also checked for the presence of fast rhythmic EEG activities over the frontal lobe and for diffuse continuous paroxysms during sleep. When available, ictal EEG recordings were also reviewed, looking at the location of ictal discharges within the frontal lobe (anterior or posterior), and their side (left, right, or indeterminate). We finally assessed the presence, type, and localization of epileptogenic lesions by reviewing the brain MRI.

2.3. Cognitive assessment and psychiatric evaluation

We assessed cognitive functioning in all patients using age-appropriate standardized tools [Griffiths Mental Development Scale Extended—Revised (GMDS-ER), Wechsler Preschool and Primary Scale of Intelligence—Third Edition (WPPSI-III), and the Wechsler Intelligence Scale for Children, Third and Fourth Editions (WISC-III and WISC-IV)] and adaptive functioning through historical information and/or the Vineland Adaptive Behavior Scales—Interview forms. Based on both IQ and adaptive functioning, we classified patients as having normal to borderline cognitive functioning (IQ > 70; standard scores for adaptive functioning up to −2 Standard Deviation [SD] from the mean), or mild to moderate ID (IQ: 35–70; standard scores for adaptive functioning ranging from −2.0 SD to −4.3 SD from the mean).

A complete psychiatric assessment was carried out through clinical observations, interviews with patients and their parents, questionnaires (Youth Self-Report—YSR; CBCL) [22,23] and the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Presents and Lifetime (K-SADS-PL) [24], leading to a categorical classification fitting the DSM-IV and DSM-5 criteria. We also classified individuals according to a dimensional approach, based on four clusters of problems that typically may result from frontal lobe dysfunction: 1) "self and hetero-aggressive behaviors", 2) "impulse control problems", 3) "attention and memory problems", and 4) "lack of involvement in social relations". The age at onset of psychiatric symptoms was considered either as a continuous or as a categorical variable (young: ≤5 years of age; old: > 5 years of age).

2.4. Statistical analyses

We analyzed clinical, psychiatric, and cognitive variables with respect to all epilepsy and EEG data, in order to investigate for significant associations. We used the IBM© SPSS© Statistics software version 20 (Armonk, New York, United States). For continuous variables (age at onset of seizures, age at onset of psychiatric symptoms, duration of active epilepsy), we performed two-tailed t-test and two-way analyses of variance (ANOVA), and post-hoc multiple comparisons using the Bonferroni correction. For categorical variables (age at seizure onset, seizures frequency, typical duration of seizures, duration of epilepsy, etiology of epilepsy, control of epilepsy, location and lateralization of interictal EEG paroxysms within the frontal lobe, intellectual functioning, age at onset of psychiatric features, categorical and dimensional psychiatric diagnoses, categorical and dimensional subgroups), we used Chi-squares tests and correspondence analyses (CA) to decompose the significant Chi-squares and reduce variable dimensions. Significance was set at $p < 0.05$.

3. Results

3.1. Clinical features of FLE

Based on our inclusion criteria, the final sample consisted of 59 patients [32 boys (54%) and 27 girls (46%)], aged between 3 and 25 years (mean: 13.9 years, SD: 4.9) at the time of the last assessment. The follow-up period ranged from 0.5 to 22.5 years (mean: 8.0 years; SD: 5.6). Frontal lobe epilepsy had structural etiology in 20/59 patients

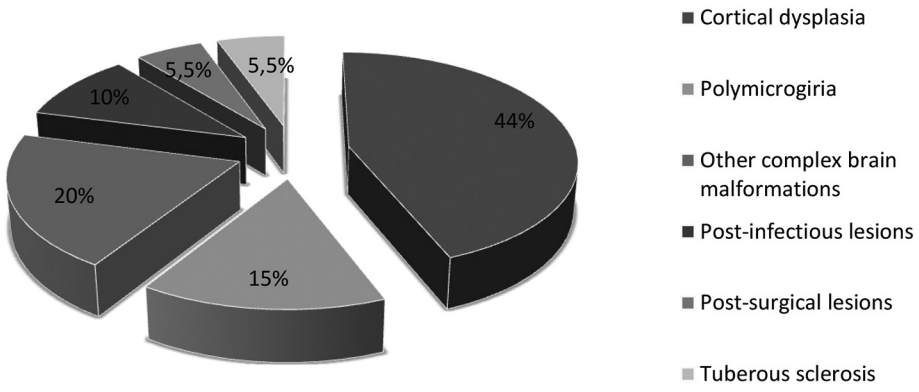

Fig. 1. Brain lesions in patients with a structural etiology of epilepsy.

(33.9%), and unknown cause in 39/59 (66.1%). Structural brain lesions in the sample are summarized in Fig. 1. Each hemisphere was involved with the same frequency (35%; 7/20), while a bilateral involvement was found in 30% of the cases (6/20).

Intellectual functioning was normal or borderline in 38/59 children (64.4%), while 21/59 (35.6%) presented a mild-to-moderate ID. There was no statistical association between the presence of ID and the etiology (structural or unknown) of epilepsy ($\chi^2 = 1.022$; df = 1; p = 0.312).

Tables 1 and 2 summarize the main seizure and epilepsy features and their statistical distribution.

The age at onset of seizures ranged from 0.2 years to 15 years (mean: 5.9 years, SD: 4.3), with significant differences between children with structural etiology (mean: 3.7 years, SD: 3.7) and those with epilepsy of unknown cause (mean: 7.1 years, SD: 4.2) (t = 3.008, df = 56, p = 0.004). Age at onset also differed significantly between children with ID (mean: 3.6 years, SD: 3.8) and with normal or borderline intellectual functioning (mean: 7.2 years, SD: 4.1) (t = 3.296; df = 57; p = 0.002).

At epilepsy onset, the frequency of seizures was higher than one episode/week in 44/59 patients (74.6%), and their duration was most frequently short (≤1 min) (41/59 cases; 69.5%). Seizures occurred less frequently on wakefulness (7/59 cases; 11.9%) than during sleep (22/59; 37.3%) or in both conditions (30/59; 50.8%) (p = 0.001). All patients received a pharmacological treatment for FLE (37.3% monotherapy, 62.7% polytherapy). Duration of active epilepsy, at the time of the last follow up, ranged from 0.5 to 22 years (mean: 7.6 years, SD: 6.2), with about half of the patients (28/55; 50.9%) having short lasting epilepsy (≤5 years). The history of epilepsy was longer in children with age at seizure onset ≤5 years (9.8 years; SD: 6.3; range: 1–22 years) compared with that in those with later onset (4.7 years; SD: 4.9; range: 0.5–17 years) (t = 3.186; df = 53; p = 0.002), as well as in those with ID (10.3 years; SD: 6.5; range: 0.5–22 years), compared with patients with normal development (6.0 years; SD: 5.6; range: 0.6–21 years) (t = −2.544; df = 53; p = 0.014). Similarly, the history was longer in children with structural etiology (10.1 years; SD: 6.2; range: 1.0–21.0) compared with that in those with unknown origin of epilepsy (6.3 years; SD: 5.9; range: 0.5–22.0) (t = −2.214; df = 53; p = 0.031). Children with long lasting epilepsy (>5 years) had higher probability of displaying long seizures (>1 min) ($\chi^2 = 4.550$; df = 1; p = 0.033), independently of the cognitive level ($\chi^2 = 2.069$; df = 2; p = 0.355) and etiology ($\chi^2 = 1.899$; df = 1; p = 0.168).

3.2. Electrophysiological features

All patients received digital video-EEG-polygraphic recordings, and 42 (71.2%) received long-term monitoring. Fifty-seven out of 59 individuals (96.6%) displayed EEG interictal abnormalities, while 2/59 (3.4%) had normal EEG results. Electrophysiological features are reported in Table 3.

Most patients (44/57; 77.2%) displayed interictal abnormalities both during sleep and wakefulness ($\chi^2 = 16.860$; df = 1; p = <0.001). Electroencephalography paroxysms either involved only the frontal lobe (37/57; 64.9%) or were also multifocal or diffuse (20/57; 35.1%) ($\chi^2 = 5.070$; df = 1; p = 0.024). Frontal abnormalities were unilateral in 9/57 individuals (15.8%) and bilateral in 48/57 (84.2%) ($\chi^2 = 26.684$; df = 1; p < 0.001). The most frequent location of paroxysms within the frontal lobe was posterior (64.9%; 37/57 patients) ($\chi^2 = 5.070$; df = 1; p = 0.024). Only a minority of cases (7/57; 12.3%) had continuous paroxysms during sleep ($\chi^2 = 32.439$; df = 1; p < 0.001). Ictal EEG recordings, in 42/59 patients (71.2%), also revealed the frontal posterior area as the most frequent location of the epileptic focus (57.1%; 24/42) ($\chi^2 = 17.714$; df = 2; p = <0.001).

Table 1
Age at seizure onset and duration of epilepsy.

	Age at seizure onset (≤5), mean (SD)	Age at seizure onset (>5), mean (SD)	Test	p
Duration of epilepsy (yrs)	9.8 (6.3)	4.7 (4.9)	t = 3.186	0.002
	Patients with intellectual disability, mean (SD)	Patients with normal cognitive abilities, mean (SD)	Test	p
Age at seizure onset (yrs)	3.6 (3.8)	7.2 (4.1)	t = 3.296	0.002
Duration of epilepsy (yrs)	10.3 (6.5)	6.0 (5.6)	t = −2.544	0.014
	Patients with structural etiology of epilepsy, mean (SD)	Patients with epilepsy of unknown cause, mean (SD)	Test	p
Age at seizure onset (yrs)	3.7 (3.7)	7.1 (4.2)	t = 3.008	0.004
Duration of epilepsy (yrs)	10.1 (6.2)	6.3 (5.9)	t = −2.214	0.031

t = two-tailed t-test, p < 0.05.

Table 2
Main clinical features of FLE.

Epilepsy features of the study group	Results	Test	p
Age at seizure onset (yrs), mean (SD)	5.9 (4.3)		
Age at seizure onset			
○ Young (≤5 years)	33/59 (55.9%)	$\chi^2 = 0.831$	0.362
○ Old (>5 years)	26/59 (44.1%)		
Seizure frequency at onset			
○ Low (≤1 seizure/week)	15/59 (25.4%)	$\chi^2 = 14.254$	**0.000**
○ High (>1 seizure/week)[a]	44/59 (74.6%)		
Duration of seizures			
○ Short (≤1 min)[b]	41/59 (69.5%)	$\chi^2 = 8.966$	**0.003**
○ Long (>1 min)	18/59 (30.5%)		
Daytime of seizure occurrence			
○ Sleep	22/59 (37.3%)	$\chi^2 = 13.864$	**0.001**
○ Awake[c]	7/59 (11.9%)		
○ Sleep and awake	30/59 (50.8%)		
Duration of epilepsy (yrs), mean (SD)	7.6 (6.2)		
Duration of epilepsy			
○ Short (≤5 years)	28/55 (50.9%)	$\chi^2 = 0.018$	0.893
○ Long (>5 years)	27/55 (49.1%)		
Therapy			
○ Monotherapy	22/59 (37.3%)		
○ Polytherapy	37/59 (62.7%)		
Controlled epilepsy			
○ Yes	25/57 (43.9%)	$\chi^2 = 0.860$	0.354
○ No	32/57 (56.1%)		

χ^2 = Pearson chi squared test; $p < 0.05$. Data on the duration of epilepsy and seizures control were not available in 4/59 and in 2/59 individuals, respectively.
Statistically significant p-values are in bold.
[a] Seizure frequency at onset was more often high (>1 seizure/week).
[b] Duration of seizures was more frequently short (≤1 min).
[c] Seizures occurred less frequently during wakefulness.

3.3. Psychiatric features

Forty-nine out of 59 patients (83.5%) received a complete psychiatric assessment using a categorical approach according to the DSM-IV and DSM-5 criteria. Furthermore, based on historical information and psychiatric assessment (including prolonged observations of interactions with peers, parents, and/or examiners), we classified the entire sample according to a dimensional approach. To this aim, we considered the clusters of psychiatric symptoms most frequently reported in frontal lobe dysfunction, i.e., aggressive behaviors, impulse control problems, attention and memory problems, and lack of involvement in social relations. No patient was seizure-free at the time of the psychiatric assessment.

We found psychiatric disorders in 34/49 (69.4%) patients, according to a categorical, DSM-oriented approach, while 40/59 (67.8%) had clinically relevant psychiatric symptoms according to a dimensional approach.

The mean age at onset of categorical psychiatric disorders was 9.1 years (SD: 4.3 years; range: 2–16 years). We found significant association between an early onset of psychiatric disorders (≤5 years) and the occurrence of ID, and between a later onset of psychiatric disorders (>5 years) and normal or borderline intellectual functioning ($\chi^2 = 4.545$; df = 1; $p = 0.033$). Consistently, the age at onset of psychiatric disorders was earlier in children with ID (7.2 years; SD: 4.6 years) compared with that in those with normal or borderline intellectual functioning (10.2 years; SD: 3.8 years), showing a trend to significance ($t = 1.993$; df = 30; $p = 0.055$) (Table 4).

The most frequent psychiatric diagnosis was major depressive disorder, detected in 12/34 (35.3%) patients, followed by disruptive behavior disorders (8/34; 23.5%), anxiety disorders (7/34; 20.6%), and bipolar

Table 3
Main EEG features in FLE.

	Results	Test	p
Interictal EEG paroxysms			
Daytiming occurrence			
Only during sleep	13/57 (22.8%)	$\chi^2 = 16.860$	<**0.001**
During sleep and wakefulness[a]	44/57 (77.2%)		
Type			
Focal[b]	37/57 (64.9%)	$\chi^2 = 31.153$	**0.000**
Multifocal/diffuse	20/57 (35.1%)		
Lateralization			
Right	9/57 (15.8%)	$\chi^2 = 26.684$	<**0.001**
Left	–		
Bilateral[c]	48/57 (84.2%)		
Location within frontal lobe			
Anterior	20/57 (35.1%)	$\chi^2 = 5.070$	**0.024**
Posterior[d]	37/57 (64.9%)		
Fast rhythmic activities			
Yes	24/57 (42.1%)	$\chi^2 = 1.421$	0.233
No	33/57 (57.9%)		
Continuous paroxysms during sleep			
No	50/57 (87.7%)	$\chi^2 = 32.439$	<**0.001**
Yes[e]	7/57 (12.3%)		
Ictal EEG			
Localization (within the frontal lobe) of epileptic focus			
Anterior	16/42 (38.1%)	$\chi^2 = 17.714$	<**0.001**
Posterior[f]	24/42 (57.1%)		
Indeterminate	2/42 (4.8%)		
Side (within the frontal lobe) of the epileptic focus			
Right	17/42 (40.5%)	$\chi^2 = 1.286$	0.526
Left	14/42 (33.3%)		
Indeterminate	11/42 (26.2%)		

χ^2 = Pearson Chi squared test; $p < 0.05$.
Statistically significant p-values are in bold.
[a] Interictal EEG abnormalities were more frequently recorded during awake and sleep.
[b] Most EEG abnormalities were focal.
[c] Most EEG abnormalities were bilateral.
[d] Most EEG abnormalities were predominant over the posterior regions of the frontal lobe.
[e] A minority of patients showed continuous paroxysms during sleep.
[f] The localization of the epileptic focus was more frequently posterior.

Table 4
Psychiatric features in children with FLE.

	Patients with intellectual disability	Patients with normal cognitive abilities	Test	p
Categorical approach				
Psychopathology				
Yes	14/18 (77.8%)	20/31 (64.5%)	$\chi^2 = 0.943$	0.332
No	4/18 (22.2%)	11/31 (35.5%)		
Age at psychopathology onset				
Young (≤5 years)	6/12 (50%)[a]	3/20 (15%)	$\chi^2 = 4.545$	**0.033**
Old (>5 years)	6/12 (50%)	17/20 (85%)		
Type of diagnosis				
- Depressive disorders	2/14 (14.3%)	10/20 (50%)	$\chi^2 = 10.531$	**0.015**
- Disruptive behavior disorders	7/14 (50%)[b]	1/20 (5%)		
- Anxiety disorders	2/14 (14.3%)	5/20 (25%)		
- Bipolar disorders/psychoses	3/14 (21.4%)	4/20 (20%)		
Dimensional approach				
Symptoms of frontal lobe dysfunction				
Yes	15/21 (71.4%)	25/38 (65.8%)	$\chi^2 = 0.197$	0.657
No	6/21 (28.6%)	13/38 (34.2%)		
Type of symptoms				
- Self and hetero-aggressive	6/15 (40.1%)[c]	1/25 (4%)	$\chi^2 = 10.743$	**0.013**
- Impulse control problems	2/15 (13.3%)	9/25 (36%)		
- Attention and memory problems	2/15 (13.3%)	9/25 (36%)		
- Lack of involvement in social relations	5/15 (33.3%)	6/25 (24%)		

χ^2 = Pearson Chi squared test; $p < 0.05$. Data on age at psychopathology onset were not available in 2/34 children with psychiatric features (categorical approach).
Statistically significant p-values are in bold.
[a] Intellectual disability was significantly associated with an early onset of psychiatric disorders (≤5 years).
[b] Intellectual disability was significantly associated with behavioral disorders (categorical approach).
[c] Intellectual disability was significantly associated with self- and hetero-aggressive behaviors (dimensional approach).

disorder/psychoses (7/34; 20.6%) ($\chi^2 = 2.000$; df = 3; p = 0.572). The presence of a categorical diagnosis was significantly associated with the "long duration of epilepsy" (>5 years) ($\chi^2 = 6.038$; df = 1; p = 0.014). In particular, the mean duration of epilepsy was 3.4 years (SD: 3.3; range: 6–12 years) in patients without psychiatric features, and 9.3 years (SD: 6.5; range: 8–22 years) in those with psychopathology (t = −3.198; df = 45; p = 0.003). The absence of a categorical psychiatric diagnosis was in turn associated with a lower risk of having interictal EEG abnormalities over the "anterior areas" of the frontal lobe ($\chi^2 = 5.557$; df = 1; p = 0.018). Among the psychiatric categories, disruptive behavior disorders were more frequent in patients with right-sided lesions at the brain MRI ($\chi^2 = 10.8$; df = 6; p = 0.030).

According to a dimensional approach, "self and hetero-aggressive behaviors" were reported in 7/40 (17.5%), while "impulse control problems", "attention and memory problems", and "lack of involvement in social relations" were each represented in 11/40 (27.5%) ($\chi^2 = 1.200$; df = 3; p = 0.753). Taken together, these symptoms were associated with the presence of "bilateral interictal abnormalities" over the frontal regions ($\chi^2 = 6.090$; df = 2; p = 0.014). In particular, the EEG of children with "attention and memory problems" frequently displayed fast rhythms over the frontal areas ($\chi^2 = 8.433$; df = 3; p = 0.038). Patients with "impulse control problems" had instead a more frequent history of controlled epilepsy ($\chi^2 = 10.315$; df = 3; p = 0.016).

We found no significant association between any of the psychiatric variables and the type of antiepileptic treatment (mono- vs polytherapy).

When evaluating the relationship between intellectual functioning and the overall risk of psychiatric features, using both the categorical and dimensional approaches, we found no differences between subjects with ID and those with normal or borderline functioning (categorical: $\chi^2 = 0.943$; df = 1; p = 0.332; dimensional: $\chi^2 = 0.197$; df = 1; p = 0.657). Intellectual disability was instead significantly associated with the categorical subgroup of disruptive behavior disorders ($\chi^2 = 10.531$; df = 3, p = 0.015) and the "self and hetero-aggressive" cluster in the dimensional classification ($\chi^2 = 10.743$; df = 3; p = 0.013) (Table 4). Child Behavior Checklist scores also showed a significant association of externalizing problems with ID ($\chi^2 = 7.80$; df = 2; p = 0.020) and the early onset of psychiatric disorders (≤5 years) ($\chi^2 = 6.66$; df = 2; p = 0.036).

4. Discussion

Psychiatric disorders are commonly reported in clinical practice in children with FLE. However, little is known about the actual rates of this clinical association, as well as about possible risk factors, especially in young people. We have investigated the epilepsy and cooccurring psychiatric features of 59 consecutive children with FLE, in order to establish the global risk of psychopathology, define possible clinical and EEG features that may underlie the concurrent condition, and stratify the heterogeneous clinical phenotypes. The age at epilepsy onset in our sample is consistent with data already reported in literature [20,21,25]. In our study, a younger age at the onset of seizures and a longer duration of active epilepsy were strongly associated with ID and with a structural etiology. A long epilepsy history (>5 years) was in turn associated with longer-lasting seizures (>1 min). We found no reciprocal associations between ID and structural etiology, which were therefore independently related to both epilepsy onset and duration. Early-onset seizures have been already recognized as a risk factor for intellectual impairment in people with focal or generalized epilepsy syndromes [26]. Only few data are available in FLE, especially in childhood, and these data report inconsistent findings, suggesting either an increased risk of ID in children with epilepsy onset before 6 years [20] or no correlation between age at onset and intelligence scores [18]. Our data suggest that children presenting with early-onset and long-lasting frontal seizures may likely be the most at-risk subgroup for developing long-term epilepsy and ID. These children need a timely exploration for possible structural brain defects and a prompt treatment to prevent cognitive consequences of epilepsy.

In our sample, most individuals (96.6%) displayed EEG abnormalities, in contrast to other studies reporting a lower (14%–67%) incidence of interictal abnormalities in FLE [21,27,28]. This could be explained by method of data collection [29], often limited to short EEG recordings rather than long-term monitoring, as is the case in 71.2% of our sample. Moreover, about 23% of our patients displayed interictal EEG abnormalities only during sleep, and this feature underlines the importance of a full recording of awake and asleep EEG.

Regarding the association between FLE and mental disorders, it is noteworthy that after a structured psychiatric assessment, more than two-thirds of the sample presented psychiatric disorders. Furthermore,

about one-third of our young patients presented mild-to-moderate ID (we excluded patients with severe ID, in order to improve the reliability of the psychiatric assessment). Although ID is usually associated with increased psychiatric risk [30,31], it is relevant that no difference was found between patients with FLE with ID and with normal or borderline intellectual functioning. However, ID was associated with an earlier onset of psychiatric disorders and with more frequent disruptive behavior disorders and aggressive behaviors, consistent with previous studies in individuals without epilepsy [31,32]. There was no correlation between psychiatric diagnoses and neuroimaging features, except for a higher frequency of disruptive behavior disorders in patients with right-sided lesions. Finally we found heavier psychiatric problems in children with long-standing epilepsy (>5 years), in accordance with similar findings from Braakman and colleagues [18].

Among psychiatric disorders, depression was the most frequently diagnosed, reported in about one-third of patients, then followed by disruptive behavior disorders (in about 1/4 of patients), and by anxiety and bipolar/psychotic disorders (in about 1/5 of patients). Finally, regarding psychiatric dimensions, about 1/4 of the patients presented impulse control disorders, attentional deficits and social problems, and 1/6 aggressive behaviors. These psychiatric dimensions as a whole were associated with EEG bilateral interictal abnormalities.

The frequency of psychiatric problems is much higher than what is seen in the general pediatric population (7%) [5], as well as in children and adolescents with other chronic disorders, such as asthma and diabetes mellitus [33,34]. The pathophysiological significance underlying the concurrence of psychopathology and FLE is still unclear. The hypothesis of a direct damage of epilepsy on cortical networks fundamental for emotional and cognitive functions, sustained by the frontal lobe, is realistic; however, it probably does not capture the whole complex mechanisms involved in psychopathology [35]. There is, indeed, mounting evidence suggesting that the frequent occurrence of psychiatric features in epilepsy does not imply necessarily causation. It may indeed result from the disruption of common brain networks or from shared pathogenic mechanisms (e.g., genetic, neuroendocrine, inflammatory, and neurotransmitter disturbances) operant in both seizure and neuropsychiatric disorders [8]. These mechanisms include simultaneous and bidirectional events leading to the disordered neuronal excitability of epilepsy, on the one hand, and the neurobiological dysfunctions underlying the failure of psychic homeostasis, on the other hand [36]. In the literature, controversial data about the prevalence of internalizing versus externalizing problems in patients with FLE emerge. While several studies, consistent with our findings, report depression as the most frequent psychiatric diagnosis in children [18,21] and adults [10,12] with FLE, others [17,20] have found ADHD as the most frequent psychiatric feature. Even if depressive symptoms may be simplistically seen as an obvious consequence of a chronic illness like epilepsy, we can speculate that epileptogenic processes and the defective mood regulation may share some pathomechanisms (in particular, the impaired homeostasis of brain serotonin) [36]. Serotonin metabolism, indeed, is one of the main contributors to specific psychiatric phenotypes, i.e., depression, anxiety, and obsessive–compulsive disorder, and it is involved in the early vulnerability of brain networks affecting the homeostasis of excitatory (glutamatergic) and inhibitory (GABA) synapses, possibly affecting the increased susceptibility to epilepsy [37,38].

By exploring the association between EEG characteristics and psychiatric features of epilepsy, we found that children without psychopathological conditions (according to a categorical approach) displayed less frequently interictal EEG abnormalities over the "anterior areas". On the other hand, attention and memory problems were often associated with fast rhythms on frontal areas. A possible explanation for these findings is that anterior frontal regions have a crucial role for the highest mental functions, such as information integration, decision-making skills, executive functions, modulation of mood and emotions, and appropriateness of social behaviors [6]. The association between psychiatric dimensions, related to frontal dysfunction, and "bilateral interictal abnormalities" is instead consistent with previous data [18] showing an association between bifrontal foci and increased "Thought Problems" on the TRF [39]. More extensive and diffuse impairment of the frontal lobe functions may therefore likely increase the psychopathological risk in children with FLE.

The association between disruptive behavior disorders and lesions in the right hemisphere fits, in part, previous data describing an association between a right-sided epilepsy focus and an increased risk for ADHD in children with FLE [17]. In addition, this result seems to complement previous data demonstrating an association between internalizing problems and a left hemisphere involvement [18]. Taken together, these data suggest that right frontal dysfunction may predispose to externalizing problems, whereas contralateral structural or functional noxae are more often associated with internalizing problems.

The finding that problems in the psychiatric dimension of impulse control are significantly associated with a well-controlled epilepsy may seem paradoxical, but it is consistent with other reports on more aggressive behaviors and externalizing problems in children with a low seizure frequency (<1/week) [18]. This may possibly reflect mechanisms belonging to the phenomenon of the "forced normalization" [40], which consists in the emergence of psychiatric symptoms following an improvement of the EEG or of the seizure frequency. However, the neurobiological processes underlying the forced normalization in epilepsy are poorly understood. They may possibly result from complex interactions between electrical (e.g., spread of still active, subcortical, epileptic activities along unusual pathways), pharmacological, and neurotransmission mechanisms, mainly dysregulations of the central dopamine metabolism [41–43].

A major limitation of the study is the unavailability of the specific medication used by the patients. Antiepileptic drugs may have negatively affected some psychiatric manifestations; not alternatively, some medications may have mitigated some behavioral and/or affective (mood, anxiety) symptoms. However, the observation that patients receiving mono- or polypharmacotherapy did not differ according to psychiatric manifestations suggests that the role of medications may have not been substantial.

We are also aware that parceling the frontal lobe in relation to the predominant site of interictal paroxysms is just an approximation of the actual and likely complex behavior of paroxysmal activity in the brain and in the frontal lobe. This limitation is also due to the poor localizing value of the surface EEG. When possible with the term predominant location, we referred to the site where the interictal activity appeared more clearly focal beyond its tendency to spread; therefore, the location that we assumed was the closest to the site of paroxysm onset. However, we could not completely rule out the possibility that in some cases, the predominant location of interictal paroxysms results from rapid propagation of activity originating from another site, thus limiting the robustness of data associating paroxysm location and brain dysfunction.

5. Conclusion

A long epilepsy history and the occurrence of bilateral or anterior EEG abnormalities over the frontal lobe may affect the risk of psychopathology in FLE. Moreover, some features, such as the right localization of the epileptogenic lesion, the presence of fast rhythmic activities over the EEG, and the degree of seizure control, including phases of epilepsy remission, may increase the risk of displaying specific psychopathological symptoms that may define relatively consistent subgroups within heterogeneous clinical conditions like FLE. Finally, children with FLE and ID, besides having an earlier onset of seizures and of psychiatric features, and longer disease history, also require a specific attention for assessing and possibly preventing the development of behavioral disturbances and aggressiveness. Approaching the psychiatric assessment in both categorical and dimensional terms may increase our diagnostic, prognostic, and therapeutic abilities, allowing us a more precise and

specific stratification in children with FLE, and more clear targets for intervention. Furthermore, studies following this approach may generate new hypotheses and research addressing the complex, common pathophysiological bases shared by different neurodevelopmental disturbances.

Conflict of interest

The authors declare no conflict of interest.

Funding

This study was partially supported by the Ministry of Health, Italy (Ricerca Corrente to ARF and FS).

References

[1] LaFrance Jr WC, Kanner AM, Hermann B. Psychiatric comorbidities in epilepsy. Int Rev Neurobiol 2008;83:347–83.
[2] Baca CB, Vickrey BG, Caplan R, Vassar SD, Berg AT. Psychiatric and medical comorbidity and quality of life outcomes in childhood-onset epilepsy. Pediatrics 2011; 128(6):e1532–43.
[3] Russ SA, Larson K, Halfon N. A national profile of childhood epilepsy and seizure disorder. Pediatrics 2012;129(2):256–64.
[4] Alfstad KÅ, Torgersen H, Van Roy B, Hessen E, Hansen BH, Henning O, et al. Psychiatric comorbidity in children and youth with epilepsy: an association with executive dysfunction? Epilepsy Behav 2016;56:88–94.
[5] Erskine HE, Baxter AJ, Patton G, Moffitt TE, Patel V, Whiteford HA, et al. The global coverage of prevalence data for mental disorders in children and adolescents. Epidemiol Psychiatr Sci 2017;26(4):395–402.
[6] Miller John W. Epilepsy surgery in the frontal lobe: terra incognita or new frontier? Epilepsy Curr 2007;7(4):98–9.
[7] Besag F, Aldenkamp A, Caplan R, Dunn DW, Gobbi G, Sillanpää M. Psychiatric and behavioural disorders in children with epilepsy: an ILAE Task Force report. Epileptic Disord 2016;18(Suppl. 1):1–86.
[8] Kanner AM, Scharfman H, Jette N, Anagnostou E, Bernard C, Camfield C, et al. Epilepsy as a network disorder (1): what can we learn from other network disorders such as autistic spectrum disorder and mood disorders? Epilepsy Behav 2017;77: 106–13.
[9] Tang WK, Lu J, Ungvari GS, Wong KS, Kwan P. Anxiety symptoms in patients with frontal lobe epilepsy versus generalized epilepsy. Seizure 2012;21(6):457–60.
[10] Rayner G, Jackson GD, Wilson SJ. Behavioral profiles in frontal lobe epilepsy: autobiographic memory versus mood impairment. Epilepsia 2015;56(2):225–33.
[11] Pizzi AM, Chapin JS, Tesar GE, Busch RM. Comparison of personality traits in patients with frontal and temporal lobe epilepsies. Epilepsy Behav 2009;15(2):225–9.
[12] Helmstaedter C, Witt JA. Multifactorial etiology of interictal behavior in frontal and temporal lobe epilepsy. Epilepsia 2012;53(10):1765–73.
[13] Boone KB, Miller BL, Rosenberg L, Durazo A, McIntyre H, Weil M. Neuropsychological and behavioral abnormalities in an adolescent with frontal lobe seizures. Neurology 1988;38(4):583–6.
[14] Riva D, Saletti V, Nichelli F, Bulgheroni S. Neuropsychologic effects of frontal lobe epilepsy in children. J Child Neurol 2002;17(9):661–7.
[15] Auclair L, Jambaqué I, Dulac O, LaBerge D, Siéroff E. Deficit of preparatory attention in children with frontal lobe epilepsy. Neuropsychologia 2005;43(12):1701–12.
[16] Hernandez MT, Sauerwein HC, Jambaqué I, De Guise E, Lussier F, Lortie A, et al. Deficits in executive functions and motor coordination in children with frontal lobe epilepsy. Neuropsychologia 2002;40(4):384–400.
[17] Zhang DQ, Li FH, Zhu XB, Sun RP. Clinical observations on attention-deficit hyperactivity disorder (ADHD) in children with frontal lobe epilepsy. J Child Neurol 2014;29 (1):54–7.
[18] Braakman HM, Ijff DM, Vaessen MJ, Debeij-van Hall MH, Hofman PA, Backes WH, et al. Cognitive and behavioural findings in children with frontal lobe epilepsy. Eur J Paediatr Neurol 2012;16(6):707–15.
[19] Lassonde M, Sauerwein HC, Jambaqué I, Smith ML, Helmstaedter C. Neuropsychology of childhood epilepsy: pre- and postsurgical assessment. Epileptic Disord 2000;2(1):3–13.
[20] Prévost J, Lortie A, Nguyen D, Lassonde M, Carmant L. Nonlesional frontal lobe epilepsy (FLE) of childhood: clinical presentation, response to treatment and comorbidity. Epilepsia 2006;47(12):2198–201.
[21] Sinclair DB, Wheatley M, Snyder T. Frontal lobe epilepsy in childhood. Pediatr Neurol 2004;30(3):169–76.
[22] Achenbach TM, Rescorla LA. Manual for ASEBA preschool forms and profiles. Burlington, VT: University of Vermot, Research Center for Children, Youth, and Families; 2000.
[23] Achenbach TM, Rescorla LA. Manual for ASEBA school-age forms and profiles. Burlington, VT: University of Vermot, Research Center for Children, Youth, and Families; 2001.
[24] Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for School-age Children—Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36(7):980–8.
[25] Braakman HM, Vaessen MJ, Hofman PA, Debeij-van Hall MH, Backes WH, Vles JS, et al. Cognitive and behavioral complications of frontal lobe epilepsy in children: a review of the literature. Epilepsia 2011;52(5):849–56.
[26] Nolan MA, Redoblado MA, Lah S, Sabaz M, Lawson JA, Cunningham AM, et al. Intelligence in childhood epilepsy syndromes. Epilepsy Res 2003;53(1–2):139–50.
[27] Salanova V, Morris III HH, Van Ness PC, Lüders H, Dinner D, Wyllie E. Comparison of scalp electroencephalogram with subdural electrocorticogram recordings and functional mapping in frontal lobe epilepsy. Arch Neurol 1993;50(3):294–9.
[28] Bautista RE, Spencer DD, Spencer SS. EEG findings in frontal lobe epilepsies. Neurology 1998;50:1765–71.
[29] Kellinghaus C, Lüders HO. Frontal lobe epilepsy. Epileptic Disord 2004;6(4):223–39.
[30] Dykens EM. Psychopathology in children with intellectual disability. J Child Psychol Psychiatry 2000;41(4):407–17.
[31] Emerson E. Prevalence of psychiatric disorders in children and adolescents with and without intellectual disability. J Intellect Disabil Res 2003;47(Pt 1):51–8.
[32] Davies LE, Oliver C. Self-injury, aggression and destruction in children with severe intellectual disability: incidence, persistence and novel, predictive behavioural risk markers. Res Dev Disabil 2016;49-50:291–301.
[33] Austin JK, Smith MS, Risinger MW, McNelis AM. Childhood epilepsy and asthma: comparison of quality of life. Epilepsia 1994;35(3):608–15.
[34] Davies S, Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. Dev Med Child Neurol 2003;45(5):292–5.
[35] Kanner AM. Psychiatric comorbidities and epilepsy: is it the old story of the chicken and the egg? Ann Neurol 2012;72(2):153–5.
[36] Kanner AM. Depression and epilepsy: a bidirectional relation? Epilepsia 2011;52 (Suppl. 1):21–7.
[37] Clinckers R, Smolders I, Meurs A, Ebinger G, Michotte Y. Anticonvulsant action of GBR-12909 and citalopram against acute experimentally induced limbic seizures. Neuropharmacology 2004;47(7):1053–61.
[38] Dunn DW, Besag F, Caplan R, Aldenkamp A, Gobbi G, Sillanpää M. Psychiatric and behavioural disorders in children with epilepsy (ILAE Task Force report): anxiety, depression and childhood epilepsy. Epileptic Disord 2016;18(Suppl. 1):S24–530.
[39] Achenbach TM. Manual for the teacher report form and 1991 profile. Burlington: Department of Psychiatry, University of Vermont; 1991.
[40] Landolt H. Some clinical electroencephalographical correlations in epileptic psychoses (twilight states). Electroencephalogr Clin Neurophysiol 1953;5:121.
[41] Wolf P. Acute behavioral symptomatology at disappearance of epileptiform EEG abnormality. Paradoxical or "forced" normalization. Adv Neurol 1991;55:127–42.
[42] Kawakami Y, Itoh Y. Forced normalization: antagonism between epilepsy and psychosis. Pediatr Neurol 2017;70:16–9.
[43] Krishnamoorthy ES, Trimble MR. Forced normalization: clinical and therapeutic relevance. Epilepsia 1999;40:S57–64.