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Neuropsychological profiles and outcomes in children with new onset frontal lobe epilepsy

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ABSTRACT

Frontal lobe epilepsy (FLE) is the second most frequent type of localization-related epilepsy, and it may impact neurocognitive functioning with high variability. The prevalence of neurocognitive impairment in affected children remains poorly defined.

This report outlines the neuropsychological profiles and outcomes in children with new onset FLE, and the impact of epilepsy-related factors, such as seizure frequency and antiepileptic drug (AED) load, on the neurocognitive development.

Twenty-three consecutive children (15 males and 8 females) with newly diagnosed cryptogenic FLE were enrolled; median age at epilepsy onset was 7 years (6–9.6 years). They underwent clinical and laboratory evaluation and neuropsychological assessment before starting AED treatment (time 0) and after one year of treatment (time 1).

Twenty age-matched patients affected by idiopathic generalized epilepsy (10 male and 10 females) and eighteen age-matched healthy subjects (9 males and 9 females) were enrolled as controls and underwent the same assessment.

All patients with FLE showed a significant difference in almost all assessed cognitive domains compared with controls, mainly in frontal functions and memory. At time 1, patients were divided into two groups according to epilepsy-related factors: group 1 (9 patients) with persisting seizures despite AED polytherapy, and group 2 (14 patients) with good seizure control in monotherapy. A significant difference was highlighted in almost all subtests in group 1 compared with group 2, both at time 0 and at time 1.

In children with FLE showing a broad range of neurocognitive impairments, the epilepsy-related factors mostly related to a worse neurocognitive outcome are poor seizure control and the use of AED polytherapy, suggesting that epileptic discharges may have a negative impact on the functioning of the involved cerebral regions.

1. Introduction

Frontal lobe epilepsy (FLE) is the second most frequent type of localization-related epilepsy, after temporal lobe epilepsy, and it accounts for 20–30% of all partial epilepsies [1].

The frontal lobes are characterized by a complex functional organization supporting high-level integration circuits. They play a central role in cognitive functioning and behavior, as they mediate essential functions: (1) motor skills, control of continence, and olfaction; (2) voluntary eye movements; (3) language abilities; (4) executive functions; (5) behavior; and (6) social skills [2].

Structural and functional lesions affecting frontal lobes can, therefore, interfere with a variety of these functions and could lead to impairments in cognitive functioning and behavioral disorders [3].

Abbreviations: FLE, frontal lobe epilepsy; WISC-IV Wechsler Intelligence Scale for Children — Fourth Edition; Full-Scale IQ, Full-Scale Intelligence Quotient; VCI, Verbal Comprehension Index; PRI, Perceptual Reasoning Index; WMI, Working Memory Index; PSI, Processing Speed Index; AA, auditory attention; RS, response set; CL, clocks; IN, inhibition; CI, comprehension of instructions; PH, phonological processing; WGS, word generation semantic category; WGI, word generation initial letter; LM, list memory; LMD, list memory delayed; WI, word list interference; MD, memory for designs; MDD, memory for designs delayed; BC, block construction; GP, geometric puzzle.

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Andresen et al. [4] analyzed the effect related to the side of surgical resection on mood and behavior outcome in a large cohort of children with drug-resistant epilepsy and outlined that children with left FLE have greater emotional and behavioral dysfunctions before surgery, mainly characterized by anhedonia, social anxiety, and aggressive behavior, which improved after surgery.

The extent of cognitive impairment has not been systematically investigated, particularly in children.

Frontal lobe epilepsy in children is most often cryptogenic and may impact a wide range of neuropsychological functions with high variability. In some patients, cognitive challenges could appear at or before seizure onset [5], suggesting the existence of an underlying condition, microstructural or functional, that may manifest with seizures and neurocognitive impairment. Children with new onset epilepsy should undergo a prompt neuropsychological assessment to detect possible neuropsychological deficits linked to epilepsy-related factors to identify specific interventions that could improve outcome [5].

The purpose of our study was to outline the neuropsychological profiles and outcomes in children affected by new onset FLE. We also focused our attention on the impact that epilepsy-related factors, such as seizure frequency and antiepileptic drug (AED) load, could have on the neurocognitive development of children affected by this epileptic syndrome.

2. Materials and methods

2.1. Subjects

In this prospective multicenter study, we enrolled 23 consecutive patients with new onset FLE.

The inclusion criteria were: age at seizure onset ranging between 6 and 16 years and normal brain magnetic resonance imaging (MRI). The series comprised 15 males and 8 females, and the median age at epilepsy onset was 7 years (range: 6–9.6 years). We excluded patients with seizures that secondarily spread to the frontal lobes, multiple seizure foci and interictal epileptiform activity on EEG in areas outside the frontal lobes, brain lesions on MRI or symptomatic epilepsy, progressive neurological disorders, or cognitive impairment due to other causes.

In the same period, we recruited 20 age-matched patients affected by idiopathic generalized epilepsy (IGE) (10 males and 10 females) and 18 age-matched healthy children (9 males and 9 females) as control groups. The median age of the 20 patients with IGE at the time of assessment was 7.4 years (range: 6–10 years), and the median age of the 18 healthy children at the time of recruitment was 7.7 years (range: 6–10.2 years). The 18 healthy children were randomly recruited from mainstream public schools in the same Italian region and were, therefore, exposed to the same educational curriculum of the patients. Past medical history reported by parents was unremarkable. We did not include children with neuropsychiatric disorders and social and educational problems.

2.2. Assessment

All patients with FLE were followed by serial longitudinal clinical and EEG evaluations for one year to monitor the seizure trend and to assess the therapeutic load.

All patients underwent clinical assessment and EEG recordings during wakefulness and sleep. The EEG recordings were performed for at least 60 min, and digital recording including awake and sleep segments was done using the international 10–20 system for electrode placement. The EEG recordings were independently analyzed by two medical doctors who are board-certified experts in neurophysiology, both blinded for clinical information.

High-resolution brain MRI according to an epilepsy protocol [6] was performed in all.

After one year from epilepsy onset (time 1), epilepsy-related factors such as seizure frequency and AED load were recorded, and all recruited patients with FLE were divided into two groups according to epilepsy-related factors: the first one (group 1) included 9 patients (6 males and 3 females; median age at seizure onset was 6.8 years — range: 6–8.6 years) with persisting seizures (more than one seizure a month) despite polytherapy; the second one (group 2) consisted of 14 patients (9 males and 5 females; median age at seizure onset was 7.6 years — range: 6–9.6 years) with a good seizure control or low seizure frequency (less than one seizure a month) on monotherapy.

2.3. Cognitive and neuropsychological testing

All children enrolled in the study (patients with FLE, patients with IGE, and healthy children) underwent cognitive and neuropsychological assessment; patients with FLE and patients with IGE were assessed before starting any AED treatment (time 0).

Within 7 days from their inclusion, two standardized tests were performed consecutively in all recruited subjects.

The first assessment was performed to evaluate cognitive functions with the "Wechsler Intelligence Scale for Children" — Fourth Edition (WISC-IV) [7]. This last edition gives more attention to working memory and processing speed. It provides a Full-Scale IQ and four composite scores about intellectual functioning in specific cognitive domains: Verbal Comprehension Index (VCI), Perceptual Reasoning Index (PRI), Working Memory Index (WMI), and Processing Speed Index (PSI). The WISC-IV includes ten principal subtests and four additional ones shared among the four indexes.

Afterwards, NEPSY-II [8] was administered to all recruited subjects to assess neuropsychological abilities. This test provides a comprehensive neuropsychological profile of children aged between 3 and 16 years. The whole battery consists of 32 subtests and 4 delayed tasks evaluating six cognitive domains: attention and executive functioning (6 subtests), language (7 subtests), memory and learning (7 subtests), sensorimotor functioning (4 subtests), social perception (2 subtests), and visual–spatial processing (6 subtests). For the present study, we assessed 15 specific subtests: auditory attention (AA), response set (RS), clocks (CL), inhibition (IN), comprehension of instructions (CI), phonological processing (PH), word generation (specific semantic category: WGS or initial letter category: WGI), list memory (LM), list memory delayed (LMD), word list interference (WI), memory for designs (MD), memory for designs delayed (MDD), block construction (BC), and geometric puzzle (GP).

At time 1, all patients with FLE (group 1 and group 2) underwent revaluation of cognitive and neuropsychological abilities using both psychometric tests.

The same medical doctor who is a board-certified expert in neuropsychology, carried out these assessments, blinded for clinical information.

The ethical committee of the University of Perugia approved the study. Parents of all recruited children, who were instructed and informed about the aim of our study, provided informed consent, and the study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.4. Statistical analysis

The obtained WISC-IV and NEPSY-II scores were transformed into standard scores. Standard scores at time 0 both in patients and in control groups were compared using Kruskal–Wallis test with a post hoc comparison with Mann–Whitney's *U*-test using a Bonferroni correction for multiple comparison. The Mann–Whitney's *U*-test with a Bonferroni correction for multiple comparisons was performed to compare standard scores obtained in group 1 and group 2 patients with FLE at time 0 and at time 1, respectively.

Finally, the composite scores obtained with WISC-IV in group 1 at time 1 were compared with those obtained at time 0 using the Wilcoxon