

Frontal Lobe Growth Retardation and Dysfunctions in Children with Epilepsy: A 3-D MRI Volumetric Study

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Abstract

Behavioral abnormalities have been noted in specific epilepsy syndromes involving the frontal lobe. Epilepsies that involve the frontal lobe, such as frontal lobe epilepsy (FLE), atypical evolution of benign childhood epilepsy with centrotemporal spikes (BCECTS), and epilepsy with continuous spike-waves during slow sleep (CSWS), are characterized by impairment of neuropsychological abilities, frequently associated with behavioral disorders. These manifestations correlate strongly with frontal lobe dysfunction. Accordingly, epilepsies in childhood may affect the prefrontal cortex and leave residual mental and behavioral abnormalities. Brain volumetry has shown that frontal and prefrontal lobe volumes show a growth disturbance in patients with FLE, atypical evolution of BCECTS, and CSWS compared with those of normal subjects. These studies also showed that seizures and the duration of paroxysmal anomalies may be associated with prefrontal lobe growth abnormalities, which are associated with neuropsychological problems. Moreover, these studies also showed that the prefrontal lobe appears more highly vulnerable to repeated seizures than other cortical regions. The urgent suppression of these seizure and EEG abnormalities may be necessary to prevent the progression of neuropsychological impairments. Treatment options to remit seizures and EEG abnormalities as soon as possible may be required to achieve the optimal prognosis in frontal lobe epilepsies. Of the new AEDs, levetiracetam (LEV) may be an important addition to the treatments available for refractory childhood epilepsies with cognitive and behavioral problems.

Keywords: Benign childhood epilepsy with centrotemporal spikes (BCECTS); Brain damage; Brain volumetry; Epilepsy with continuous spikes and waves during slow sleep (CSWS); Frontal lobe epilepsy (FLE); Levetiracetam (LEV); Prefrontal lobe; Seizure recurrence

Introduction

Behavioral changes in patients with frontal lobe seizures can be related to multiple causes. Patients with frontal lobe seizures due to identifiable frontal lobe lesions (e.g., tumor, cortical dysplasia, and encephalomalacia) may exhibit behavioral disorders consistent with lesion location. However, patients without clear lesions can exhibit similar disorders. Indeed, behavioral abnormalities have also been noted in specific epilepsy syndromes involving the frontal lobe. In rolandic epilepsy, which involves the primary motor cortex, a negative correlation has been observed between the amount of electroencephalogram (EEG) spiking and performance on cognitive function measures. It has been suggested that this cognitive/behavioral profile is related to frontal lobe dysfunction. However, it is unclear whether these cognitive/behavioral impairments are due to an unidentified lesion, intermittent epileptiform paroxysmal discharges and spread thereof, or frequent seizures.

The frontal lobes comprise about a third of the cerebral cortex in humans. The prefrontal parts constitute a massive network that links the brain's motor, perceptual, and limbic regions [1]. This extensive system of connections makes it possible for the prefrontal cortex to receive information from practically all parts of the brain, as well as to influence the information processing in those parts. In contrast, prefrontal functions can show an unusually long period of increased vulnerability, in which neurons and glial cells are readily affected by many factors, including genetic influences, the hormonal milieu, and external insults, such as infections, toxins, and trauma [2]. In these investigations, the prefrontal lobe appears more highly vulnerable to repeated seizures than other cortical regions [3].

Previous studies have shown that patients with epilepsy have many health-related quality of life (QOL) concerns, and these frequently involve issues related to a desire for greater independence, less

stigmatization, improved mood and cognition, absence of drug-related adverse effects, and complete control of seizures [4-6]. Thus, successful management of patients with epilepsy requires individualized treatment. It is generally accepted by most workers in the field that the degree of behavioral problems associated with epilepsy is greater than would be expected on the basis of the existence of a chronic illness alone in children. In the past, the emphasis has been on the outcome in terms of seizure control. However, there has been an increasing recognition of the value of pediatric epilepsy syndrome classification with regard to other factors, particularly cognition and behavior.

In general, focal epilepsies are often associated with neuropsychological, behavioral, and emotional problems that can also affect a patient's adaptive functioning [7]. In particular, frontal localization of the epileptic focus correlates with executive dysfunction. Epilepsies with involvement of the frontal lobe, such as frontal lobe epilepsy (FLE), benign childhood epilepsy with centrotemporal spikes (BCECTS), and epilepsy with continuous spike and waves during slow sleep (CSWS), were formerly invariably considered to be the consequences of overt or obscure brain lesions. Children with frontal lobe epilepsies manifest significant psychosocial problems relative to normative standards [8]. These studies suggest that treatment may be required to remit seizures as soon as possible to achieve optimal

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prognosis with respect to cognitive and behavioral outcomes in children with several epilepsies.

The maturing processes of the frontal lobes are protracted. Current research suggests that damage to the frontal regions during childhood may interrupt normal maturational processes and organization, resulting in impairments to neurobehavioral development. On the other hand, the effects of seizures on neuronal survival and brain growth have remained controversial [9,10]. However, recent review articles have reached the conclusion that seizures impair the developing brain [11]. The likelihood that even morphological damage may depend on the age at which epileptic seizures develop must be taken into account [12]. Frequent and severe seizures may lead to cognitive and behavioral impairments.

Brain Volumetric Analyses in Central Nervous System (CNS) Diseases

Magnetic resonance imaging (MRI)-based volumetry has become established as a versatile, reliable method for investigating the biology of the human brain [13]. Brain volumetric analysis has contributed to the search for structural correlates of developmental disorders such as autism [14] and seizure disorders such as temporal lobe epilepsy [15]. These studies showed stronger correlations between disability and the quantitative assessment of cerebral atrophy. In addition, using three-dimensional (3D) MRI, it has been confirmed that decreased frontal lobe volumes correlated with clinical regression in subacute sclerosing panencephalitis [16]. Volumetric analysis of the brain may predict function in the affected regions [17]. Thus, quantification of brain volume is a useful way of characterizing abnormal development due to various CNS diseases. The maturation-associated changes detectable during development will be important for comparison with maturational sequences in developmental disorders.

	Seizure duration	Prefrontal lobe growth retardation	Recovery
FLE			
with behavioral problems			
patient 1	2 y 8 mo	present	delayed
patient 2	1 y 4 mo	present	rapid
without behavioral problems			
patients (n=4)	5.5 mo (mean)	absent	n.a.
BCECTS			
with atypical evolution			
patient 1	2 y 11 mo	present	delayed
patient 2	1 y 5 mo	present	rapid
with typical course			
patients (n=5)	4 mo (mean)	absent	n.a.
CSWS			
with longer seizure duration			
patient 1	1 y 2 mo	present	delayed
patient 2	1 y 7 mo	present	delayed
patient 3	1 y 9 mo	present	delayed
with shorter seizure duration			
patients (n=2)	5 mo (mean)	present	rapid

Abbreviations: FLE: Frontal Lobe Epilepsy; BCECTS: Benign Childhood Epilepsy with Centrottemporal Spikes; CSWS: Epilepsy with Continuous Spike-Waves during Slow Wave Sleep; n.a: Not Applicable

Table 1: Volumetric analyses of the prefrontal lobe in children with frontal epileptic origin seizures.

Serial 3D-MRI Volumetric Studies of the Prefrontal Lobe in Children with Epilepsy that Impacts Cognition and Behavior

FLE

From a clinical point of view, it is important to understand the impact of FLE on the life of affected patients. The consequences of the long-lasting process of myelination of the prefrontal lobes for neuropsychologic functioning have been discussed. The likelihood that even morphological damage may depend on the age at which epileptic seizures develop must be taken into account [18]. Severe and recurrent seizures may lead to cognitive and behavioral impairments. On the basis of these observations, prospective measurements of frontal and prefrontal lobe volumes using 3D-MRI-based volumetry were performed in patients with FLE presenting with the same seizures [3]. As shown in Table 1, frontal and prefrontal lobe volumes and the prefrontal-to-frontal lobe volume ratio increased serially in FLE patients without cognitive/behavioral impairments and controls. In contrast, frontal and prefrontal lobe volumes showed no obvious growth during the active seizure period in the FLE patients with cognitive/behavioral impairments. In addition, the prefrontal-to-frontal lobe volume ratio was stagnant or showed a reduction during the active seizure period in the FLE patients with cognitive/behavioral impairments. Patients with a shorter active seizure period soon achieved a restored growth ratio. Conversely, the growth ratio was delayed in patients with a longer active seizure period (Table 1). Growth of prefrontal lobe volume gradually normalized in all patients after seizure disappearance [3]. These results suggest that the occurrence of frequent seizures in patients with FLE might be associated with prefrontal lobe growth retardation, which relates to neuropsychological problems and ultimate neuropsychological outcome.

Atypical evolution of BCECTS

BCECTS is the most frequent of the benign focal epilepsies of childhood [19]. Children with BCECTS are often noted to be free of neurological and psychological impairments. However, increasingly, a considerable proportion of children with BCECTS have been shown to have behavioral problems such as hyperactivity and impulsivity [17]. Such impairments are more prevalent in children with atypical EEG features or atypical seizure semiology [20,21]. With up to 20% of children, two or more antiepileptic drugs (AEDs) are needed to achieve adequate seizure control [22].

Serial 3D-MRI studies were performed in BCECTS patients with or without cognitive/behavioral problems [17,23]. This study showed that frontal and prefrontal lobe volumes and prefrontal-to-frontal lobe volume ratio increased serially in BCECTS without cognitive/behavioral problems in a manner similar to controls (Table 1). In contrast, frontal and prefrontal lobe volumes showed no obvious growth during seizures in BCECTS patients with cognitive/behavioral problems [23]. In addition, the prefrontal-to-frontal lobe volume ratio was stagnant or decreased in BCECTS with cognitive/behavioral problems. Moreover, prefrontal growth also showed more rapid recovery in a BCECTS patient with cognitive/behavioral problems with a shorter active seizure period in that study (Table 1). These findings suggested that clinical symptoms, such as frequent seizures, and clinical investigations, such as paroxysms on EEG, might be associated with prefrontal lobe growth disturbance, which relates to neuropsychological problems in BCECTS children.

CSWS

CSWS is characterized by an impairment of neuropsychological abilities, frequently associated with behavioral disorders (reduced attention span, aggressiveness, difficulty interacting with the environment), hyperactivity, learning disabilities and, in some instances, psychotic regression [24]. These manifestations correlate strongly with frontal lobe dysfunction. Neuropsychological impairment occurs in almost all cases of CSWS, usually being coincidental with the detection of electrical status epilepticus during slow sleep (ESES) and representing one of the crucial signs of the syndrome [25]. The severities and persistence of cognitive and behavioral impairments seem to be correlated with the duration and severity of the EEG pattern [26]. In recent studies, frontal and prefrontal lobe volumes using 3D-MRI were measured in patients with CSWS [24,27]. All patients had normal findings on routine MRI studies, but they showed behavioral disturbances and/or cognitive impairments. As shown in Table 1, patients with CSWS duration of less than 6 months showed remarkable improvements of behavioral disturbances. In contrast, patients with CSWS duration longer than one year developed progressive cognitive and behavioral deteriorations, even after seizure and paroxysmal EEG activities disappeared [27]. In these studies, frontal and prefrontal lobe volumes showed growth disturbance in all CSWS patients compared with those of normal subjects [27]. In addition, prefrontal to frontal lobe volume ratios increased serially in normal subjects, whereas the ratios decreased in all CSWS patients. Moreover, these studies revealed that, in the patients with shorter seizure durations and CSWS periods, prefrontal to frontal lobe volume ratios were soon restored to normal values, whereas growth disturbances of the prefrontal lobes were persistent in the patients with longer seizure durations and CSWS periods (Table 1). The durations of symptoms such as seizures and paroxysmal abnormalities were longer in patients with poor outcomes than in those who had better outcomes. These findings suggest that seizures and the duration of paroxysmal anomalies might be associated with prefrontal lobe growth disorders that are associated with neuropsychological problems such as behavioral impairments.

Pathological Mechanisms Underlying Cognitive and Behavioral Impairments in Children with Epilepsy

Studies of children with known involvement of the frontal lobes, animal research, and recent imaging studies in healthy subjects and patient groups have provided much knowledge related to the role played by these structures in human behavior. This knowledge has facilitated the selection of methods for assessing the neuropsychologic effects of frontal lobe epilepsies, and it has pointed out the kinds of deficits to look for, assuming that epilepsy mimics other kinds of damage [28]. Given the frequent occurrence of seizures in children, and the unquestionable risk of vigorous medical treatment, the question of vulnerability of the developing brain to seizure-induced damage acquires great importance. For instance, while the majority of children with epilepsy do well, a small percentage of children with epilepsy have cognitive and behavioral problems. A frontal localization of the epileptic focus correlates with executive dysfunction. The immature brain appears to be more resistant to the toxic effects of glutamate than the mature brain [29]. In contrast, excitotoxic neuronal death is affected by brain maturation [30]. Since apoptosis plays an important role in early brain development, the immature brain may be particularly vulnerable to programmed cell death in response to seizures [3].

MRI is currently the most effective method for detecting gross

structural lesions in patients with various CNS diseases. Although a quantitative measure of contrast variance on MRI is not readily available for routine imaging, given the possibility that some functional changes may have structural correlates, MRI could also play a pivotal role in elucidating the mechanisms underlying epileptogenesis. Quantification of brain volume using 3D-MRI is thus a useful way of characterizing normal growth and abnormal development due to various CNS diseases [31]. Furthermore, volumetric analysis of the brain may predict function in corresponding regions [17].

To confirm the behavioral findings, studies on brain volumetry using 3D-MRI confirmed anomalies in prefrontal lobe growth and functioning in children with epilepsy. In BCECTS, the prefrontal-to-frontal lobe volume ratio increased serially in patients with cognitive/behavioral functioning, as in controls, but it was stagnant or decreased in patients with cognitive/behavioral impairments. Moreover, prefrontal growth also recovered more rapidly in the BCECTS patient with shorter active seizure periods [22]. Similarly, in CSWS, prefrontal lobe volume, especially the prefrontal-to-frontal lobe volume ratio, showed a growth disturbance during CSWS. This finding provided further support for consideration of the pathological mechanisms, in that seizures and the duration of paroxysmal anomalies may be associated with prefrontal lobe growth disorders that are associated with neuropsychological problems such as behavioral impairments. In FLE, frontal and prefrontal lobe volumes showed growth patterns similar to control subjects in patients without cognitive/behavioral impairments. In contrast, frontal and prefrontal lobe volumes and the prefrontal-to-frontal lobe volume ratio in particular showed growth disturbances during the seizure period. These findings suggest that repeated seizures combined with EEG abnormalities may lead to prefrontal growth disturbance, reflecting cognitive and behavioral impairments. Children with frontal lobe epilepsies such as BCECTS, CSWS, and FLE presenting with cognitive and behavior deficits may show frontal/prefrontal lobe retardation, which reflects poor frontal lobe functioning. Therefore, these investigations show strong evidence for the vulnerability of the immature brain to seizure-induced damage, which bears features of both necrotic and apoptotic death and contributes to synaptic reorganization [32].

Seizure Recurrence and Cognitive/Behavioral Impairments

There are controversial data relating to the correlation between seizure recurrence and neuropsychological findings. In early studies, frequent and severe seizures were associated with behavioral problems [33,34]. The frequency of complex partial seizures in the previous year was regarded as the strongest predictor of behavioral problems [35]. In another study by Lendt et al, behavioral impairments were reduced in a group of children after successful surgery for epilepsy compared with children experiencing persistent focal seizures [36]. In contrast, some studies have shown no association between behavioral problems and more frequent seizures [37]. Although this aspect has been debated as above, in a more recent prospective study, seizure recurrence significantly predicted behavioral problems [38]. This investigation combined with brain volumetry findings suggests that repeated seizures can induce behavioral impairments. According to Austin, possible explanations for this relationship are summarized as follows: a) seizures and behavioral problems are associated because both are related to an underlying factor; b) seizure activity per se disrupts behavior; or c) children have a negative psychological response to seizures [38]. In a brain volumetric study in children with FLE [3], seizure recurrence was associated with prefrontal lobe growth disturbance,

which is related to neuropsychological impairments. In children with epilepsies involving the frontal lobe, such as BCECTS and CSWS, the active seizure period of frequent spike-waves coupled with frequent seizures may be associated with prefrontal lobe growth disturbance [17,22,23,26]. Damage to the frontal regions during childhood may interrupt normal maturational processes and organization, resulting in impairments of neurobehavioral development. Current research in epilepsies involving the frontal lobe may clarify the factors that affect volumetric abnormalities, such as seizure frequency. These results may support the second possibility suggested by Austin et al. [34]. However, it is important to note that the majority of the studies contained only qualitative data analysis without using statistical analyses. Further research is needed to clarify this point.

How do we Treat Children with Epilepsy Presenting with Cognitive/Behavioral Problems?

Since neuronal damage and cognitive decline have long been recognized as sequelae of intractable epilepsy in children, early seizure control is crucial for physiological and social reasons [39]. Several studies, including prospective brain volumetric research, have shown that repeated seizures can induce neuropsychological impairments. Based on these volumetric and prospective studies, in considering outcomes for children with epilepsy, control of seizures must be weighed against the incidence of neurological impairment. We should consider that, from a therapeutic viewpoint, the most critical fact is whether seizures themselves can damage the brain. Treatment to remit seizures immediately may be required to achieve the optimal outcome in children with cognitive or behavioral involvement. However, seizures originating from the frontal lobe may often be difficult to control. A previous study showed that only half of patients were controlled on anti-epileptic medications [8]. Although seizures and EEG abnormalities in children, such as atypical evolution of BCECTS and CSWS, are age-dependent and self-limiting, neuropsychological impairments are often intractable before adolescence. The objective of treatment is not necessarily a seizure-free state, but rather improvements in alertness, cognition, mood, and behaviors.

Few AEDs may control intractable epilepsy involvement of the frontal lobe, such as atypical evolution of BCECTS, CSWS, and FLE, but none of them has been proven to be effective in a randomized study. Conventionally, valproate sodium (VPA) alone or in combination with a benzodiazepine (BDZ) is the treatment of choice for epilepsies with CSWS [24]. In addition, VPA in combination with BDZ and ethosuximide (ESM) has been shown to decrease interictal epileptiform discharges in patients with CSWS and atypical evolution of BCECTS [22,23]. However, these suggestions are based primarily on case reports. Despite the introduction into clinical practice of 10 or more new AEDs during the past 20 years, these drugs have had insufficient impact on the prognosis of intractable epilepsy. Of the new AEDs, levetiracetam (LEV) is a new AED approved as adjunctive treatment for partial epilepsy [40-42]. Recently, LEV has been shown to have efficacy and safety in children with intractable epilepsy [43]. In addition, LEV has been observed to have an effect in children with refractory epilepsy with secondary bilateral synchrony (SBS) [44]. In this study, LEV showed effectiveness for seizure and EEG abnormalities in children with epilepsy presenting with SBS, such as CSWS, atypical evolution of BCECTS, and FLE, in whom cognitive and behavioral problems were serious. Furthermore, LEV was also shown to decrease hyperactivity and impulsivity in these patients [44]. LEV may represent an important

addition to the treatments available for refractory childhood epilepsies with SBS on EEG.

Conclusion

In conclusion, long seizure duration, seizure recurrence, and paroxysmal EEG abnormalities can induce brain damage. Moreover, these may be associated with prefrontal lobe growth disturbances resulting in neuropsychological problems and ultimate neuropsychological outcome in children with epilepsy involving the frontal lobe, such as FLE, atypical evolution of BCECTS, and CSWS. To prevent these disturbances and problems in children with epilepsy, treatment to remit seizures and EEG abnormalities as soon as possible may be required to achieve optimal outcomes for children with cognitive/behavioral problems.

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