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CRITICAL REVIEW AND INVITED COMMENTARY

Cognitive and behavioral complications of frontal lobe epilepsy in children: A review of the literature

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Summary

Frontal lobe epilepsy (FLE) is considered the second most common type of the localization-related epilepsies of childhood. Still, the etiology of FLE in children, its impact on cognitive functioning and behavior, as well as the response to antiepileptic drug treatment in children has not been sufficiently studied. This review focuses on these aspects of FLE in childhood, and reveals that FLE in childhood is most often cryptogenic, and impacts on a broad range of cognitive functions. The nature and severity of cognitive deficits are highly variable, although impaired attention and executive functions are most frequent. Young age at seizure onset is the only potential risk factor for poor cognitive outcome that has been consistently reported. The behavioral disturbances associated with FLE are also highly variable, although attention deficit/hyperactivity disorder seems most frequent. In 40% of children with FLE satisfactory seizure control could not be achieved. This is a higher percentage than reported for the general population of children with epilepsy. Therefore, pediatric FLE, even if cryptogenic in nature, is frequently complicated by impairment of cognitive function, behavioral disturbances, and therapy-resistance. Given the impact of these complications, there is a need for studies of the etiology of frontal lobe epilepsy-associated cognitive and behavioral disturbances, as well as pharmacotherapy-resistance.

KEY WORDS: Epilepsy, frontal lobe, Cognition, Behavior, Child, Magnetic resonance imaging, Drug therapy.

Frontal lobe epilepsy (FLE) is considered the second most common type of the localization-related (partial) epilepsies of childhood, after temporal lobe epilepsy, and accounts for 20–30% of partial epilepsies, although data on its exact incidence are lacking (Manford et al., 1992).

The frontal lobes play pivotal roles in cognitive functioning and behavior, as they mediate essential functions: (1) basic neurologic functions, including motor functions, control of continence, and olfaction; (2) voluntary eye movements; (3) speech and language abilities; (4) executive functions; (5) motivational behaviors; and (6) social competency (Cummings & Miller, 2007). Consequently, both structural lesions and functional lesions, such as an epileptic focus, within the frontal lobes may interfere with a variety of these functions and can lead to impairments of cognitive functioning and behavioral disturbances. In adults with FLE, cognitive deficits and behavioral disturbances range from impaired attention to difficulty with the more complex behaviors involved in planning, selecting goals, anticipating outcomes, and initiating actions (Helmstaedter et al., 1996, 1998; Upton & Thompson, 1996, 1997a,b; Exner et al., 2002). The impact of FLE on cognitive functioning and behavior in children remains largely unknown.

In addition to neuropsychological complications, FLE is frequently complicated by pharmacotherapy resistance. In adult patients referred to epilepsy surgery centers, frontal lobe epilepsy represents 15–30% of pharmacotherapy-resistant seizure disorders (Helmstaedter et al., 1996; Helmstaedter, 2001). For adults, pharmacotherapy-resistant epilepsy is associated with increased morbidity from seizures and medication, social isolation, unemployment, and overall reduced quality of life (Sillanpää et al., 1998). Yet not all patients with FLE will develop pharmacoresistance, and the mechanisms that result in either seizure control or refractoriness have not been explored. This review summarizes the available literature on the etiology of FLE in children, its impact on cognitive functioning and behavior, as well as the response to antiepileptic drug treatment, and it explores areas for future research. Surgical therapy and the effects of surgical therapy on cognitive and behavioral outcomes fall outside the scope of this review.

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Search Strategy and Selection Criteria

Data for this review were identified by searches of PubMed (National Center for Biotechnology Information; NCBI; http://www.ncbi.nlm.nih.gov/pubmed/) in January 2010 using the Medical Subject Heading (MeSH) terms "Epilepsy, Frontal Lobe," "Epilepsies, Partial," and "Epilepsy, Complex Partial." For the latter two, the text variable "frontal" was added to narrow the search. Subheadings "classification," "complications," "drug therapy," "epidemiology," "etiology," "psychology," "radiography," and "therapy" were applied, with limits: "All child 0–18 years" and "English." References from relevant original and review articles and book chapters were also used.

Etiology of FLE in Childhood

The average age at onset of FLE ranges from 4.6 to 7.5 years (Kral et al., 2001; Lagae et al., 2001; Lawson et al., 2002; Sinclair et al., 2004). From the available literature, it is difficult to assess the relative incidences of the three etiologies of FLE: symptomatic, cryptogenic, and idiopathic. In general, most studies focus on adults. Moreover, existing pediatric studies are case series that frequently include etiology in their exclusion criteria, or reports of single cases, leading to substantial bias (Boone et al., 1988; Lassonde et al., 2000; Kral et al., 2001; Culhane-Shelburne et al., 2002; Lawson et al., 2002; Lendt et al., 2002; Riva et al., 2002; Hernandez et al., 2003; Sinclair et al., 2004; Riva et al., 2005; Prévost et al., 2006). We found seven studies, with a total of 122 children with FLE that applied magnetic resonance imaging (MRI) to determine FLE etiology in unselected groups; we have summarized their respective findings in Table 1 (Lagae et al., 2001; Lawson et al., 2002; Nolan et al., 2004; Sinclair et al., 2004; Aoyagi et al., 2005; Auclair et al., 2005; Jocić-Jakubi et al., 2009). Cryptogenic FLE was most common in children, as MRI revealed no structural abnormalities in 91 of 122 children (75%), whereas 31 children (25%) had lesions suggesting a symptomatic nature of their FLE.

In studies that included children with symptomatic FLE, the etiology of the lesions differed (Lawson et al., 2002; Nolan et al., 2004; Sinclair et al., 2004; Aoyagi et al., 2005; Auclair et al., 2005; Jocić-Jakubi et al., 2009). We found a total of six studies, including 31 patients; focal cortical dysplasia (n = 13) (see Fig. 1), infarction (n = 5), and low-grade and high-grade tumors (n = 3) (see Fig. 2) were most frequent. Rarely, lesions resulted from hemorrhage (n = 1), cortical tuber (n = 1), or porencephaly (n = 1) (Lawson et al., 2002; Sinclair et al., 2004; Aoyagi et al., 2005; Auclair et al., 2005; Jocić-Jakubi et al., 2009). In one study, MRI lesions were not further specified (n = 7) (Nolan et al., 2004).

Table 1. Etiology of frontal lobe epilepsy in children

References	Number of patients	Etiology on basis of MRI
Auclair et al. (2005)	8	3/8 symptomatic 5/8 cryptogenic
Aoyagi et al. (2005)	12	5/12 symptomatic 7/12 cryptogenic
Jocić-Jakubi et al. (2009)	10	10/10 cryptogenic
Lagae et al. (2001)	7	7/7 cryptogenic
Lawson et al. (2002)	38	12/38 symptomatic 26/38 cryptogenic
Nolan et al. (2004)	25	7/25 symptomatic 18/25 cryptogenic
Sinclair et al. (2004)	22	4/22 symptomatic 18/22 cryptogenic
Total	122	31/122 (25%) symptomatic 91/122 (75%) cryptogenic

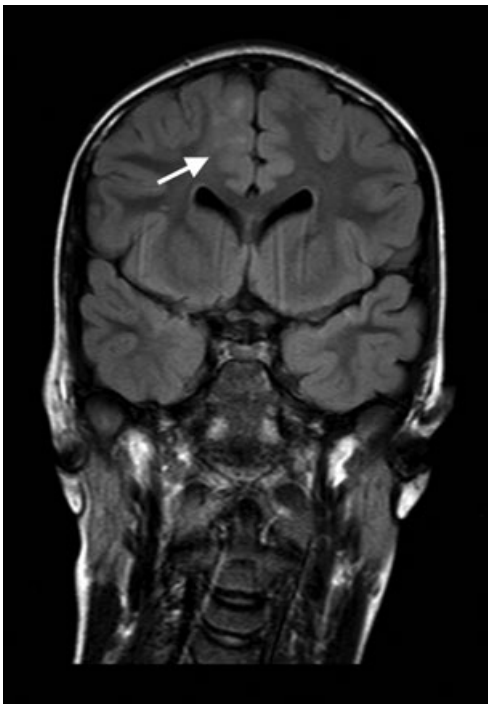

Figure 1.
Coronal fluid-attenuated inversion recovery (FLAIR) image; arrow marks an area of focal cortical dysplasia.
Epilepsia © ILAE

Cognitive and Behavioral Functioning in Children with FLE

Cognitive functioning in children with FLE

The associations between FLE and cognitive and behavioral functioning have been studied in more detail. The first representative case describing cognitive deficits associated with cryptogenic FLE was reported by Boone et al. (1988).

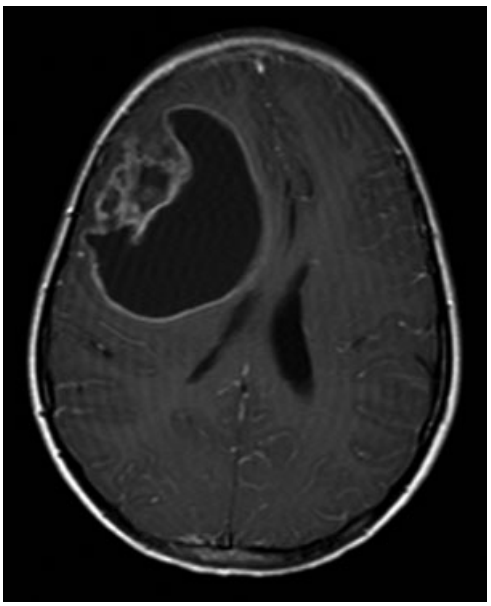

Figure 2.
Axial T_1-weighted gadolinium-enhanced image of a high-grade astrocytoma.
Epilepsia © ILAE

They described a 13-year-old girl with impaired performance on tasks that measure attention and concentration and impairments of verbal fluency, ability to shift cognitive set, motor speed, motor functioning, planning abilities, and response inhibition. Other frontal lobe executive functions such as categorization, sequencing, and conceptual flexibility had remained intact. The deficits were reversible once seizures were sufficiently controlled with antiepileptic drug (AED) treatment. Similarly, Jambaqué and Dulac (1989) observed deterioration of verbal fluency and attention span and marked behavioral and affective changes in an 8-year-old boy of normal intelligence, as well as reduced motor speed and planning ability with deterioration of handwriting, which abated with adequate seizure control. The fact that cognitive deficits improved in these two patients with the initiation of successful AED treatment suggests that they were caused by the seizures or interference by underlying epileptiform activity in affected frontal areas. In addition to these two illustrative case reports, our literature search yielded 10 case series, with a total of 149 children with FLE who had undergone neuropsychological assessment (Lassonde et al., 2000; Culhane-Shelburne et al., 2002; Lendt et al., 2002; Riva et al., 2002; Hernandez et al., 2003; Nolan et al., 2003; Sinclair et al., 2004; Auclair et al., 2005; Riva et al., 2005; Prévost et al., 2006). A summary of the main studies and their findings is recorded in Table 2. Most existing studies are comparative in nature and compare cognitive functioning of children with FLE with children with temporal lobe epilepsy and generalized epilepsy (Lassonde et al., 2000; Culhane-Shelburne et al., 2002; Hernandez et al., 2003; Nolan et al., 2003). In this comparison, children with FLE typically have impairments in executive functions [mainly planning ability, response inhibition, (visuospatial) organization, verbal search, mental flexibility, impulse control, working memory and programming of complex motor sequences], motor coordination, and attention deficits (Lassonde et al., 2000; Culhane-Shelburne et al., 2002; Hernandez et al., 2003; Nolan et al., 2003). The term ''executive functions'' refers to the mental processes involved in the realization of goal-directed behavior, whether expressed through a mental or a motor act (Lezak, 1995). They are generally thought to control formulation, planning, and effective performance of goal-directed actions (Lezak, 1995). Perhaps as a result, the impairments in executive functions also give rise to impaired reading and mathematical skills (Lagae et al., 2001).

FLE impacts on a wide scale of cognitive domains other than the executive functions. In one case series of six children with a left frontal epileptogenic focus, a clear dissociation in linguistic performance between comprehension and production was noted (Cohen & Le Normand, 1998). Linguistic comprehension was initially impaired, but gradually improved to reach normal performance levels by age 7,

Table 2. A summary of the main studies of children with FLE who had undergone neuropsychological assessment and their findings

References	Number of patients	Neuropsychological impairments
Auclair et al. (2005)	8	Attention deficits
Culhane-Shelburne et al. (2002)	12	Deficits in executive functions
Hernandez et al. (2003)	16	Deficits in executive functions, attention, and behavior
Lassonde et al. (2000)	16	Deficits in executive functions, attention, behavior, and motor skills
Lendt et al. (2002)	12	Deficits in motor coordination, short- and long-term memory, attention, and executive functions
Nolan et al. (2004)	25	Memory impairment
Prévost et al. (2006)	21	Deficits in attention, behavior, language, memory, and cognition
Riva et al. (2002)	8	Deficits in attention, behavior, and executive functions
Riva et al. (2005)	17	Deficits in executive functions
Sinclair et al. (2004)	14	Below normative IQ scores, impaired fine-motor coordination, deficits in attention, behavior and executive functions

whereas linguistic production, even at later stages, remained poor. This dissociation in the development of linguistic performance in children with left-sided FLE suggests a complex interplay between brain maturation dynamics and FLE-associated dysfunction, modulating the succession of stages in language development. Other researchers have also noted language deficits in children with FLE, including impaired verbal fluency and impaired verbal search (Boone et al., 1988; Jambaqué & Dulac, 1989; Lassonde et al., 2000; Prévost et al., 2006).

Memory deficits have long been attributed mainly to temporal lobe epilepsy; their association with FLE remains controversial. Because memory deficits have been associated specifically with mesial temporal lobe pathology, children with FLE may not be routinely tested for their memory skills. Nevertheless, four studies have noted these deficits in their patients with FLE (Jambaqué et al., 1993; Lendt et al., 2002; Nolan et al., 2004; Prévost et al., 2006). In one study, longer duration of active epilepsy was the most significant risk factor for memory impairment (Nolan et al., 2004). In contrast, other case series have examined this subject and found memory functions intact (Jambaqué & Dulac, 1989).

The overall impact of FLE on intelligence, as measured by intelligence quotient (IQ) scores, remains a subject of debate. Intelligence is defined as a person's capacity to (1) acquire knowledge (i.e., learn and understand), (2) apply knowledge (solve problems), and (3) engage in abstract reasoning (Wechsler, 1994). Although some case series of children with FLE have reported that IQ was spared, despite various impairments of cognitive function (Riva et al., 2002, 2005), others have reported a decline in IQ scores (Nolan et al., 2003; Sinclair et al., 2004; Prévost et al., 2006). Here, too, selection bias is an important issue; a normal IQ score has been used as an inclusion criterion for neuropsychological assessment in case series (Lassonde et al., 2000; Culhane-Shelburne et al., 2002; Hernandez et al., 2003).

Interesting similarities between the cognitive impairments of children and adult patients with FLE exist. In adults, neuropsychological deficits are also prevalent. The nature and severity of cognitive deficits in adult FLE patients are highly variable, although here, too, impaired attention and executive functions are most frequent (Helmstaedter et al., 1996; Upton & Thompson, 1997a,b; Helmstaedter et al., 1998; Exner et al., 2002). Unfortunately, studies tend to focus on the typical frontal lobe functions (e.g., executive functions), disregarding functions typical of other lobes, such as memory, which is regarded as a temporal lobe function (Hernandez et al., 2002; Riva et al., 2002, 2005).

How site-specific are cognitive deficits?

One would assume that the pattern of deficits observed in patients with epilepsy reflects the functions controlled in the area that yields the epileptic focus. Indeed, temporal lobe epilepsy is associated with cognitive deficits specific to the temporal lobe functions, mainly learning (especially reading) and memory. Yet, frontal lobe dysfunction has been noted in up to 84% of children and adolescents with temporal lobe epilepsy (Igarashi et al., 2002; Rzezak et al., 2007). These patients had impairments in mental flexibility and set shifting, perseveration, inhibitory control, verbal fluency, and maintenance of attention (Rzezak et al., 2007). It has been hypothesized that a wider anatomic and functional network connects temporal and frontal lobes and allows the temporal epileptogenic focus to affect the frontal and prefrontal functional regions (Igarashi et al., 2002; Rzezak et al., 2007). In accordance with this hypothesis, recent functional neuroimaging studies demonstrated hypometabolism in the prefrontal regions of patients with TLE (Nelissen et al., 2006). This hypometabolism may represent a dynamic process of protection against epileptiform discharge propagation by frontal lobe function inhibition (Nelissen et al., 2006). Nevertheless, it is likely responsible for the cognitive deficits, suggestive of frontal lobe dysfunction, presented by these patients.

There is more evidence that localized epileptic foci impact on connected distal structures and regions. In patients with an epileptogenic focus in the hippocampus, ipsilateral reductions in gray-matter density in the lateral temporal lobe, as well as extratemporal regions, including the thalamus, posterior cingulate cortex, cerebellum, and frontal and parietal opercular cortex have been noted (Cormack et al., 2005). This suggests that structural changes occur in areas connected to, although not part of, the epileptogenic focus (Cormack et al., 2005).

Whether these structural changes in areas connected to the epileptogenic focus are permanent (Rzezak et al., 2007) or reversible (Nelissen et al., 2006) remains a subject of debate. Similarly the post aut propter debate is relevant here; we do not know whether such structural changes precede or follow functional disconnection and thus whether they are causally associated with cognitive impairment.

The same principle applies to hemispheric specificity in the frontal lobes. Although one expects linguistic impairments specifically in FLE with a left hemispheric epileptogenic focus, no such correlations between the affected hemisphere and hemisphere-specific cognitive deficits have been noted (Helmstaedter et al., 1996; Hernandez et al., 2002; Riva et al., 2005). Because epileptic discharges have a tendency for fast propagation, it is possible that the functioning of other connected frontal areas is simultaneously affected (Riva et al., 2005). This may include areas of the contralateral lobe (Helmstaedter et al., 1996). Two separate case series did not detect differences in test performance between subjects with bilateral and unilateral foci (Culhane-Shelburne et al., 2002; Hernandez et al., 2002).

All previously discussed studies provide evidence that, through neural networks, epileptogenic foci affect connected regions and the functions that are organized in such

areas. It is, therefore, clear that the relationship between site of the epileptogenic focus and type of cognitive impairment is far from straightforward. Studying the frontal neural networks in patients with FLE, or in fact temporal lobe epilepsy with frontal lobe dysfunction, may yield important clues on the association between the site of the epileptogenic focus and the pattern of cognitive deficits. Recently, prospective memory, that is, the ability to fulfill previously planned intentions, was studied in patients with juvenile myoclonic epilepsy (JME), their unaffected siblings, and healthy controls. Not only patients with JME, but also their siblings, showed deficits on the prospective memory task (Wandschneider et al., 2010). These findings strongly support a genetic predisposition of the distinct neuropsychological impairment patterns, which might be caused by thalamo-frontal-cortical network dysfunction. This hypothesis is supported by a quantitative MRI study on newly diagnosed patients with JME demonstrating impaired executive functioning and structural changes in both the frontal lobes and thalami in early disease (Pulsipher et al., 2009).

Risk factors

Risk factors for the development and severity of cognitive deficits in children with FLE are unclear. Studies of the impact of epilepsy-related factors, such as age at seizure onset and seizure type or frequency, have revealed mostly conflicting results. Age at onset has been proposed as a risk factor associated with cognitive impairments (Hernandez et al., 2002; Riva et al., 2002; Nolan et al., 2003; Riva et al., 2005; Prévost et al., 2006; Derry et al., 2008), as has seizure frequency (Riva et al., 2002; Nolan et al., 2003; Derry et al., 2008), localization of the epileptic focus (Riva et al., 2002), use of more than two AEDs (Nolan et al., 2003; Derry et al., 2008), and duration of epilepsy (Nolan et al., 2004; Riva et al., 2005). Although these associations seem to have some merit, they have been opposed by other studies (Hernandez et al., 2002; Prévost et al., 2006). Developmental regression associated with periods of poor seizure control or status epilepticus has been described in patients with autosomal dominant nocturnal FLE (Derry et al., 2008). In other studies, similar correlations between cognitive impairment and seizure frequency could not be established (Riva et al., 2005). The only potential risk factor that came up in multiple studies was the age at seizure onset; younger ages at onset were a risk factor for poor cognitive outcome. An early onset of epilepsy and longer duration of the disorder, rather than the frequency of the seizures, led to impairments in frontal functions; these, however, show large interindividual differences (Lassonde et al., 2000; Riva et al., 2002, 2005; Prévost et al., 2006).

Prevalence of cognitive impairment in FLE: the great unknown

The prevalence of cognitive impairment in children with FLE remains unclear. Very few epidemiologic studies have been performed, and this is an area that warrants future research. Upon examination of the existing case series, it seems that cognitive impairment is frequent in children with FLE, although considerable intra- and interindividual variation in cognitive performance exists (Riva et al., 2002). Interestingly, in children with FLE, the learning difficulties may even precede seizure onset (Prévost et al., 2006). This suggests an underlying condition—which could be microstructural or functional in nature—that manifests itself both in cognitive impairment and seizures.

Behavioral disturbances in children with FLE

It has long been recognized that frontal lobe dysfunction can result in a range of behavioral problems, including distractibility, disinhibition, and aggression (Boone et al., 1988), and direct evidence exists of frontal lobe dysfunction in schizophrenia and depression (Mayberg, 1994; Derry et al., 2008). Because the cognitive impairments associated with FLE include attention deficits and impairments of response inhibition and impulse control (Lassonde et al., 2000; Culhane-Shelburne et al., 2002; Hernandez et al., 2002; Lendt et al., 2002; Hernandez et al., 2003), it makes sense that these give rise to behavioral disturbances. Several case series mention behavioral disturbances in children with FLE (Boone et al., 1988; Jambaqué & Dulac, 1989; Lassonde et al., 2000; Lagae et al., 2001; Culhane-Shelburne et al., 2002; Lendt et al., 2002; Riva et al., 2002; Hernandez et al., 2003; Sinclair et al., 2004; Auclair et al., 2005; Prévost et al., 2006; Derry et al., 2008; Jocić-Jakubi et al., 2009). Behavioral disturbances come in many varieties in children with FLE; they can be (1) the only manifestation of frontal seizures, (2) be characteristic of the postictal phase, or (3) represent a lasting ''interictal'' condition associated with FLE.

FLE seizures can manifest themselves with various behavioral changes such as mood change, sudden agitation or quietness, subtle changes of awareness or awakening, and subtle decrease in motor activity or social interaction (Fohlen et al., 2004).

In one report of two cases, postictal or interictal psychosis was noted secondary to frequent frontal lobe seizures, which presented as delusional thinking, depression, paranoia, aggression, and bizarre behaviour in conjunction with brief stereotypic events of sudden screaming, agitation, and physical aggression (Sinclair & Snyder, 2008). Psychosis disappeared with adequate seizure control.

The behavioral disturbances associated with FLE are highly diverse, although attention deficit/hyperactivity disorder (ADHD) seems most frequent. ADHD is defined as symptoms of inattentiveness and/or hyperactivity and impulsivity inappropriate for age and gender, to a degree sufficiently significant to cause impairment in daily functioning (Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR, 2000). The attention deficits in these children are thought to be attributable to an inability to

ignore irrelevant stimuli (Auclair et al., 2005). Combined with a tendency to respond impulsively, ADHD is likely to develop in children with FLE (Riva et al., 2002; Hernandez et al., 2003; Prévost et al., 2006). The prevalence of ADHD in children with FLE has not been systematically studied, although a prevalence of up to 67% has been reported in a case series (Prévost et al., 2006). The majority of these children exhibited typical ADHD, whereas a minority exhibited oppositional behavior, impulsivity, or anxiety as a comorbidity of FLE (Prévost et al., 2006). Other studies have described psychotic as well as autistic features in children with FLE (Fohlen et al., 2004; Sinclair & Snyder, 2008).

Parent ratings of behavior and social functioning in their children with FLE indicated greater than normal problems with attention (Lassonde et al., 2000; Hernandez et al., 2003; Sinclair et al., 2004), social withdrawal (Lassonde et al., 2000; Sinclair et al., 2004), thought problems (Lassonde et al., 2000; Sinclair et al., 2004), and internalizing behavior in general (Hernandez et al., 2003; Sinclair et al., 2004).

The risk factors for these behavioral disturbances are not fully understood. Seizure frequency and poor seizure control have been proposed as risk factors associated with attention difficulties and inability to inhibit impulsive responses, as these disturbances improved with adequate seizure control (Jambaqué & Dulac, 1989; Lendt et al., 2002; Riva et al., 2002; Derry et al., 2008). The efficacy of seizure control in these cases suggests that a functional disturbance of the brain regions involved in the regulation of attention and behavior is responsible for the induction of these symptoms.

Even if the behavioral disturbances seem FLE-related, it needs to be emphasized that no systematic studies have investigated whether these behavioral disturbances are more prevalent in children with FLE than in the normal population. Regardless of whether they are FLE related, these behavioral disturbances interfere with the children's school performance, which may be aggravated by cognitive deficits. In a previously discussed case series, all children with FLE and attention deficits with or without hyperactivity required special academic support (Lassonde et al., 2000).

Given the impact of these behavioral disturbances and their seemingly high prevalence, there is a need for studies of the etiology of FLE-associated behavioral disturbances. Various hypotheses now exist. First, functional anatomic relationships have been considered; the high prevalence of similar psychiatric changes among patients with primary frontal and primary temporal epileptogenic zones has been related to the intimate connection of the frontal and temporal limbic systems (Blumer et al., 1998). Second, cognitive and behavioral problems can be the result of the epilepsy-related factors, including the age of onset of seizures, the number of seizures, the occurrence of secondary generalized seizures, and the location and extension of the epileptic focus (Fohlen et al., 2004). Third, the association between psychosis or ictal fear and FLE has been related to the reciprocal connections between amygdala, orbitofrontal, and anterior cingulated regions and between the frontal and temporal lobes through the uncinate fasciculus and the superior longitudinal fasciculus (Mega et al., 1997). Fourth, aggressive behavior has been related to activation of limbic structures and loss of frontal suppression of limbic activity. Spreading of discharges from primary foci to other frontal, temporal, or limbic structures may be another explanation (Sumer et al., 2007). Separately, the epileptic activity may impact on the normal maturation of the brain; in epilepsy of early onset this disturbed maturation may explain specific deficiencies (Fohlen et al., 2004).

Response to Antiepileptic Drug Treatment

Treatment failure is a significant problem in epilepsy, including FLE. Treatment failure is defined as recurrent seizure(s) after the intervention has been adequately applied (Kwan & Brodie, 2009). Drug-resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al., 2010). Seizure freedom is defined as freedom from seizures, for a minimum of three times the longest preintervention interseizure interval or 12 months, whichever is longer (Kwan & Brodie, 2009).

To assess the prevalence of treatment failure in FLE, we have combined data of all studies that reported on treatment content and outcome. We found only four studies, describing a total of 72 children with FLE, that recorded response to AED treatment (Lagae et al., 2001; Sinclair et al., 2004; Prévost et al., 2006; Jocić-Jakubi et al., 2009). The response to therapy varied between these studies and is recorded in Table 3, showing that seizure control was eventually achieved in 43 of the 72 children assessed (60%); seizure freedom was achieved after 8 weeks (Jocić-Jakubi et al., 2009) to 37 months (Prévost et al., 2006). None were seizure free without AED use, 29 of 43 were seizure free with monotherapy, and 14 of 43 with polytherapy. Monotherapy most frequently consisted of valproic acid or carbamazepine (Riva et al., 2002; Hernandez et al., 2003; Riva et al., 2005; Prévost et al., 2006; Derry et al., 2008), whereas clobazam, lamotrigine, vigabatrin, phenytoin, phenobarbital, topiramate, levetiracetam, and oxcarbazepine were used most

Table 3. Therapy-resistance observed in existing studies

References	N (total)	% Therapy resistance
Jocić-Jakubi et al. (2009)	19	0 (0/19)
Lagae et al. (2001)	10	70 (7/10)
Prévost et al. (2006)	21	52 (11/21)
Sinclair et al. (2004)	22	50 (11/22)
Total	72	40 (29/72)

frequently as adjunctive drugs (Hernandez et al., 2003; Prévost et al., 2006; Derry et al., 2008). Importantly, 29 (40%) of 72 children assessed in these studies could not attain seizure control. This exceeds the 30% reported for the general epilepsy population (Kwan & Brodie, 2000).

Most studies investigating treatment outcome in children with FLE assess outcome after epilepsy surgery in children with drug-resistant FLE. These studies have been performed in tertiary reference centers or centers for epilepsy surgery and are, therefore, subject to selection bias (Kral et al., 2001; Lawson et al., 2002; Lendt et al., 2002; Nolan et al., 2004).

In epilepsy in general, regardless of localization, young age at seizure onset, a history of status epilepticus, the presence of underlying pathology, changes in type of epilepsy during the clinical course, and neonatal seizures have been identified as risk factors for therapy resistance (Ohtsuka et al., 2000). Specific causes of therapy resistance in FLE remain elusive. Drug target availability and drug delivery are among the many aspects that warrant additional study.

Conclusions

Pediatric FLE, even if cryptogenic in nature, is frequently complicated by impairment of cognitive function, behavioral disturbances, and therapy resistance. Cognitive impairment generally consists of impairment of executive functions and attention deficits, with consequences for school performance, although interindividual variability is high, and even ''typical'' temporal lobe impairments such as memory impairment are found. Risk factors remain controversial, although a young age at seizure onset has been associated with cognitive impairments during childhood.

The behavioral disorders show even stronger interindividual variability and might have a negative impact on existing cognitive impairment. ADHD is the most common disorder complicating pediatric FLE. AED therapy-resistance may be more frequent in children with FLE than in other types of epilepsy, although its causative mechanisms need further research.

The fact that all these complications occur at a young age is troublesome. The brain is at its most vulnerable in childhood, when neurologic disturbances such as FLE can impact on brain maturation and the acquisition of cognitive skills. FLE can impact on cognitive functioning in childhood, leading to learning disabilities. In turn, these disabilities may have a negative influence throughout life, in terms of social skills and level of education.

Disclosure

All coauthors have been substantively involved in the study and/or the preparation of the manuscript. All coauthors have seen and approved the submitted version of the paper and accept responsibility for its content. None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

The authors declare no conflicts of interest.

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