Language Dysfunction in Pediatric Epilepsy

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Epilepsy is one of the most common and severe neurologic diseases in children, affecting 0.9%-2% of the pediatric population. Children and adolescents with epilepsy and their parents indicate that quality of life is driven as much or more by cognitive comorbidities as by seizure control. Surveys of these families found that cognitive problems were second only to medication side effects in terms of decreasing quality of life. The new International League Against Epilepsy classification considers the cognitive comorbidities seen in epilepsy to be part of the condition. Of the cognitive problems seen in epilepsy, language disorders (Table) are particularly important to identify and address, as language dysfunction can contribute to academic underachievement and long-term social, professional, and psychological problems.

The impact of epilepsy on language is relevant not only from a clinical perspective but also because it sheds light on the underlying neurobiology of both processes. Advances in imaging and neurophysiology techniques have demonstrated that normal language development is a complex process, subserved by bilateral but usually left-predominant networks (Figure 1). We increasingly are understanding that epilepsy is a network disorder in which even focal seizures have widespread impact on many parts of the brain. Given this, childhood epilepsy likely affects the normal development of language on several levels. First, common underlying pathophysiology, such as a genetic mutation or a structural lesion, may lead to both language disorders and seizures. This is supported by the fact that language problems are noted in children with new-onset seizures and do not always resolve completely even with excellent seizure control. Second, interictal epileptiform discharges (IEDs), spike waves that occur outside of seizures, are known to cause transient disruptions in local cortical function and likely also affect the function of more widespread networks. Finally, childhood is a critical window for the development of language pathways, and abnormal electrical activity during this time may interfere with typical development. Multiple neurocognitive and imaging studies have shown atypical language lateralization and network connectivity in pediatric subjects with epilepsy, which does not always resolve even after the seizures and IEDs have ceased.

Many children with epilepsy have underlying conditions that lead to significant intellectual disability (ID), making specific assessment of language extremely difficult; this review will therefore focus on studies of children with normal or near-normal intelligence. This paper will first review studies characterizing language deficits in pediatric epilepsy from the most severe forms with total loss of language to the more common forms of language impairment found in the inappropriately termed “benign” epilepsies of childhood. Next, we will describe what is known about the structural and electrophysiologic changes associated with language dysfunction, reviewing the neuroimaging, electroencephalogram (EEG), and genetic studies related to language dysfunction. Epilepsy surgery planning and resection of epileptic foci provide additional tools to understand the impact of focal epilepsy on language network development and interaction with overall cognition in children with epilepsy. We will review studies on language mapping in children highlighting the unique challenges and emerging promising techniques to ensure preservation of language.

Clinical Overview

Epilepsy–Aphasia Spectrum

Much of what we know regarding language and epilepsy in children is derived from disorders on the epilepsy–aphasia spectrum. Landau and Kleffner in 1957 first described the relationship between epilepsy and language dysfunction in an article detailing 6 children with previously normal language development who became aphasic after the onset of focal seizures. These patients all had EEGs with a significant burden of spike waves, especially in sleep. In general, the severity of the patients’ language disorder fluctuated with the degree of EEG epileptiform activity. Since then, a spectrum of disorders, often referred to collectively as the epilepsy–aphasia spectrum, have been described that share features of sleep-potentiated EEG abnormalities, cognitive problems, and rare or even absent clinical seizures. The 2 best-characterized disorders are Landau-Kleffner syndrome (LKS) and benign epilepsy with centrotemporal spikes (BECTS).

Landau-Kleffner Syndrome. LKS is the canonical example of the epilepsy–aphasia spectrum. Children with previously normal development undergo a progressive language regression over weeks to months in which they lose the ability to understand...
speech and sometimes other meaningful sounds, such as a telephone ring. Eventually, speech production diminishes. Neuropsychological testing in LKS suggests that impaired phonologic decoding is the primary deficit that leads to the language regression. Children with LKS may simultaneously develop psychiatric symptoms, including irritability, inattention, and autistic traits. Rare and easily controlled seizures, including generalized tonic clonic, focal motor, and atypical absence seizures, emerge. Age of onset is typically between 3 and 8 years. Corresponding with the acquired auditory agnosia, an EEG pattern of electrical status epilepticus of sleep (ESES) appears in which extremely frequent spike and slow waves

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![Diagram](image)

Figure 1. Diagrammatic representation of primary language areas on anatomical T2-weighted fluid-attenuation inversion recovery MRI and 3D reconstruction images, highlighting left temporal lobe (Wernicke area in posterior temporal region, vertical arrows/dotted hatching), frontal lobe (Broca area in middle frontal region, horizontal arrows/diagonal hatching), and the white matter (arcuate fasciculus, gradient shading) that connects these regions. Historically, language has been conceptualized as a lateralized function, with dominance typically in the left hemisphere. fMRI studies confirm that language is a left-hemispheric dominant process in the vast majority of healthy adults but also that language requires input from distributed networks, including homologous right hemispheric regions.
emerge at the onset of sleep and are near continuous through the majority of non-rapid eye movement sleep. Spikes tend to be maximum in the temporal regions.

The ESES pattern is also a defining feature of another epileptic syndrome called continuous spike waves in slow-wave sleep (CSWS). The regression in CSWS tends to be more global rather than language-specific, and EEG spikes usually have a more frontal predominance. One study described language in a small group of children with CSWS and found significant problems with lexical and syntactical skills but intact comprehension. Overall, LKS and CSWS are quite rare. A clear incidence has not been reported, likely in part due to the lack of agreement among epileptologists regarding the exact definition of ESES, CSWS, and LKS. Studies of long-term prognosis of these conditions likewise suffer from imprecise definitions. In general, there is agreement that children with underlying structural or metabolic causes of ESES, EEG abnormalities that persist longer than 18 months, treatment failure, or young age of onset are more likely to have permanent cognitive problems even after resolution of the nocturnal EEG findings. Approximately 45%-70% of affected patients have permanent cognitive impairment, including language dysfunction.

**BECTS or Rolandoic Epilepsy.** BECTS or rolandic epilepsy is the most common focal epilepsy syndrome in childhood, consisting of 15%-25% of all cases of pediatric epilepsy. It is an idiopathic epilepsy syndrome characterized by focal sensorimotor seizures that usually involve the face but that often spread to the arm or generalize. The typical EEG findings include centrotemporal spike waves that become markedly more prominent during sleep. Spikes in children with BECTS are not as frequent as in children with ESES. Onset of BECTS is between 3 and 13 years. Compared with many other causes of epilepsy, seizures are rare, with most patients having only 2-10 seizures in their lifetime. Many children are never treated with antiseizure medications and, for those who are, seizures are usually easy to control.

BECTS has been considered “benign” because seizures predictably stop after puberty, by age 16 years, and affected children typically have a normal full-scale IQ. Detailed neuropsychological profiles of children with BECTS, however, show deficits in many subdomains, including language, visual spatial skills, attention, memory, fine motor skills, and behavior. Smith et al recently performed a meta-analysis of 22 studies that included formal language testing of children with BECTS. Patients consistently demonstrated diminished reading, expressive language, and receptive language abilities compared with healthy children; the authors estimated a 0.7 SD between the 2 groups for these measures. These authors speculate that, as in ESES, phonological processing difficulties might explain the language and reading difficulties, as these were also selectively impaired in children with BECTS.

Interestingly, the language differences were more pronounced in older children with BECTS, raising the question as to whether there is a cumulative effect of epilepsy on cognition over time. This question is challenging to answer, as many neurocognitive studies of the BECTS population are confounded by the fact that included patients have had epilepsy for varying lengths of time and have pursued differing treatment plans. Interestingly, a recent study of neuropsychological functioning in unmedicated children with newly diagnosed BECTS found only small, nonsignificant differences in language and cognitive skills compared with healthy control
at the start of their disorder. Prospective studies of children with BECTS that can better account for the effects of antiseizure medication will be important in disentangling the effects of this disorder on language. Finally, although IQ was an important moderator of language abilities, even children with BECTS and above-average IQs still showed a gap in receptive and expressive language.37

These language difficulties translate to meaningful academic problems, even after resolution of the epilepsy. Up to 54% of children with BECTS have educational problems, the majority of which are attributed to language impairment.38 Follow-up studies have reported mixed outcomes in children with BECTS after remission of the seizures and EEG abnormalities. Interview-based measures39,40 typically find good psychosocial outcomes in adults with resolved BECTS, but structured neurocognitive testing shows persistent deficits in language processing in almost 50% of subjects.41,42

Language Disorders in Other Epilepsy Syndromes

Although the epilepsy–aphasia syndromes are the most studied, other types of epilepsy also are associated with language disruption. Several large cohort studies of children with new-onset epilepsy have found subtle language abnormalities at the time of seizure onset.14-16,43 There has been some disagreement as to which types of epilepsy have the greatest impact on language. Several studies15,44 found that children with absence epilepsy (a generalized seizure disorder) had worse language performance than children with focal epilepsy (seizures originating in one area in the brain). In contrast, Hermann et al found that children with focal but not generalized epilepsy had poorer language than controls; the cognitive differences seen in this cohort remained stable over time.41,45 Although patient selection may have contributed to study differences, language dysfunction is common irrespective of epilepsy type.

Older children, particularly adolescents, seem to have worse language performance than younger children. Jones et al found that approximately 50% of adolescents with epilepsy had reading and language scores greater than 1 SD below average, compared with only one-quarter of children <8 years.16 Greater duration of illness likely explains some,43 but not all,16 of this finding; studies suggest refractory seizures may predict stagnation of language skills during long-term follow-up. Similarly, a recent study from Finland prospectively followed a cohort of children with epilepsy for 5 decades; 75% of the group were in remission and had been off seizure medications for at least 5 years and 25% of the group still had active epilepsy. The entire cohort had impairments in language and semantic functions in late middle age compared with healthy control subjects, but these problems were especially pronounced in those with continued seizures.46

Etiology of Language Dysfunction

Insight from Functional Imaging and Epilepsy Surgery

Functional magnetic resonance imaging (fMRI) studies have demonstrated that epilepsy of various underlying etiologies affects language network consolidation. In children with BECTS, neuropsychological testing42,47 and fMRI48-50 indicate that children fail to lateralize cortical functions normally. These children have greater bilateral activation for language tasks that typically involve the left hemisphere, including verb generation,48 sentence generation,49 and semantic decision tasks, as well as right hemisphere tasks, such as prosody discrimination.50 Similarly, in 58 children with focal epilepsy, fMRI found that patients were significantly more likely to demonstrate bilateral or right hemispheric language dominance compared with left hemispheric language in control subjects.51 A more recent series of 23 children with atypical language dominance found that atypical lateralization strongly correlated to a more widespread disruption in network integration.52

In children with BECTS, there is some evidence that atypical language lateralization persists even after the seizures have abated and the EEG pattern has normalized.42 In addition to differences in lateralization, children with epilepsy have different connectivity patterns within their language networks. For example, Croft et al showed that children with epilepsy with a left hemispheric focus specifically have decreased activity in the ventral components of the language network that develops earlier in childhood compared with the dorsal components.53 This decrease in activity correlates with poorer language function. In addition, the authors found that the deficits persisted in older age groups, suggesting that early-life epilepsy causes chronic deficits rather than just delayed maturation of the network. Taken together, these findings suggest that it is not only acute seizures or epileptiform discharges that cause language dysfunction but that chronic changes to underlying networks may cause persistent language problems.

Patients who have undergone epilepsy surgery provide insight into language development in the context of epilepsy as well as the potential for recovery after control of seizures. A recent comprehensive review of the behavioral effects of epilepsy surgery supports associations of better outcomes, including language outcomes, with early surgical intervention and postoperative seizure freedom.54 As described previously, children with early left-hemispheric epilepsy are much more likely to have language lateralized to the right hemisphere than the general population.55 In the most extreme cases, children with hemimegalencephaly, Rasmussen encephalitis, or other large unilateral epileptic lesions typically have significant preoperative deficits in verbal function across multiple behavioral measures.56-58 Such deficits may be more frequent and severe when the lesions involve the left hemisphere but are common regardless of side.59 These children often require extensive resections up to hemispherotomy to control their seizures, but many demonstrate improvements in language function after such surgery. When language was formally assessed in a group of 28 children with seizure freedom achieved by hemispherotomy, language skills improved by 50% after surgery, with those patients whose EEG sleep patterns normalized after surgery showing the greatest gains.46 Similarly, Loddenkemper et al reported that 8 patients with ESES due to focal lesions visible on standard MRI had a significant improvement in developmental quotient—with an average
increase of 9.8 points—after resective surgery improved the nocturnal EEG.\textsuperscript{29}

Remapping of language is likely associated with underlying structural changes. In a group of 10 children after left hemispherotomy, the right hemispheric arcuate fasciulus showed compensatory reorganization on postsurgical diffusion tensor imaging\textsuperscript{29} correlating with improved or stable language function. Imaging studies have shown that children with large left hemispheric lesions who undergo early hemispherotomy will remap language to the intact right hemisphere in a thorough enough manner to have complete acquisition of syntax and grammatical construction.\textsuperscript{37} Language recovery has been reported to be more rapid and complete in younger children after hemispherotomy,\textsuperscript{41} suggesting a critical window for remodeling after surgery that would support an “earlier is better” approach to large resections in terms of language recovery. A recent analysis of language reorganization after acquired unilateral insults during childhood supports this notion, suggesting more complete and functional reorganization to the nondominant hemisphere after acute lesions occurring before, as opposed to after, age 5 years.\textsuperscript{62}

Not all investigators agree. Curtiss and de Bode reported that children with large developmental lesions (present since birth) had worse language if the lesion was in the right hemisphere and children with acquired lesions had worse language outcomes if the lesion was in the left hemisphere.\textsuperscript{56,60} They proposed the “critical impact point” hypothesis in explanation—that there are genetically determined substrates in both hemispheres that are critical for language development at different stages.\textsuperscript{56,58} Although more work is still needed to fully elucidate this interaction, it seems most would agree that age at epilepsy surgery may be an important predictor of language outcome.

Interictal Discharges

The impact of IEDs on cognition has been an area of significant research. Substantial evidence suggests that both generalized and focal IEDs cause transient changes in perception, processing, and reactivity and that the nature of these disruptions is related to the location of the activity.\textsuperscript{64} Evidence from studies in rodents indicates that single spikes can impair memory formation.\textsuperscript{64} Similarly, video–EEG studies in humans have demonstrated transient disruptions in visual, visual–spatial, and language performance based on the location of the spike wave.\textsuperscript{49} In children, there is evidence suggesting that spike burden during a task affects performance. Nicolai et al performed a 2-hour neuropsychological battery on 188 children who were simultaneously undergoing EEG recordings.\textsuperscript{65} They found a graded difference across various neurocognitive measures, including language—control subjects did better than those with IEDs on >1% of the recording, who did better than those with subclinical seizures.

It has been hypothesized that in addition to transient cognitive impairment, IEDs also can cause persistent problems with cognition. For example, language skills in patients with LKS fluctuate depending on the severity of nocturnal discharges.\textsuperscript{66,67} Several studies of BECTS have found a correlation between diurnal\textsuperscript{68} and nocturnal\textsuperscript{67,69} spike burden with the degree and type of cognitive dysfunction; for example, left IEDs seem to affect language and right IEDs affect spatial skills.\textsuperscript{42,47,70} However, not all studies on BECTS have found this correlation.\textsuperscript{71,72} Fewer studies have assessed the effects of IEDs on language in other types of pediatric epilepsy. Ebus et al found that spikes in >10% of the diurnal recording were associated with poorer cognitive function, although they did not look at language-specific measures.\textsuperscript{73} In children with lesional epilepsy, IEDs had a negative association with IQ, with additive effects seen for frequent, bilateral, and sleep-potentiated IEDs.\textsuperscript{74} Left-lateralized IEDs had a prominent effect on verbal intelligence above that expected from the lesion alone and sleep-potentiated IEDs were associated with poorer expressive and receptive language, reading, spelling, and numerical skills. In summary, although there seems to be a correlation between frequent IEDs, particularly nocturnal ones, and poor language function, the evidence for a causative relationship is relatively weak.

Several interesting studies combining spike detection with fMRI have found that IEDs affect distributed neural networks, influencing both language and resting networks. An EEG–fMRI study of children with BECTS found increased connectivity between the rolandic areas and expressive and receptive language areas during centropetal spiking,\textsuperscript{75} suggesting that the spikes themselves have a brief, disruptive impact on these remote regions. Ibrahim et al used magnetoencephalography paired with fMRI to test the effect of individual IEDs on several neural networks; they found that children with less perturbation of baseline network activity during IEDs scored better on neurocognitive tests.\textsuperscript{76} IEDs also can inappropriately deactivate the default mode network—the “resting network” of the brain that is active during quiet, self-referential thought and deactivated during tasks—in children with BECTS\textsuperscript{77} and CSWS.\textsuperscript{77} Children with BECTS also demonstrate difficulty activating and deactivating the default mode network in response to specific language tasks.\textsuperscript{78} Appropriate modulation of the default mode network is necessary for higher order cognitive tasks like language.

Genetics

GRIN2A. In the last several years, there have been major advancements in our knowledge of the genetics of epilepsy–aphasia syndromes. Perhaps the most important discovery has been the identification of mutations in GRIN2A, a gene on chromosome 16p13 that encodes a subunit of the glutamate N-methyl-D-aspartate receptor. The N-methyl-D-aspartate receptor is a cell-surface receptor important in brain development, synaptic plasticity, memory, and sleep and is distributed throughout cortical and subcortical regions.\textsuperscript{9,79} Since 2013, a variety of mutations in GRIN2A have been identified in families and individuals with ESES, CSWS, and other disorders on the epilepsy–aphasia spectrum. GRIN2A mutations have been identified for 9%–20% of cohorts with LKS and CSWS but only 3.6% of patients with typical BECTS.\textsuperscript{80,82} Turner et al described a language phenotype seen with these mutations that includes speech dyspraxia as well as dysarthria, with poor articulation and disturbances in prosody.\textsuperscript{9}
Descriptive studies of affected families have suggested that the **GRIN2A** mutation may cause language dysfunction independent of causing epilepsy. In families affected by epilepsy–aphasia spectrum disorders, there are some **GRIN2A** mutation carriers without epilepsy. In addition, up to 70% of children in these pedigrees have developed speech disorders before onset of epileptiform abnormalities on EEG. **GRIN2A** mutations seem to be specific for epilepsy–aphasia disorders, as they were not found in screens of patients with other types of epileptic encephalopathies.81

**RFOBX**. Rare mutations in **RFOBX1** and **RFOBX3**—genes responsible for the splicing of neuronal transcripts important in control of membrane excitability—also have been reported in patients with epilepsy–aphasia disorder. One study of 289 unrelated patients with BECTS found 3 **RFOBX** variants compared with no variants in 6503 subjects without BECTS.82 Ten family members of proband cases were also carriers; 5 had BECTS, 1 had ESES, and 1 had the EEG features of centrottemporal spikes. Mutations in **RFOBX** have also been reported in a variety of other neurologic disorders, including generalized epilepsy, attention disorders, and ID.30,84 At least one group has argued, however, that **RFOBX** variants may actually be seen in similar proportions in control populations.85

**FOXP2/SRPX2/CNTNAP2**. **FOXP2** encodes an important neuronal transcription factor. It was the first gene to be associated with a severe speech disorder—developmental verbal dyspraxia without epilepsy—in which patients are often unintelligible.83,84 Two downstream targets of **FOXP2** have been associated with speech disturbances and epilepsy. **SRPX2** mutations were identified in a family with autosomal-dominant rolandic seizures, speech dyspraxia, and ID as well as in patients with bilateral perisylvian polymicrogyria; both conditions are associated with language dysfunction and epilepsy.87 The role of **SRPX2** in language, however, was called into question when the family cohort with autosomal-dominant rolandic seizures and speech dyspraxia were later found to also carry a **GRIN2A** mutation.79 **FOXP2** is also upstream of **CNTNAP2**, a gene associated with cortical dysplasia, focal epilepsy, and language regression after seizure onset.88

**BECTS**. Many researchers have searched for a genetic cause of BECTS. Family members of children with BECTS have a greater rate of epilepsy, particularly febrile seizures, but the common form of this epilepsy syndrome itself does not seem to have clear Mendelian inheritance85; several studies in twins, in fact, showed zero concordance among twin pairs.86 Susceptibility genes identified in families with multiple affected members (ie, **SRPX2**) are not causal in the majority of affected patients. Sequencing of γ-aminobutyric acid type A receptor genes in a large BECTS cohort has shown enrichment of rare variants compared with controls, but a causative role of these variants has not been proven.87 Interestingly, components of the syndrome may be linked more consistently to specific genes. For example, family association studies have shown that the centrottemporal spike wave trait is often inherited in an autosomal-dominant fashion92,93 and may be associated with mutations of the elongator protein complex 4 (**ELP4**) gene on chromosome 11,94 but this association has not been consistent.95 Additional analyses have suggested linkage of speech sound disorder in BECTS to 11p1394 and reading disability to chromosome 7q21 and 1q42.95,96 Although BECTS is a common disorder, the genetics underlying it are complex and still being investigated.

**Other Copy Number Variants**. Various studies have identified increased frequency of copy number variants—rare microduplications or deletions—in children with BECTS,88 ESES, and CSWS.97-99 The importance of each of these has not been clearly verified, and a detailed review is beyond the scope of this article.

**Seizure Medications and Language**

We have focused this review on the impact that epilepsy itself has on language, but pharmacologic treatment for epilepsy also can have significant, complex effects on language and cognition. It can be difficult to disentangle the cognitive benefits of improved seizure control from the negative side effects of these medications. For example, phenobarbital is one of the oldest available seizure medications and is still widely used in pediatric epilepsy, especially for the treatment of neonatal seizures. Hyperactivity and trouble with memory and attention has been reported in exposed children.100 Farwell et al performed serial developmental assessments on children with febrile seizures randomly assigned to prophylaxis with phenobarbital or placebo.101 Children in the phenobarbital group had lower IQs than those in the placebo group, and this difference persisted even 6 months after phenobarbital was withdrawn. Follow-up of this cohort into the school years showed that the difference in IQs of the groups diminished but that children who had taken phenobarbital had worse performance on reading scores.102 Of all the seizure medications, topiramate and a similar but newer medication, zonisamide, have most specifically been associated with language problems and speech difficulties in adults103-105 and children.106-108 Several fascinating fMRI studies109-111 have shown that patients receiving topiramate and zonisamide have altered activation of the language networks compared with patient receiving other seizure medications and healthy controls. Although these medications are particularly associated with language difficulties, many patients tolerate them well. Conversely, some patients complain of cognitive problems on other medications that are typically well-tolerated. Clinicians should recognize that some cognitive problems may improve with a change in treatment. For a thorough discussion of the cognitive impact of seizure medications, we refer you to the recent review by Aldenkamp et al.100

**Concluding Remarks**

Epilepsy imparts significant morbidity through its effects on cognition and language. Some of this burden, arising
independently from the underlying structural or metabolic causes, may not be directly ameliorated by treatments directed toward seizure. However, a growing body of data, particularly from patients with BECTS and its more severe counterparts in the epilepsy–aphasia spectrum, indicates that IEDs and spike burden affect cognitive and language development in a dynamic manner yet to be fully described. In this context, physicians of children with epilepsy should maintain a high index of suspicion for language disorders and should consider early referral to therapies if problems are suspected, even in children with diagnoses of “benign” syndromes like BECTS. Although modern neuroimaging and genetic testing may provide definitive etiologic diagnoses for many of the children with more severe forms of epilepsy aphasia syndromes, much remains to be learned about their genetic causes. Further research to understand how interictal discharges may disrupt normal network function holds promise to suggest novel therapeutic targets or modalities for the cognitive and language comorbidities of epilepsy. ■

References