Pediatric epilepsy and psychopathology

Monisha Goyal, *MD.*

ABSTRACT

The association of psychiatric disorders and pediatric epilepsy is under appreciated by clinicians. Behavioral disorders, especially depression, are often perceived as "reactionary" processes. In fact, these comorbid disorders can be more disabling than the epilepsy itself. This review discusses the common behavioral comorbidities associated with epilepsy including autistic spectrum disorders, psychosis, attention deficit hyperactivity disorders, and mood disorders.

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From the Rainbow Babies and Children's Hospital, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio, United States of America.

Address correspondence and reprint request to: Dr. Monisha Goyal, Rainbow Babies and Children's Hospital, University Hospitals of Cleveland, Case Western Reserve University, 11100 Euclid Avenue, M/S 6090, Cleveland, Ohio 44106-6090, United States of America. Tel. +1 (216) 8443691. Fax. +1 (216) 8448966. E-mail: monisha.goyal@uhhs.com

Any chronic illness is associated with inherent stressors including social stigma, medication regimens, unpredictability of the disease process, and coping mechanisms of the family unit. However, while the frequency of behavioral issues in many chronic pediatric illnesses not involving the CNS is 11-12%, the percentages are much higher in epilepsy. Several studies have shown that the frequency of psychiatric disorders is 26-29% in children with idiopathic seizures, and increases to 56-58% in those with both seizures and any associated neurological dysfunction (**Figure 1**).[1,2] In addition to an increased frequency of behavioral problems in children with chronic seizures, several studies have shown similar trends with new onset or recent onset seizures.[3,4] The etiologies of these associated behavioral issues are manifold and may, partly, be due to clinical and subclinical seizures, underlying brain dysfunction, antiepileptic drug regimens, and the psychosocial environment. These psychiatric comorbidities contribute significantly to the overall disability experienced by children with epilepsy. Yet, despite its prevalence, psychopathology accompanying pediatric epilepsy is often under appreciated or ignored by clinicians. This review discusses the common conditions that frequently accompany pediatric epilepsy, including autistic spectrum disorders, psychosis, attention deficit hyperactivity disorder, and anxiety, and depression.[5]

Seizures occur in up to one-third of children with autistic spectrum disorders. Those with both autism and epilepsy, or epileptiform EEG abnormalities, have more severe cognitive impairment and autistic features than those with autism alone.[6] There also tends to be a positive family history of epilepsy or febrile seizures.[7] The seizure subtype is usually partial onset or multifocal, rather than primary generalized epilepsy.[8] Since decreased or altered social responsiveness and stereotypes can be seen with both complex partial epilepsies and autistic spectrum disorders, appropriate diagnosis may warrant video EEG monitoring. Up to 20-25% of children with autism show EEG abnormalities without seizures.[9] There is usually no associated structural lesion, or history of prenatal or perinatal insult, in autistic children with an abnormal EEG. The abnormalities are focal or multifocal, often in the centro-temporal region, but occasionally with a frontal predominance.[10] To date, there are no controlled trials showing improvement in cognition and behavior if the EEG abnormalities are treated in this subgroup.

Two epilepsy syndromes that have many features in common, and may be confused with autistic spectrum disorders, are Landau Kleffner Syndrome (LKS) and Continuous Spike and Wave during Slow Wave Sleep (CSWS).[11] Children with LKS develop subacute verbal auditory agnosia between 2 and 8 years of age. This may progress to impairment in speech production. There may be spontaneous relapses and remissions, but appropriate social interactions are maintained. Typically, two-thirds of children have seizures, usually of focal onset, that resolve by adolescence. There is no direct relationship between seizure exacerbation and language dysfunction; even after seizures remit during adolescence, language dysfunction may persist. Although language dysfunction also occurs in CSWS, this syndrome is characterized by more global "regression" and autistic features. Both LKS and CSWS show continuous spike

and wave discharges during slow wave sleep, which helps differentiate them from autistic spectrum disorders.

Psychosis is less common in pediatric epilepsy than in adult epilepsy (1% in children verus 2-9% in adults).[12,13] The prevalence is much higher than in the general pediatric population and may be dependent on the localization and lateralization of the epileptic focus. Schizophrenia-like psychosis and illogical thinking patterns occurred in 6 of 30 children (20%) with complex partial seizures compared to 0 of 24 with generalized epilepsy.[14] Psychosis may be temporally associated with either the ictal, postictal, or interictal phase of seizures. It may also occur after seizure remission (forced normalization), or be iatrogenic (with antiepileptic drugs or following surgery).[15] Ictal psychosis is typically seen with nonconvulsive status epilepticus, both partial and generalized. Postictal psychosis is a rare phenomenon in children, typically occurring many years after seizure onset (mean of 15 years in one series).[16] Risk factors for interictal psychosis include a positive family history, young age at epilepsy onset, cognitive delay, and complex partial seizures. Antiepileptic drug-induced psychosis is rare but has been reported with phenobarbital, phenytoin, lamotrigine, levetiracetam, ethosuximide, vigabatrin, topiramate, tiagabine, and zonisamide. Postoperative psychosis, seen after 3-9% of surgeries, typically occurs after a temporal lobectomy. Risk factors include a positive family history, right hemispheric surgery, and temporal lobe cortical dysplasia.

The cause of the psychosis should be determined before any referral is made, or treatment initiated. If the psychosis is ictal or iatrogenic, an antiepileptic drug change may be warranted; otherwise, antipsychotic medication is necessary. There is a risk for seizure exacerbation with antipsychotic drugs, but it is low and should not prevent or delay the necessary treatment. Risperidone has a low potential for seizure exacerbation and is a good choice for children with epilepsy.[15]

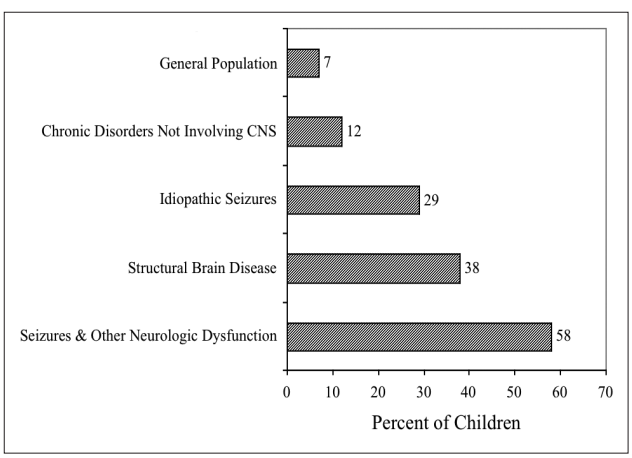

Figure 1 - Frequency of psychiatric comorbidities in children.

Attention deficit hyperactivity disorder has a frequency of 35-40% in children with epilepsy and has a direct correlation with school problems.[17] It is typically the inattentive rather than the combined type and has no male predominance, diagnosed equally in girls and boys.[18] Several diagnoses should be considered when evaluating a child for poor attention, including subclinical seizures, undiagnosed learning disabilities, and sleep disturbances (which are significantly increased in this population). Video EEG monitoring may help clarify the diagnosis. Generalized epilepsies are more likely to produce impairment of attention than focal epilepsies. Many studies have shown transient cognitive impairment (TCI) in association with subtle impairment of attention during subclinical epileptiform discharges.[19] Tests of attention and recall show TCI during one third of discharges and in two-thirds of patients with absence epilepsy.[20]

The commonly implicated antiepileptic drugs that may exacerbate attentional problems include barbiturates, gabapentin, topiramate, and zonisamide. For example, the most common side effect of phenobarbital in childhood is hyperactivity. Along with behavior and cognitive therapies, pharmacotherapy is the mainstay of treatment for inattention. It is imperative that iatrogenic causes of poor attention, learning disabilities, and mood disorders are ruled out before therapy is initiated. Stimulants remain first-line therapy for inattention and clinical trials have not shown seizure exacerbation in children with epilepsy.[21,22]

Several studies show an increased frequency in 30-40% in mood disorders and anxiety in children with epilepsy.[23] Mood disorders are more severe in children with both epilepsy and mental retardation, while anxiety is increased in children with comorbid learning and attentional difficulties. There is a trend for anxiety in prepubertal children and depression in adolescents. Polytherapy, as well as poorly controlled seizures, are associated with a higher risk for anxiety.[24] There is also a higher risk of suicide with epilepsy onset in the pediatric age group, especially during adolescence. The suicide risk is not associated with seizure lateralization, seizure frequency, or polytherapy.[25]

Depression should not be considered a "normal" response to having epilepsy. Indeed, epilepsy and depression may have a reciprocal relationship. Epilepsy is a risk factor for depression, but depression also increases the risk for unprovoked seizures.[26] Genetics plays a prominent role as reflected by a positive family history for mood disorders in at least 50% of patients with epilepsy associated with depression. Iatrogenic depression may be secondary to antiepileptic drugs especially in children

with a predisposition to psychiatric disorders. Implicated medications, such as phenobarbital, vigabatrin, tiagabine, and topiramate, have mechanisms predominantly affecting Gamma-aminobutyric acid (GABA). Zonisamide and levetiracetam may also cause similar symptoms. Occasionally, withdrawal of an antiepileptic drug with positive behavioral effects, like lamotrigine or valproic acid, may result in depressive ideation. In a child on psychotropic medication, symptoms may emerge if an enzyme-inducing antiepileptic drug is added and the psychotropic drug levels drop. Therefore, clinicians should be mindful of pharmacokinetics and drug-drug interactions. Antiepileptic drugs may also decrease folic acid levels, which may contribute to depression in some patients.[27] The rare phenomenon of "forced normalization" may also manifest as depression after seizure control is attained.[14]

Childhood mood disorders can be particularly difficult to recognize. Given the internalizing nature of symptoms, caregivers are often unaware of depressed mood in their children. Children do not necessarily show sadness or inability to enjoy things but may be irritable, oppositional, and aggressive. Academic achievement may suffer, and somatic complaints such as headaches may increase. Children may be hyperactive, reluctant to go to bed, and become increasingly fussy on food. Changes in sleep patterns and behavior without provocation, and a family history of alcoholism or depression, are strong risk factors for depression in children. The diagnosis of depression in children with epilepsy and mental retardation is even more difficult. These children become more withdrawn, are irritable, and show an increase in violent outbursts. In addition, psychogenic nonepileptic events are increased by up to 40% in children with mental retardation and mood disorders, when compared to those with epilepsy and normal intelligence.[28]

To decrease suicidal risk and improve quality of life, treatment of depression is paramount. Along with psychotherapy, antidepressant drug therapy remains the mainstay of treatment. Similar to neuroleptics, there is concern regarding lowering seizure threshold with antidepressant drug therapy. Selective serotonin reuptake inhibitor (SSRIs), the first-line treatment in this population, have not shown to increase seizure frequency in a significant or consistent fashion. In fact, their characteristic serotonergic activation may have an anticonvulsant effect, a mechanism of action shared by some antiseizure medications such as zonisamide.[29] Recent anecdotal reports of increased suicidal ideation with SSRIs necessitate close monitoring of the patient especially while the drug is initially titrated.

Since psychiatric issues occur in both new onset and chronic seizures, clinicians should begin monitoring for behavioral problems from seizure onset. Several instruments can be used as screening tools such as the Child Behavior Check List (CBCL) and Child and Adolescent Symptom Inventories. Quality of life scales specific for epilepsy broadly screen for problems in multiple spheres including academic and social functioning; the commonly used instruments are the Quality of Life in Epilepsy for Adolescents (QOLIE-AD-48), the Quality of Life in Childhood Epilepsy (QOLCE), the Impact of Pediatric Epilepsy Scale (IPES), and Impact of Childhood Illness Scale.[5] Screening tools developed specifically to help identify psychiatric problems in patients with mental retardation include Aberrant Behavior Checklist, Emotional Disorder Rating Scale for Developmental Disabilities, and Reiss Screen for Maladaptive Behavior.[14] Brief screening tools for attention and mood that can be used in the office setting by the clinician are summarized in **Table 1**.[14,30]

Screening tools identify individuals who potentially are at risk for a disorder but do not make the diagnosis. Further history and referral to a child psychiatrist may be warranted if a screening tool is positive. Since signs and symptoms of psychopathology may manifest in a seemingly indolent fashion, a high index of suspicion should be continuously maintained. Additionally, since iatrogenic effect is under a clinician's control, choosing an appropriate antiepileptic drug is vital. However, psychopathology may emerge after seizure remission is achieved or after drugs are weaned, such as with benign or absence epilepsies.[31]

In conclusion, epilepsy is typically considered a disorder of paroxysmal events. However, it also encompasses a broad spectrum of disabilities including autistic syndromes, attention deficit hyperactivity disorder, psychosis, and mood disorders. These psychiatric "comorbidities" often impact a child's quality of life more than the seizures themselves. Due to their variable expression, and the complex interactions of underlying brain dysfunction, psychosocial environment, and treatment regimen, they may be as much or more of a challenge than the epilepsy. A high index of suspicion and routine screening is needed to diagnose and treat the entire disease burden carried by children with epilepsy.

Table 1 - Short clinical screening tools for attention and mood disorders.

Behavior	Screening tools
Attention	Conners' rating scales
	Disruptive behavior rating scale
	Digit span subtest of WISC or WAIS
	Coding subtest of WISC or WAIS
Mood/Anxiety	Short mood and feelings questionnaire
	Children's depression inventory
	Child anxiety scale

WISC - Wechsler intelligence scale for children,
WAIS - Wechsler adult intelligence scale

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