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Review

Should pediatric neurologists play a role in the management of the most common psychiatric comorbidities in children with epilepsy? Practical considerations

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ABSTRACT

Child neurologists should provide initial care for the mental health problems of children and adolescents with epilepsy. Attention deficit hyperactivity disorder (ADHD), autism spectrum disorders are common comorbidities of childhood epilepsy. The psychotropic drugs used to treat mental health disorders can be safely employed in children with seizures. Child neurologists can diagnose common behavioral problems, should be comfortable with first-line agents to treat common psychiatric illnesses, and should recognize when support from psychologists or child and adolescent psychiatrists is needed.

This article is part of the Special Issue "Obstacles of Treatment of Psychiatric Comorbidities in Epilepsy".

1. Introduction

Should pediatric neurologists play a role in the management of the most common psychiatric comorbidities in children with epilepsy? The simple answer is yes. Not only should the pediatric neurologist manage common comorbidities in the child with epilepsy, but also, the pediatric neurologist may be the best person to provide care for the emotional and behavioral aspects of childhood epilepsy. First, mental health problems are common and affect approximately half of the children attending an epilepsy clinic. Second, the pediatric neurologist will have a working relationship with the child and family and will be providing ongoing care and follow-up. Third, the pediatric neurologist will be monitoring seizure control and will be the provider most likely to recognize adverse effects of antiepileptic and psychotropic medications. Finally, child and adolescent psychiatrists are in short supply, insurance coverage for mental health is often limited, families may be reluctant to see a mental health provider, and psychiatrist may be uncomfortable managing medication in a child with epilepsy.

Why would the child neurologist avoid treating behavioral comorbidities? The reasons may be similar to those expressed by pediatricians. In one survey, 85% or more of pediatricians were comfortable diagnosing ADHD, depression, and anxiety and were willing to treat ADHD, but less than 20% would treat depression or anxiety. More than half of the sample noted lack of training and lack of confidence in treating mental health problems, lack of time for treatment, and inadequate reimbursement for time spent treating mental health problems [1].

There were three main goals of this paper. First is to list the most common emotional and behavioral comorbidities of childhood epilepsy. Second is to discuss assessment, screening, and diagnosis. Third is to review treatment with an attempt to delineate therapy within the providence of the child neurologists and to acknowledge conditions that merit referral to the child and adolescent psychiatrist. Not covered in this review are intellectual disability and the learning disorders associated with epilepsy.

2. Common comorbidities: prevalence and risk factors

The most common psychiatric comorbidities in children with epilepsy are ADHD, anxiety, depression, and autistic spectrum disorder. The prevalence of behavioral disorders in children with epilepsy differs by study, but, on average, population-based studies find that one-fourth of children with epilepsy have symptoms of ADHD, 15% anxiety, 10% depression, and 5–10% autism spectrum disorder. Most of the recent (i.e., last 10 years) epidemiological studies have used large databases with diagnosis of psychiatric disorders based on insurance or hospital registries [2–4] or on parental report of a prior diagnosis [5], thus, potentially resulting in underdiagnosis. In contrast, Reilly et al. [6] assessed all children 5–15 years of age with active epilepsy defined as on one or more antiepileptic drugs (AEDs) and/or one or more seizures in the past year that had been born in a specific geographic area. Parents and teachers completed behavioral questionnaires, and the child underwent psychological testing. They found that 60% of the children

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with epilepsy met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for one or more psychiatric diagnoses. There was a prevalence of 33% for ADHD, 21% for autism spectrum disorder, 13% for anxiety, and 7% for depression, with only one-third of those with a psychiatric diagnosis having a prior diagnosis. In this sample, 40% had a full scale intellectual quotient (IQ) < 70, 15% 70–84, and 45% >85. These data show how common behavioral and emotional problems are in this population. The child neurologist treating children with epilepsy should expect to encounter psychiatric problems in every clinic.

The presence of certain risk factors increases the likelihood of psychiatric problems in children with epilepsy. Demographic variables are minor predictors. Gender is usually not a predictor in childhood, but by adolescence, girls may have a slightly increased risk of anxiety compared with the boys. Young age of seizure onset is a better predictor of cognitive problems than behavioral disorders. Epileptic encephalopathies are associated with intellectual disability, autism spectrum disorder, and other behavioral and emotional disorders, but in cognitively healthy children, epilepsy syndrome has not been consistently associated with specific behavioral problems. Increased seizure severity and seizure frequency are risk factors for psychopathology. Antiepileptic drugs and polypharmacy have been associated with behavioral and emotional problems. Both family history of psychiatric problems and family disruption are predictors of psychopathology [7,8].

3. Screening for emotional and behavioral comorbidities

Recognition of psychiatric comorbidities can come from a focused history, broadband screening tools, or disorder specific screening instruments. If problems are identified with screening questions or measures, a more complete history should be taken. The history should come from both the child and the parent. In the case of adolescents, it is essential to obtain information from the adolescent. It is also best to ask the adolescent about problems, separate from the parent. Parents give reliable information on disruptive behavior disorders but may miss anxiety and depression. For the child with intellectual disability, most of the history must come from caregivers.

Ideally, the comprehensive epilepsy clinic is multidisciplinary, and behavioral, emotional, and social issues can be assessed by nurses, social workers, or psychologists [9]. However, when resources are limited, the mental health history can be completed in a reasonable amount of time by the child neurologist. There are excellent resources available that outline brief methods of assessing behavior and emotion in children and adolescents with epilepsy. Kanner and Weisbrot [10] list 22 questions that cover aggression, mood, anxiety, and disruptive behaviors, plus 11 additional questions for psychosis, obsessive–compulsive disorder, and abuse. The consensus statement on affective disorders in patients with epilepsy suggests questions and techniques for diagnosing depression and anxiety in children and adolescents with epilepsy [11].

Multiple screening tools are available and can reduce the time required for assessment [12,13]. The Strengths and Difficulties Questionnaire (SDQ) [14] and the Pediatric Symptoms Checklist (PSC) [15] are broadband screening instruments available in parent and youth report forms that cover ADHD, disruptive behaviors, anxiety, and depression. Both are brief and freely available. The SDQ has 25 items and has been translated into multiple languages. The PSC has 17-item and 35-item forms and is available in English, Spanish, and Chinese.

A second option for screening is to use disorder-specific forms when a particular disorder is suspected. There are multiple instruments that are freely accessible [12,13]. Screening instruments for depression include the Neurological Disorders Depression Inventory for Epilepsy-Youth, a 9-item scale for children and adolescents 10–17 years of age, and the Modified Patient Health Questionnaire (PHQ-9) for assessing depression in adolescents [16,17]. The Generalized Anxiety Disorders 7-item scale has been used in studies of anxiety in children and adolescents with epilepsy [18]. The Vanderbilt Assessment Scale is often used as a screen for ADHD and disruptive behavior disorder screening. Both parent and teacher forms are available [19]. The Modified Checklist for Autism in Toddlers (mCHAT) is widely used as a screening instrument for autism in toddlers 16 months to 3–4 years and has been evaluated in children with epilepsy. The mCHAT may result in many false positives in children with developmental delay and epilepsy [20].

4. Treatment of comorbidities in the child with epilepsy

Once the child neurologist recognizes the presence of psychiatric comorbidity, there are several important initial steps. First, reassess seizure control and seizure-related factors. Are seizures causing the behavioral difficulties? Has an AED been recently started, or have doses been changed? Consider the possibility of behavioral adverse effects of AEDs. The severity of the emotional problems will often determine the best initial treatment. Some children and families may need education or supportive counseling. Others may need a more detailed assessment or referral to a mental health provider if complexity causes confusion about diagnosis or severity requires additional resources. If the diagnosis is clear and the condition is mild or moderate, the child neurologist should be able to start treatment.

5. Treating ADHD

As a first step, assess seizure control. Frequent nonconvulsive seizures may impair attention. Nocturnal seizures may disrupt sleep leading to impaired attention during the day. The frequency of spike discharges may be important. Aldenkamp and Arends [21] found that frequent epileptiform discharges during testing resulted in lower scores on a computerized test of visual search. Increased attention difficulties in children with focal epilepsy with centrotemporal spikes have been associated with more frequent epileptiform discharges [22].

Impairment in attention may be an adverse effect of AEDs [23]. Barbiturates, topiramate, valproate, and zonisamide have been reported to cause difficulty with attention. Changing AED could reduce symptoms of ADHD.

Treatment of ADHD is reasonably straightforward [24]. In the past, there was a concern that stimulants might cause seizures or increase seizure frequency. Most recent reports do not support this worry. Wiggs et al. [25] used a large database to assess over 800,000 patients with ADHD. They found that children with ADHD were at an increased risk of seizures, but the risk was lower when patients were on medication for the treatment of their ADHD. Clinical studies that have assessed seizure control after starting medications for ADHD have not documented an increase in seizure frequency. This has been seen in patients with well-controlled seizures and in patients with intractable seizures [26,27]. Only one new retrospective study, using doses of methylphenidate close to 1 mg/kg/day, found an increase in seizures [28].

There are no large, double-blind, placebo-controlled trials of medications for ADHD in children with epilepsy. Methylphenidate was compared with placebo in a small sample of 10 children. Attention improved without worsening of seizures [29]. Another blinded study used varying doses of OROS-methylphenidate in one-week blocks. There was improvement in attention without an increase in seizures [30]. A third study used a single-dose design in adults with epilepsy and found methylphenidate to be more effective than placebo for attention [31]. Open-label studies in child with well-controlled seizures and in children with intractable seizures have found that methylphenidate was effective without worsening of seizures [26,27]. There are less data for amphetamine and atomoxetine, though both may be effective in reducing symptoms of ADHD without increasing seizure frequency [32]. Alpha-adrenergic drugs are approved for the treatment of ADHD, but there are no trials in children with epilepsy. Sedation is a potential adverse effect and might be problematic if the child is on a

sedating AED. High dose tricyclic antidepressants and moderate to high dose bupropion may lower seizure threshold and should probably be avoided [33].

6. Treating anxiety and depression

Anxiety and depression are frequently comorbid conditions, and treatment of the two conditions is similar [24]. As with ADHD, the first step is to assess seizure control and AED use. Anxiety symptoms may be a component of seizures. Anxiety can be an aura in focal onset seizure, and fear or apparent panic attacks may occur in focal seizures originating in the temporal lobe [34]. Postictal depression has been described in adults but seems to be less common in children and adolescents [35].

Antiepileptic drugs may contribute to the occurrence of anxiety and depression or may help ameliorate symptoms. Anxiety and depression may be adverse effects of many of the AEDs. Anxiety may be seen more often with felbamate, lamotrigine, and levetiracetam and depression with barbiturates, vigabatrin, zonisamide, topiramate, and levetiracetam. Depression may also occur with the removal of lamotrigine, valproate, and carbamazepine in children at risk for mood disorders [23].

Treatment of anxiety and depression involves varying combinations of education, psychotherapy, and medication. Educational programs that address fears and concerns about epilepsy and that teach basic coping techniques and problem-solving have been helpful in reducing the child's and parent's anxiety [36–38]. If symptoms of anxiety or depression are mild, supportive counseling or providing educational self-help materials may be sufficient. Family or group classes can be led by an epilepsy nurse or social worker.

For moderate to severe anxiety and depression, a combination of cognitive behavioral therapy and medication is recommended in the guidelines from the American Academy of Child and Adolescent Psychiatry [39,40]. Cognitive behavioral therapy (CBT) is most often provided by a psychologist with knowledge of epilepsy, ideally a member of the treatment team. Trials have shown that CBT for children with epilepsy is helpful in preventing depression and in reducing symptoms of anxiety and depression [41,42].

Medication can be started by the child neurologist. For both anxiety and depression, the serotonin reuptake inhibitors (SSRIs) are first-choice medications [43]. There are no controlled trials of SSRIs in children with epilepsy, but open-label trials of fluoxetine and sertraline showed improvement in emotional symptoms without adverse effects on seizure control [44]. Patients should be started on a low dose with an increase in dose if needed after 3–4 weeks.

The SSRIs do not seem to worsen seizures in children and adolescents. An assessment of adverse reports from regulatory trials found fewer seizures in patients on SSRIs than in patients on placebo [45]. The tricyclic antidepressants have not been shown to be effective in childhood or adolescent anxiety or depression. At high doses, the tricyclic antidepressants may lower seizure threshold and should be avoided. The antidepressant bupropion and the antianxiety agent clomipramine have been associated with an increased risk of seizures. Fluoxetine and fluvoxamine are potent inhibitors of the cytochrome P450 system and may cause elevations of serum levels of phenytoin and carbamazepine [46].

7. Treating autism spectrum disorder

There is an overlap in symptoms of autism and certain epilepsy syndromes including Landau–Kleffner and continuous spike–waves in slow-wave sleep syndromes. There may be behavioral improvement with effective treatment of the seizure disorders [47]. Children with tuberous sclerosis and early-onset seizures are at substantial increased risk for autism. Initial open-label trials of mechanistic target of rapamycin (mTOR) inhibitors suggest that successful treatment of seizures in children with tuberous sclerosis might result in improved behavior [48]. Unfortunately, a controlled trial of an mTOR inhibitor was no better than placebo in treatment of behavioral problems in children with tuberous sclerosis [49]. There is an association between impaired social cognition and frontal lobe and nondominant temporal lobe function, but there is no evidence that medical or surgical treatment of frontal or temporal lobe localization-related epilepsy improves social cognition [50].

In utero exposure to valproate is associated with autism, but there is no evidence that later valproate or other AEDs contribute to symptoms of autism [51]. Nevertheless, AEDs with negative effects on behavior and cognition should be avoided. Franz et al. [52] found that lamotrigine was effective for patients with tuberous sclerosis and localization-related seizures and had a positive effect on behavior and alertness in one-third of the patients.

Treatment of autism spectrum disorder must include educational and behavioral interventions. The child neurologist can prescribe medication for specific symptoms [53]. Risperidone and aripiprazole are approved for the treatment of children with autism and irritability and/or aggression. Though certain antipsychotic medications may lower seizure threshold, risperidone and aripiprazole have not been associated with an increase in seizures [45]. Because of the weight gain found with these agents, combination with valproate should be avoided. When there is comorbid autism, ADHD, and epilepsy, methylphenidate or atomoxetine can be used, though the response is less than what can be seen with ADHD alone [54]. Fluoxetine has been used to treat the repetitive behaviors seen in children with autism.

8. When to refer

The child neurologist should work collaboratively with a psychologist when learning disability coexists with ADHD, to provide cognitive behavioral therapy for anxiety and depression and cognitive assessment and behavioral therapy for the child with autism spectrum disorder. Referral to a child and adolescent psychiatrist should occur if adequate trials of two first-line psychotropic agents fail or if the child or adolescent develops comorbid mania, psychosis, or suicidal ideation or attempts.

9. Summary

Children and adolescents with epilepsy often have comorbid ADHD, anxiety, depression, and autism spectrum disorder. Child neurologists should be able to diagnose these disorders and should be comfortable to start treatment. The stimulants, atomoxetine, serotonin reuptake inhibitors, risperidone and aripiprazole are frequently effective and are reasonably safe to use in children with epilepsy.

Conflict of interest

None.

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