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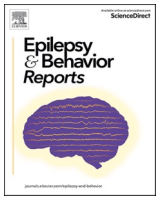

Anxiety and school avoidance in an 8-year-old child with epilepsy

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ABSTRACT

Anxiety is ubiquitous in school age children. Co-occurring medical illness adds to the complexity of identifying pathologic anxiety as opposed to that of typical development such as with social interactions or academic pressures. Anxiety may also occur in the context of cognitive difficulties or inattention, both of which may be exacerbated by epilepsy or by anti-seizure medicines themselves. Treatment strategies may require patience and long-term observations to account for the typical range of stressors that may be expected with disease progression or with development through childhood. This section illustrates the challenge of diagnosis and management of anxiety in the context of epilepsy in a school aged child and addresses nuances that neurology clinicians need to consider. Practical strategies for management including stepwise options for pharmacologic treatment will be emphasized.

Illustrative case study

Abby is an 8-year-old female with childhood absence epilepsy. She was generally healthy until the onset of third grade when she began to exhibit escalating nervousness, interspersed with sudden bouts of tearfulness on nights before school days. She began complaining that her stomach hurt such that she could not go to school. Occasionally she would vomit, though usually only had nausea. She had no apparent prior history of anxiety or depression, and had no difficulties with peer interactions, but was described as being very quiet and sometimes appeared tired. Her teachers said that she had never been disruptive in class and had good academic abilities.

Two years earlier, Abby was observed by parents and teachers to have staring spells and would sometimes "freeze" in the middle of an activity. She was diagnosed with absence seizures with an ambulatory EEG, showing 3 Hz spike and wave in a generalized pattern. Her seizure control improved markedly with divalproex sodium, which was the first anti-seizure medicine attempted. However, 3–5 s staring spells were still noticed by parents and teachers several times a day, despite good treatment adherence and no clear antecedents. An MRI was normal and there were no focal neurologic findings on exam. Developmental milestones were within normal limits. Family and social history and review of systems were unremarkable.

Two months into the school year, she worsened and missed school on several more occasions because of severe stomach pain. An urgent care visit did not reveal any specific pathology for the gastrointestinal complaints. She refused to attend school when her stomach was upset, and vomited more often in the mornings and was typically late to school even when she was able to attend. Her parents acquiesced to her missing school because she seemed so distressed. She was brought to the neurologist's office because the parents suspected that the stomach pain was seizure related in some way.

In the office, she was calm though acknowledged being worried about mean people and robbers. When asked whether she was afraid of having seizures, she said no because she could not tell when the seizures were happening. However, she did say that her mother knew and was always around to take care of her. She denied feeling sad and did not have abnormal patterns of sleep or appetite. When asked why she sometimes missed school, she said that she was too tired to go to school and that being tired made her stomach hurt. The clinical impression was that this was a normal developmental phase in the context of having epilepsy and no specific treatment was recommended.

A few weeks later, the parents insisted upon a follow up appointment because the symptoms had continued, and Abby seemed "out of it" during some of the stomach pain episodes. During the visit, Abby was pleasant and cooperative, though was again tired and very quiet. Her mother noted that Abby no longer wanted to go to friends' houses and was described as being "clingy". She was not comfortable in a room by herself and would only go to sleep if a parent stayed with her until she fell asleep. She was hesitant to speak, but did not have symptoms of

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dysphoria, or panic attacks. She acknowledged having fears about seizures but did not want to discuss them. The neurologist did not suspect that the symptoms were seizure related, but did not know what to do and left the exam room abruptly.

Symptom Identification

A few key points are worth mentioning at this stage. This is the second visit in rapid succession for the same symptoms. Abby's parents are clearly frustrated and desperate, and consider that they are not getting adequate answers. The physician is also frustrated because of the confusing symptoms that do not seem to be epilepsy related. However, modern day comprehensive epilepsy management requires attention to one main thing, that is to take the patient seriously. It is unfortunate that Abby was sent home without a thorough assessment of the anxiety symptoms. An astute pediatric physician would have a sense that her anxiety was outside of the normal range. Resisting school is the first clue that a child is not on typical developmental course and requires further assessment. Worsening of function is the next clue, especially in a patient who had been functioning reasonably well in the past despite having active epilepsy. Abby's demeanor, being quiet, hesitant to speak and having physical symptoms in order to avoid anxiety provoking environments are additional clues that anxiety seems to be present.

All that being said, Abby presents a complex combination of epilepsy plus psychiatric comorbidity, which is well outside of the comfort zone of many clinicians in both neurology and psychiatry. Furthermore, such conditions may not be well accommodated by a singular disciplinary approach. Neuropsychiatric approaches in neurology or in psychiatry are uncommon but nonetheless necessary in epilepsy and in many other ostensibly brain-based diseases. Psychiatric comorbidity in epilepsy is extremely common, so clinicians need to be alert to complaints that may indicate the need for more detailed assessment.

Differential diagnosis

While it is clear that anxiety is present, how pervasive the symptoms are may not be as clear. Many children with epilepsy, even the perceived relatively benign childhood absence epilepsy (CAE) have anxiety about having seizures, especially in a public setting such as in school. Even if able to go to school, many children are aware that they have disrupted attention for some reason that is unpredictable in nature and they may be on some level worried about missing important details either academically or socially. Children with epilepsy commonly have academic problems [1–6] and learning disabilities [7,8]. Even though absence seizures are brief in duration, the consequences of disrupted attention may have effects well beyond the time span of the active seizure. Cognitive dysfunction may be worse with a longer duration of epilepsy. In a very real sense, the academic problems may be cumulative, well beyond the overt physical impact of the seizure [9,10]. Disrupted attention may independently lead to anxiety symptoms. Thus attention problems may be an important differential diagnosis even in the context of apparent primary anxiety disorder.

Anxiety may also result from the fear of having a seizure in a setting without a parent or astute caregiver present who can provide support [11–13]. Such fears are ubiquitous in children with epilepsy, and many are reticent to venture into novel environments or separate from a parent for fear of having a seizure in a setting where no one can take care of them. The fears are often reinforced by parents who routinely make accommodations to mitigate the impact of seizures and to assure a healthy recovery from such events. Unfortunately, these efforts may result in a maladaptive dynamic or vicious cycle of overprotection and resistance to independent functioning as parents and children reinforce the other's fears of medical instability. As a result, children with epilepsy are often delayed in terms of social maturity, unable to experience age expected norms of autonomous social functioning. Although Abby did not attribute her symptoms to the fear of having seizures, it may be expected that separation anxiety or school avoidance could be a natural consequence of this sort of fear cycle between Abby and her parents. The absence of depressive symptoms suggests that anxiety may be the primary problem and would allow a clinician to narrow down the comorbid conditions in that way.

Key features of anxiety disorder diagnoses often involve the consequences of excessive worry or fear. Hesitation in engaging with potentially pleasing activities or even frank avoidance of such events is common. A child may find it difficult to control the worry and it may be out of proportion to the actual events or threats. School phobia or avoidance, though not technically independent diagnostic categorizations, may nonetheless be the most evident manifestation of such excessive worry and may be present in multiple anxiety disorders such as social anxiety or separation anxiety. Worry or fear can magnify and develop into physical complaints such as GI discomfort, headaches, fatigue, and muscle tension. Such physical complaints are typical of generalized anxiety disorder. Ultimately, anxiety symptoms that compromise function are essential ingredients of all subtypes of diagnosable anxiety disorders.

It is also important to note that anxiety is typical in school aged children as a part of normal development. As children progress through developmental stages, anxiety is often the result of a mismatch between chronologic age and emotional maturity. Social development is often impaired and children may be uncomfortable in typical social settings. As children age into middle childhood and adolescence, social anxiety may be common, especially if seizures are omnipresent as a potential social embarrassment. In Abby's case, she no longer was comfortable interacting with peers and retreated to the family house in order to avoid anxiety in social situations. Being unable to confidently navigate social interactions can lead to a preference for social isolation which may be difficult to undo. Common symptomatic and diagnostic overlaps for anxiety are described in Table 1.

Iatrogenic Causes

At the outset, the neurologist would have done well to address the fact that Abby's absence seizures appear to be incompletely treated, so it may be that anti-seizure medicines would have needed to be re-evaluated as an initial step in management. It would have been fortuitous if the physician had selected an adjunct anti-seizure medicine that had the added benefit of treating mood and anxiety. Although the evidence base in pediatrics is not robust, the best examples may include lamotrigine or oxcarbazepine which are often used as primary or adjunctive treatments in mood and anxiety disorders in persons without epilepsy. Incomplete treatment of the epilepsy may also compromise overall function which could increase vulnerability to anxiety. Although some controversy exists regarding issues of forced normalization, in most cases behavior and mental function improve as seizure control improves.

Direct iatrogenic causes for her symptoms may also be present, as in this case, side effects of valproate may include sedation or disorientation, exacerbating anxiety and inattention. Abby appeared tired, so it may be that side effects of the anti-seizure medicine aggravated her difficulties with alertness. Any anti-seizure medicine that causes sedation may potentially be an iatrogenic cause of anxiety. Examples include phenobarbital or benzodiazepines, though in some cases, benzodiazepines such as clobazam may improve anxiety in low doses.

Decision flow chart

1. Accept that discussion of psychiatric symptoms is necessary to appropriately treat epilepsy.
2. Assess whether symptoms are part of the underlying illness. Anxiety itself may be part of the ictal event for many types of epilepsy. For seizures localized to the mesial temporal lobe or in frontotemporal regions, ictal fear, either as a seizure aura or as the experience of the

Table 1
Comparison of Common Symptoms in Inattentive subtype of ADHD, Social Phobia, Separation Anxiety, Generalized Anxiety Disorder (GAD), Panic Disorder and School Avoidance.

Predominant Symptom of Anxiety	Inattentive subtype of ADHD	Social Phobia	Separation Anxiety	GAD	Panic Disorder	School Avoidance
Excessive worry or fear	[ ]	[X]	[X]	[X]	[X]	[X]
Restlessness or edginess	[X]	[X]	[X]	[X]	[X]	[X]
Irritability	[ ]	[ ]	[ ]	[X]	[ ]	[ ]
Muscle tension	[ ]	[ ]	[ ]	[X]	[X]	[X]
Difficulty concentrating	[X]	[X]	[ ]	[X]	[X]	[X]
Sleep disturbances	[ ]	[ ]	[X]	[X]	[ ]	[X]
Rapid heartbeat	[ ]	[ ]	[ ]	[ ]	[X]	[ ]
Shortness of breath	[ ]	[ ]	[ ]	[ ]	[X]	[ ]
Sweating excessively	[ ]	[X]	[X]	[ ]	[X]	[ ]
Trembling or shaking	[ ]	[X]	[X]	[X]	[X]	[ ]
Nausea or GI discomfort	[ ]	[X]	[X]	[X]	[X]	[X]
Feeling lightheaded/dizzy	[ ]	[ ]	[X]	[X]	[X]	[ ]
Avoidance of triggers	[ ]	[X]	[X]	[ ]	[X]	[ ]
Fear of judgment	[X]	[X]	[ ]	[X]	[ ]	[X]
Fear of separation	[ ]	[ ]	[X]	[ ]	[ ]	[X]
Excessive concern about the future	[X]	[ ]	[X]	[X]	[ ]	[X]
Excessive need for reassurance	[ ]	[X]	[X]	[X]	[ ]	[X]
Physical complaints	[ ]	[ ]	[X]	[X]	[ ]	[X]

seizure itself may be common [14]. This seems unlikely for Abby as her seizures are generalized in nature, but anxiety surrounding the events may exist as an interictal phenomenon.

3. Consider whether symptoms are iatrogenic in nature. If sedation is a problem, then a careful assessment of risks and benefits of anti-seizure medicines should be done. It may be that another anti-seizure medicine should be attempted either as a primary treatment or as an adjunct treatment.
4. Identify symptoms as related to an anxiety disorder. This may be challenging, but if steps 1–3 are completed, then the task will be easier to accomplish. Rating scales may be helpful and selected tools are shown in Table 2.

Rating scales

Rating scales are useful tools, especially the SCARED which is available free of charge and has a long history of use clinically and in research studies with well-established normative data. Proprietary scales include the MASC, which is a widely used anxiety scale designed for children to self-report, and the BASC, which is a broad scale assessing symptoms in a variety of psychiatric illnesses. Both measures are easily self-scored and do not require additional training to administer or score. The SCARED deserves special attention as it is a readily accessible 41-item questionnaire with a three-point Likert scale (0, 1, or 2), and a threshold score of 25 reflecting clinical significance for an anxiety disorder. The scale is amenable for child self-report or for a parent report. Subscale scores are also available for anxiety subtypes such as social anxiety or school avoidance.

Although a scaled score can be helpful to clarify diagnoses, clinicians should develop treatment plans geared to problematic symptoms rather than rigidly adhering to scoring schemes. Individual items may be particularly meaningful to clarify anxiety as a primary diagnosis as opposed to a condition secondary to *peri*-ictal events or iatrogenic causes. Furthermore, follow up questionnaires may suitably track treatment responses.

Table 2
Common rating scales for anxiety and other psychiatric conditions in children.

Rating scale	Description	Reference
Multidimensional Anxiety Scale for Children | Second Edition (MASC-2)	Self-report and parent-report versions, copyrighted by Pearson Assessments	[15,16]
Screen for Child Anxiety Related Disorders (SCARED)	Parent, teacher, patient self-report measures, available online, obtain free of charge at https://www.aacap.org	[17]
Behavior Assessment System for Children | 3rd ed. (BASC-3)	Parent, teacher, patient self-report measures, used for a variety of psychiatric conditions available through Pearson Assessments	[18]

Treatment strategies

Psychopharmacology

Medications are a mainstay of treatment for severe anxiety and depression in children without epilepsy, and the evidence base is well developed. Although placebo response rates are high, many patients have tangible improvement with medicines addressing anxiety. Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), benzodiazepines, buspirone, guanfacine and clonidine are commonly used to treat anxiety disorders in children [19,20]. However, an important initial treatment option that is mild in nature includes alpha-adrenergic agonists, which are norepinephrine modulators that may improve impulsivity in ADHD as well as anxiety symptoms [21]. A medicine that modulates the sympathetic nervous system may be useful given that hypothalamic pituitary adrenal (HPA) axis disruptions are common with epilepsy as well as with numerous psychiatric conditions, including anxiety and agitation [22,23]. Although not indicated by the FDA for such use, a substantial evidence base suggests that guanfacine particularly may reduce excess sympathetic tone and effectively treat symptoms of anxiety and post-traumatic stress disorder [24,25]. That makes guanfacine a useful initial step for a patient like Abby who has anxiety symptoms that are notably compromising function. Details of selected medications are described in Table 3.

Guanfacine

Guanfacine may be initiated either with a half or a full tablet of immediate release 1 mg or with a full tablet of extended release 1 mg pills. Extended-release tablets should not be split. The most common side effect is sedation, though that often mitigates within 2–3 weeks. If problematic, then the medicine may be given at night. Typically, guanfacine is effective as a once daily medicine, but patients who are fast metabolizers may require twice daily dosing. There are no known contraindications or interactions with medicines for epilepsy; however, sedation may be more pronounced if also taking an ASM that also causes sedation. In those circumstances, slow titration is recommended. Although in pediatrics, no such adverse effects have been reported with

Table 3
Details of Selected Medications to treat Anxiety in Epilepsy.

Medicine	Formulations	FDA Indication	Dosing Regimen
Guanfacine [28]	Immediate release 1,2mg and Extended-release 1,2,3,4mg formulations available. Central alpha2A-adrenergic receptor agonist	Monotherapy for maintenance treatment of ADHD. Commonly used off-label for anxiety and reported to be effective for anxiety in PTSD (24)	–start with 1 mg extended release QAM. Increase by 1 mg every week until symptom resolution. –if sedation occurs then switch to QHS dosing. –max 4 mg/day for children
Sertraline	Tablets of 25 mg, 50 mg, 100 mg	Monotherapy for obsessive compulsive disorder in ages 13–17, off label use for a variety of anxiety disorders and for depression in pediatrics	–Start with 12.5 mg for children or with 25 mg QAM for adolescents, take with food, assess mental status every 1–2 weeks. –Increase dose by 12.5–25 mg every 2–4 weeks only if well tolerated. –max 100 mg/day for children, 150 mg/day for adolescents

guanfacine, it has very mild hypotensive effects that may be notable in patients with existing cardiac disease, so cardiology consultation is recommended for patients with pathologic tachycardia, postural hypotension, or suspected arrythmias.

Sertraline

If a response to guanfacine is insufficient, then serotonin selective reuptake inhibitors (SSRIs) may be a good option, as they are commonly used treatments for both anxiety and depression in pediatrics. The most commonly studied medicines in pediatrics are fluoxetine, sertraline, citalopram, and escitalopram [26]. However, in the case of sertraline, the pivotal trials were geared to obsessive compulsive disorder, so technically use for depression or anxiety would be off label. However, the advantage of sertraline is a relatively short half-life, multiple dosing formulations that allow very gradual titration and widespread accepted usage in pediatrics. Seizure exacerbation has not been reported in pivotal studies, but clinical trials typically exclude prospective participants with epilepsy. One small study suggests minimal seizure exacerbation following antidepressant treatment in pediatric epilepsy [27].

Titration of sertraline as well as with any SSRI must be very slow. Therapeutic effects often take several weeks or more to be evident. However, side effects such as nausea, insomnia, and activation may occur in the first week or two after dosage initiation or increase. It is critical then for some sort of check in with the patient to occur every week or two after initiating the medication or increasing the dose. Activation is a problematic side effect. Any report of hyperactivity or mood worsening should result in discontinuation of the medicine.

Role of anti-seizure medication

Anti-seizure medicines (ASMs) are multi-faceted, often serving as primary or adjunctive treatments for mood and anxiety disorders in persons without epilepsy. Although the evidence base is low, it is intuitive to use an ASM for psychiatric comorbidity in epilepsy, particularly if complementary mechanisms may improve seizures and psychiatric symptoms simultaneously [29]. Some of the most robust findings for ASMs in treating anxiety include lamotrigine and clobazam [30]. Although risks and benefits would need to be considered, in Abby's case, improving seizure control would be an important goal and suggests that adjunctive ASMs with the added benefit of improving anxiety symptoms would be preferred options. Selection of ASMs with beneficial effects for psychiatric comorbidities is rapidly becoming the conventional approach to treatment.

Psychotherapy

In pediatrics, it is important to remember that the school environment is critical in terms of anxiety and mental health. Gravitating towards peer connections is developmentally appropriate for school aged children, and in many cases, even modestly successful positive peer engagement may be curative for school avoidance or even social phobia. With that goal in mind, individual psychotherapy to focus upon relaxation techniques or coping skills may be reasonable strategies, and likely represents the first choice of treatment for most patients. Some psychotherapists emphasize a certain modality, but most evidence suggests that style of therapy, cognitive behavioral, psychodynamic, supportive, insight oriented, etc., matters less than the rapport and therapeutic relationship that a patient has with a therapist [31]. It may take time for therapeutic gains to be evident. So long as symptoms are mild, patients and clinicians have the luxury of being patient with the psychotherapeutic process.

REFERRAL TO PSYCHIATRY

Referral to a specialist is often a challenge since experience with epilepsy is uncommon among most child psychiatrists, and specialty pediatric neuropsychiatrists are rare. The clearest reason for an epileptologist to refer to a mental health clinician is when initial treatment strategies to address comorbidities prove to be ineffective. For most mental health conditions, a conservative approach beginning with psychotherapy is more palatable as an initial treatment for mild to moderate severity of symptoms. Medication options are many, but epilepsy specialists who gain acumen with at least one or two options may see beneficial results. Acuity and severity will usually dictate subsequent treatment approaches and referral to psychiatry.

Key reasons for referral to psychiatry

- If symptoms persist or significant depressive symptoms emerge.
- If there are side effects that prevent titration.
- If treatment yields only a partial treatment response.

Summary and recommendations

Abby, an 8-year-old female with a history of childhood absence epilepsy (CAE), presented with symptoms including GI discomfort, separation anxiety, and school avoidance. She had experienced ongoing absence seizures despite treatment with an ASM. Initial management approaches include embracing the need for a neurologist to address the anxiety, considering the impact of partially treated seizures and iatrogenic causes of anxiety, and use of rating scales or other interview tools to establish diagnoses. Treatment for anxiety is often multifaceted, but in many cases, judicious use of commonly prescribed medicines such as guanfacine or sertraline can improve symptoms. Psychotherapy is also a useful option in many cases and may be the first choice for a treatment strategy. A comprehensive and practical approach often proves useful and is essential for modern day epilepsy treatment.

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Jay Salpekar: Writing – review & editing, Writing – original draft, Conceptualization. **D. Dilara Ertenu:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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