EPILEPSY CURRENTS

Current Review
In Clinical Science

Seizure and Psychosocial Outcomes of Childhood and Juvenile Onset Generalized Epilepsies: Wolf in Sheep's Clothing, or Well-Dressed Wolf?

Katherine Nickels, MD
Mayo Clinic, Rochester, MN
Address correspondence to: Katherine Nickels, MD, Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: nickels.katherine@mayo.edu

Studies of generalized electroclinical syndromes can provide guidance regarding long-term seizure, cognitive, and psychosocial outcomes. Childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and idiopathic generalized epilepsy with generalized tonic–clonic seizures alone are electroclinical syndromes typically associated with normal intellect and good response to antiseizure medications. However, studies have demonstrated significantly poorer psychosocial outcomes than expected for these syndromes, regardless of seizure control. Potential causes for this include underlying abnormalities in social skills, social stigma, and underlying abnormalities in brain development and maturation.

When children are diagnosed with epilepsy, parents want to know the long-term outcome, such as whether the seizures will be pharmacoresponsive, will the epilepsy be outgrown, and how it will affect learning and development. These are difficult questions for the physician to answer. However, studies of long-term outcomes of specific electroclinical syndromes can help provide guidance.

The previously labeled "idiopathic generalized epilepsy" syndromes—including childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized epilepsy with generalized tonic–clonic seizures alone—are typically associated with normal intellect and good response to antiseizure medications. Therefore, it was previously felt these syndromes had a relatively benign course. However, further long-term studies have demonstrated this is not necessarily the case, suggesting they are "wolves in sheep's clothing" (1). This article will review the long-term seizure outcome, as well as the cognitive and psychosocial outcomes of these syndromes.

Childhood Absence Epilepsy

Childhood absence epilepsy (CAE) presents with frequent typical absence seizures in otherwise healthy school-age children, most often between the ages of 6–8 years. This has been viewed as a pharmacoresponsive, self-limited syndrome associated with good neurodevelopmental outcome.

Seizure Outcome

In children with CAE, terminal seizure remission (seizure-free and off anti-epileptic medications) occurs in approximately two-thirds of patients, typically 4 years after seizure onset, or by ages 9–12 years (2–4). In a population-based study of the long-term outcome of CAE, 44% of those with continued seizures or who were still taking anti-seizure medications (AEDs) met criteria for juvenile myoclonic epilepsy. Those with ongoing seizures 10 years after epilepsy onset, myoclonic seizures while taking AEDs, absence status epilepticus, and a family history of generalized seizures in a first-degree relative were unlikely to have terminal remission. The presence of generalized tonic–clonic seizures may also be a risk factor for lack of terminal remission (4). Furthermore, poor seizure control in the first 6 months after AED initiation may also be associated with lack of terminal remission (3).

A prospective, community-based study also demonstrated that children treated first with ethosuximide had higher rates of complete remission compared to those first treated with valproic acid. While those with atypical EEG features were more often treated with valproic acid, use of ethosuximide as first medication was associated with higher rates of complete remission than valproic acid, regardless of EEG findings (2).

Cognitive and Psychosocial Outcome

Although children have normal overall intelligence with typical CAE, inattentiveness, learning disorders, anxiety, and depression are more likely to occur when compared to children without epilepsy. When Caplan et al. (5) compared children with CAE who had IQ of 70 or higher to normal children, they found those with CAE had significantly lower IQ across all subcategories. Furthermore, those with CAE were more likely to have attention deficit hyperactivity disorder (ADHD) (26% vs 6%) and anxiety (20% vs 7%), and this was correlated with longer duration of illness and higher seizure frequency. They were also noted to have more difficulties with internalizing (including social withdrawal and feelings of worthlessness), somatic

Epilepsy Currents, Vol. 15, No. 3 (May/June) 2015 pp. 114–117

complaints, and social problems. Overall, 61% of children with CAE had a psychiatric diagnosis, although only 23% received intervention (5, 6).

These findings may initially be attributed to high seizure frequency, which is supported by the Childhood Absence Epilepsy Study Group's finding that 36% of all children in their cohort exhibited some attention deficits at the time of diagnosis. However, there was continued inattention in those who became seizure free (7).

Juvenile Absence Epilepsy

Juvenile absence epilepsy (JAE) occurs later than CAE, with onset between ages 10–17 years. The absence seizures are less frequent, occurring less than once per day in some, and generalized tonic–clonic seizures are common (8). Unlike CAE, this epilepsy syndrome is unlikely to spontaneously remit and is associated with more pharmacoresistance.

Seizure Outcome

In a long-term study of children and adolescents with absence epilepsy, those with JAE were more likely than those with CAE to evolve to juvenile myoclonic epilepsy (19% vs 3%). Approximately two-thirds were able to be seizure free for at least 2 years (9). Up to one-third have been able to discontinue AEDs (10). However, those with absence seizures alone were much more likely to have seizure remission than those with absence and generalized tonic–clonic seizures (78% vs 35%, respectively) (9).

Cognitive and Psychosocial Outcome

Children and adolescents with absence epilepsy at any age (both CAE and JAE) appear to have difficulties with school performance, even when compared to children with other chronic diseases. Wirrell et al. (1) compared the long-term psychosocial outcome of patients with childhood or juvenile absence epilepsy to that of children and adolescents with juvenile rheumatoid arthritis (JRA). Those with a history of absence seizures were more likely to require special education, have below-average academic performance, and behavior problems. These children and adolescents were less likely to graduate from high school or attend college. Furthermore, those with absence seizures were also more likely to have a history of heavy alcohol use and have relationship problems with family and friends. Finally, children and adolescents with absence epilepsy were more likely to work unskilled jobs and worked fewer months over the previous year compared to those with JRA.

Although some of these findings could be attributed to ongoing seizure activity, this was not supported by this study. The children and adolescents with absence epilepsy were significantly more likely to have remission than those with JRA (57% vs 28%). When only those with epilepsy remission were compared to the JRA patients, the epilepsy patients still had poorer academic-personal and behavioral outcomes (1).

Juvenile Myoclonic Epilepsy

Juvenile myoclonic epilepsy (JME) typically occurs in previously healthy adolescents, although there can be onset in the early twenties (11). All children will experience myoclonic seizures, which may be triggered by photic stimulation. The majority will have generalized tonic–clonic seizures and often do not come to medical attention until this occurs. Up to one-third will also have absence seizures (12).

Seizure Outcome

JME is typically a pharmacoresponsive syndrome with up to two-thirds being seizure free with medication. Those with continued seizures can also have prolonged periods (more than 5 years duration) of seizure freedom (13). Continued seizures while on medication are often due to lack of compliance to medication and lifestyle recommendations (11). It was previously believed that treatment for JME was lifelong, even in those who had prolonged seizure freedom. Long-term studies of cohorts of adolescents with JME have demonstrated that approximately one-fourth of those who become seizure free are able to remain seizure free off AEDs (12–14). Those with longer duration of epilepsy and continued seizures before achieving seizure freedom, requiring AED polytherapy to become seizure free, or absence seizures at diagnosis were less likely to achieve seizure remission (13, 14).

Cognitive and Psychosocial Outcome

The majority of adolescents with JME graduate from high school and go on to post-high school education; 65 to 77 percent have reported being "very satisfied" with life (12). In spite of this, two long-term studies reported only 42 to 69 percent of patients were employed in jobs that provided sufficient income to support themselves. Furthermore, 74 to 88 percent had at least one major unfavorable social outcome, such as unemployment, unplanned pregnancy, or failure to complete high school (12, 15). In one study, up to 80% of pregnancies were unplanned, and two women decided not to have children because of their epilepsy. There was no relationship between social outcome and seizure control or continued use of AEDs (12).

Generalized Epilepsy with Generalized Tonic–Clonic Seizures Alone (GE-GTC)

Adolescents with generalized epilepsy with generalized tonic–clonic seizures (GE-GTC) are otherwise normal and experience only generalized tonic–clonic seizures. The seizures can present throughout childhood and adulthood, although most present at ages 11–23 years. The seizures are pharmacosensitive and infrequent, with approximately half experiencing less than 11 seizures total (16).

Seizure Outcome

While it was previously thought that lifelong AED therapy was necessary even though the majority of patients become seizure free, a long-term retrospective population based study of patients diagnosed with GE-GTC before age 16 years demonstrated that 75% were able to attain complete terminal remission (seizure free and discontinued AEDs). None of the patients in this study had intractable epilepsy (16).

Cognitive and Psychosocial Outcome

The previously discussed epilepsy syndromes (CAE, JAE, and JME) all may be associated with frequent seizures, especially

prior to diagnosis. Therefore, some of the poor psychosocial outcomes in these syndromes may be attributed to high seizure frequency. By comparison, children with GE-GTC experience infrequent seizures. Given the low seizure frequency, low total seizures throughout the course of epilepsy, and the pharmacoresponsiveness of this syndrome, it would be expected that these patients would have a better psychosocial outcome than the patients with the other syndromes. However, the psychosocial outcome in these patients is also concerning. Of the 30 patients in the one study followed for more than 20 years, 77% had learning problems, only 60% graduated from high school, and one-third were unemployed as adults (16).

Why Are Cognitive and Psychosocial Outcomes Poor in Childhood and Juvenile Onset Epilepsies?

All of these pharmacoresponsive epilepsy syndromes associated with overall intelligence quotients (IQ) within the normal range have worse psychosocial outcomes than expected, regardless of age of epilepsy onset or seizure frequency. These findings are not easily explained. Children and adolescents with epilepsy may have underlying abnormalities in their social skills. Tse et al. (17) compared the social skills of cognitively normal children and teens with epilepsy to those of their nonepileptic siblings and found those with epilepsy had lower social skills standard scores, poorer total competence, poor school competence, and lower social competence scores. However, another study showed that those with epilepsy are more likely to be bullied, regardless of social skills (18).

The social stigma of epilepsy may be a significant contributing factor. When cognitively normal adolescents with and without chronic disease were surveyed, epilepsy was reported to have negative physical and social impact (19). Specifically, epilepsy was perceived as being associated with mental handicap, causing injury to the person and the bystander, and leading to death. Compared to other chronic diseases—including asthma, diabetes, leukemia, HIV, and Down syndrome—epilepsy had a similar impact to HIV and a worse impact than all others except Down syndrome. Those with epilepsy were also viewed as being dishonest, unpopular, bad at sports, and without compassion (19). Twenty (14%) of the adolescent survey responders said they would be reluctant to befriend someone with any chronic disease, but 19 of them were specifically against epilepsy. Furthermore, 12 thought their parents would not want them to befriend someone with chronic disease, and 10 of these pertained only to epilepsy (19).

Outcome may also be attributed to underlying abnormalities in interictal brain function, not directly caused by seizure activity. Although children with generalized epilepsy typically have normal neuroimaging, careful analyses have demonstrated significant differences when compared to controls. Children with CAE have significantly smaller frontal and temporal lobe gray matter volumes (20). Furthermore, children with CAE lack the normal age-related changes in cortical thickness throughout multiple cortical areas (21). Duration of epilepsy, seizure frequency, and medications had no effect on the results of these studies. In addition, adolescents with new-onset generalized epilepsy have smaller thalamic and frontal volumes compared to controls, and these differences are not affected by medication (22). These studies suggest diffuse abnormalities in brain development are present by epilepsy onset, become more pronounced with time, and likely contribute to learning and behavioral difficulties.

Finally, rats with genetic absence epilepsy treated with AEDs had more depressive symptoms than controls also treated with AEDs, even when seizures were well-controlled (23). Furthermore, these rats have also been shown to have more depression and anxiety behaviors evident prior to onset of seizures (24). This suggests the epilepsy and depression/anxiety may originate from a common pathology.

Conclusions

Although seizure outcomes in these generalized epilepsy syndromes are generally good, with the majority of patients achieving long-term seizure control and a significant number also being able to discontinue AEDs, the effects of epilepsy go far beyond just the seizures. Even in those who are seizure free, there is significant long-term psychosocial and educational impact of childhood and juvenile onset epilepsy, suggesting these epilepsy syndromes are more than "wolves in sheep's clothing": They may just be well-dressed wolves. It is important to recognize these comorbidities to provide counseling and intervention when possible.

Summary Points

1. Children and adolescents with generalized epilepsy are at increased risk for:
   a. Learning disorders (especially inattentiveness) and difficulties with school performance, even with normal IQ;
   b. Psychiatric comorbidity.

2. As adults, those with a history of generalized epilepsy are at increased risk for unfavorable social outcomes and continued psychiatric comorbidities, regardless of seizure control.

3. Contributing factors likely include diffuse brain developmental abnormalities present at, or prior to, seizure onset, which persist or worsen throughout the course of epilepsy.

References

1. Wirrell EC, Camfield CS, Camfield PR, Dooley JM, Gordon KE, Smith B. Long-term psychosocial outcome in typical absence epilepsy: Sometimes a wolf in sheeps' clothing. *Arch Pediatr Adolesc Med* 1997;151:152–158.
2. Berg AT, Levy SR, Testa FM, Blumenfeld H. Long-term seizure remission in childhood absence epilepsy: Might initial treatment matter? *Epilepsia* 2014;55:551–557.
3. Callenbach PM, Bouma PA, Geerts AT, Arts WF, Stroink H, Peeters EA, van Donselaar CA, Peters AB, Brouwer OF. Long-term outcome of childhood absence epilepsy: Dutch study of epilepsy in childhood. *Epilepsy Res* 2009;83:249–256.
4. Wirrell E, Camfield C, Camfield P, Gordon K, Dooley J. Long-term prognosis of typical childhood absence epilepsy: Remission or progression to juvenile myoclonic epilepsy. *Neurology* 1996;47:912–918.
5. Caplan R, Siddarth P, Stahl L, Lanphier E, Vona P, Gurbani S, Koh S, Sankar R, Shields WD. Childhood absence epilepsy: Behavioral, cognitive, and linguistic comorbidities. *Epilepsia* 2008;49:1838–1846.

6. Guttmannova K, Szanyi JM, Cali PW. Internalizing and externalizing behavior problem scores: Cross-ethnic and longitudinal measurement invariance of the Behavior Problem Index. *Edu Psychol Meas* 2007, December. doi: 10.1177/0013164407310132.
7. Masur D, Shinnar S,. Cnaan A, Shinnar RC, Clark P, Wang J, Weiss EF, Hirtz DG, Glauser TA. *Pretreatment cognitive deficits and treatment effects on attention in childhood absence epilepsy. Neurology* 2013;81:1572–1580.
8. Tovia E, Goldberg-Stern H, Shahar E, Kramer U. Outcome of children with juvenile absence epilepsy. *J Child Neurol* 2006;21:766–768.
9. Trinka E, Baumgartner S, Unterberger I, Unterrainer J, Luef G, Haberlandt E, Bauer G. Long-term prognosis for childhood and juvenile absence epilepsy. *J Neurol* 2004;251:1235–1241.
10. Pavlović M, Jović N, Pekmezović T. Antiepileptic drugs withdrawal in patients with idiopathic generalized epilepsy. *Seizure* 2011;20:520–525.
11. Baykan B, Altindag E, Bebek N, Ozturk A, Aslantas B, Gurses C, Baral-Kulaksizoglu I, Gokyigit A. Myoclonic seizures subside in the fourth decade in juvenile myoclonic epilepsy. *Neurology* 2008;70(pt 2):2123–2129.
12. Camfield CS, Camfield PR, Juvenile myoclonic epilepsy 25 years after seizure onset: A population-based study. *Neurology* 2009;73:1041–1045.
13. Senf P, Schmitz B, Holtkamp M, Janz D. Prognosis of juvenile myoclonic epilepsy 45 years after onset. Seizure outcome and predictors. *Neurology* 2013; 81:2128–2133.
14. Geithner J, Schneider F, Wang Z, Berneiser J, Herzer R, Kessler C, Runge U. Predictors for long-term seizure outcome in juvenile myoclonic epilepsy: 25–63 years of follow-up. *Epilepsia* 2012;53:1379–1386.
15. Schneider-von Podewils F, Gasse C, Geithner J, Wang ZI, Bombach P, Berneiser J, Herzer R, Kessler C, Runge U. Clinical predictors of the long-term social outcome and quality of life in juvenile myoclonic epilepsy: 20–65 years of follow-up. *Epilepsia* 2014;55:322–330.
16. Camfield P, Camfield C. Idiopathic generalized epilepsy with generalized tonic-clonic seizures (IGE-GTC): A population-based cohort with >20 year follow up for medical and social outcome. *Epilepsy Behav* 2010;18:61–63.
17. Tse E, Hamiwka L, Sherman EM, Wirrell E. Social skills problems in children with epilepsy: Prevalence, nature and predictors. *Epilepsy Behav* 2007;11:499–505.
18. Hamiwka LD, Cara GY, Hamiwka LA, Sherman EM, Anderson B, Wirrell E. Are children with epilepsy at greater risk for bullying than their peers? *Epilepsy Behav* 2009;15:500–505.
19. Cheung C, Wirrell E. Adolescents' perception of epilepsy compared with other chronic diseases: "Through a teenager's eyes." *J Child Neurol* 2006;21:214–222.
20. Caplan R, Levitt J, Siddarth P, Wu KN, Gurbani S, Sankar R, Shields WD, Frontal and temporal volumes in childhood absence epilepsy. *Epilepsia* 2009;50:2466–2472.
21. Tosun D, Siddarth P, Toga AW, Hermann B, Caplan R. Effects of childhood absence epilepsy on associations between regional cortical morphometry and aging and cognitive abilities. *Hum Brain Mapp* 2011;32:580–591.
22. Pulsipher D, Dabbs K, Tuchsherer V, Sheth R, Koehn M, Hermann B, Seidenberg M. Thalamofrontal neurodevelopment in new-onset pediatric idiopathic generalized epilepsy. *Neurology* 2011;76:28–33.
23. Russo E, Citraro R, Scicchitano F, De Fazio S, Perrota I, Di Paola ED, Constanti A, De Sarro G. Effects of early long-term treatment with antiepileptic drugs on development of seizures and depressive-like behavior in a rat genetic absence epilepsy model. *Epilepsia* 2011;52:1341–1350.
24. Jones NC, Salzberg MR,. Kumar G, Couper A, Morris MJ, O'Brien TJ. Elevated anxiety and depressive-like behavior in a rat model of genetic generalized epilepsy suggesting common causation. *Exp Neurol* 2008;209:254–260.