Epileptic Syndromes in Childhood: Clinical Features, Outcomes, and Treatment

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Summary: We reviewed the clinical features, outcome, and treatment of many of the epileptic syndromes that begin in the childhood from 2 to 12 years of age, using a review of the literature and personal experience, with most references to authoritative texts. The developmental tasks of childhood are centered on refinement of motor skills and development of complex intellectual and social skills. The childhood onset epilepsies can be divided into benign, intermediate, and catastrophic based on their impact on childhood development. The clearest benign epilepsy is benign rolandic epilepsy, which often does not require medication treatment. The definition of benign occipital epilepsy is still often vague. In the intermediate category, childhood absence epilepsy often has associated learning disorders and a poor social outcome. About 50% of children with cryptogenic partial seizures have a very benign course, even though their epilepsy syndrome is not well defined. Generalized epilepsy with febrile seizures plus (GEFS+) has a dominant inheritance with a defined defect in cerebral sodium channels, but varies considerably in severity within affected members of the same kindred. The catastrophic epilepsies in childhood all have an inconsistent response to AED treatment and include continuous spike-wave in slow sleep (with variable severity), Landau-Kleffner syndrome (with a confusing overlap with autistic regression), the Lennox Gastaut syndrome (with broad defining features), and myoclonic-astatic epilepsy (with important overlaps with Lennox-Gastaut). Many of the epilepsies that begin in childhood are benign. Others interfere seriously with cognitive and social development. Key Words: Epilepsy—Childhood—Syndromes—Review—Prognosis—Treatment.

The annual incidence of epilepsy is lower in the childhood years (~45/100,000 population) than in infancy but still higher than in adolescence (1). Many of the epilepsies beginning in childhood are relatively benign, although there are a few major exceptions. Most, but not all, of the truly catastrophic secondarily generalized epilepsies begin in infancy. When a resistant partial epilepsy begins in childhood, it may take several years for the disorder to declare itself as unresponsive to antiepileptic drugs (AEDs). Only when the child becomes an adolescent is it clear that the epilepsy will not go away.

Childhood stretches from 2 to 12 years. This is still “the age of innocence.” All basic developmental motor skills have already been acquired but now are refined as children move from clumsy running to skateboards and ice skates. The major developmental tasks in childhood are cognitive and social. The cognitive tasks still largely center around basic skill acquisition, as opposed to the abstract application of ideas. Children learn to communicate in sentences and develop complex grammar. They understand the sound/symbol relationships and phonic skills that lead to reading. They learn to print, write, and draw. Numeric concepts evolve from rote counting to long division, but they are not yet ready to understand Karl Marx or the theories of relativity. Cause and effect become clear. For example, if Suzie pulls Johnny’s hair, she learns that he will hit her. Children learn that life is finite, but are free of deep thoughts about the meaning of life. These cognitive developments depend on synaptic complexity with cell proliferation and “dying back” long since complete.

Socially, this is the time of first real friendships, cooperative play, and the understanding of competitiveness, compassion, and basic right and wrong. The declining age of puberty in girls has pushed some sexual relationships into childhood; however, this is not a common issue.

When epilepsy appears during childhood, effects on development are to be anticipated. Sometimes there are big problems—a catastrophic epilepsy. Sometimes there are no problems—a benign epilepsy. The distinction between “benign” and “catastrophic” epilepsy is not clear-cut, and there must be a category between these extremes. A truly benign epilepsy must be characterized by infrequent seizures that are mild and not associated with cognitive or psychosocial effects. A benign epileptic disorder must resolve fairly promptly. Truly cata-

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Benign rolandic epilepsy is well documented to have a genetic etiology, although to date, there has not been a confident localization of the gene(s). The work of Bray and Wiser (6) indicated that the EEG marker is inherited as an autosomal dominant with age-related penetrance. Only ~10% of children inheriting the EEG trait actually have recognized seizures. So, in establishing the diagnosis, the family history is often amusing but not usually helpful.

The prognosis is wonderful—by the mid-teenage years, the disorder vanishes in 100% of cases (3,7). In the very few adults with persistent epilepsy after benign rolandic in childhood, their adult epilepsy syndrome has been different (3).

Treatment is entirely optional. In our population-based experience with 79 children with classic benign rolandic epilepsy, only 50% eventually received daily AED treatment, a choice that even fewer parents are making, as concern about AED side effects has increased (7). Treated or not treated, all of our patients remitted within 5 years of diagnosis, with no evidence of psychosocial impact. In this cohort, the children had >900 seizures recorded, with only a single injury. This happened to a child who became frightened during a simple partial seizure, started running for the comfort of her parent’s bedroom, and fell down stairs. A few cases of status epilepticus have been noted in children with benign rolandic, but none have been reported to have neurologic sequelae. By the mid-teenage years, the epilepsy is gone, and the youngsters are normal—a miraculous disorder.

Virtually every AED is efficacious, although the only randomized trials are with gabapentin (GBP) (8) and sulthiame (9). If forced to treat, we usually start with clobazam (CLB) given as a single dose at bedtime. From our cohort, it appears that the secondarily generalized attacks respond more readily to medication than do the simple partial attacks.

Benign rolandic epilepsy disrupts development in childhood only if it interferes with the child’s chances for normal friendships. In our experience, the biggest issue arises when the child wishes to sleep overnight at a friend’s house. Communication between the two sets of parents will usually deal with the concern about a nocturnal seizure. Alternately, a single dose of an AED for these special nights may suffice, although this approach is not evidence based.

Benign occipital epilepsy is everything that benign rolandic is not. There is no typical seizure type and no clearly defined clinical course (10). The seizures may be of any type, although the diagnosis appears most palatable if there is at least a visual aura. The EEG shows occipital spike-waves that appear in chains and block with eye opening. An identical EEG can be seen in
symptomatic partial occipital epilepsies. There is no clear etiology, and the categorization of this epilepsy as “idiopathic” seems speculative, because a genetic etiology is not proven. The nonspecificity of the clinical disorder and EEG makes an early confident diagnosis difficult. It may be best diagnosed after it has vanished; a retrospective diagnosis is of little value to the clinician!

A subset of children in this category have “Panayiotopoulos” syndrome (11). Here the clinical diagnosis is more clear cut. The seizures typically start in a 4- to 8-year-old during sleep and are associated with remarkable vomiting and eye deviation. The clinical course usually involves only a few seizures, even though the seizures may last ≅30 min. The EEG is as that described earlier and indistinguishable from other “benign occipital epilepsies,” except that the discharge may not be restricted to, or include the occipital electrodes (!). Panayiotopoulos insists that the disorder is common and easily diagnosed. We are less certain.

Gastaut (10) summed up these issues very well. He retired in 1984, and in 1992 noted, “Yes, EOP as I described it does exist, even though it is a rare condition (I have only observed 7 new cases in the last 4 years) and though an accurate prognosis is difficult to determine.”

In our opinion, this group of benign occipital epilepsies needs more study. The clinician should be wary of making this diagnosis.

Treatment seems to proceed with the usual AEDs that are effective in partial epilepsies, although there are no clinical trials to establish efficacy.

SYNDROMES BETWEEN BENIGN AND CATASTROPIC

Childhood absence epilepsy

Everyone familiar with childhood epilepsy has encountered childhood absence epilepsy (CAE). The onset is between ages 4 and 10 years. The children are neurologically normal, and sometimes, but not often, there is a family history of idiopathic generalized epilepsy. The absence attacks are frequent and last 5–15 s. The ictal and interictal EEG shows “classic” 3-Hz spike-and-wave with a normal background. Treatment with ethosuximide (ESM), valproic acid (VPA), or lamotrigine (LTG) is proven to be efficacious (12,13), so why is this well-known disorder of an intermediate category between benign and catastrophic? First, medication may be unsuccessful—the rate of failure is unclear, but in our experience with 86 cases, only 60% were successfully treated with the first AED (14). Second, CAE is often associated with cognitive/learning problems (15). It may be argued that these problems are not caused by the epilepsy itself, but they are so common that we consider them part of CAE. The learning disorder may outlast the epilepsy and be a serious life-long problem. Third, ≅15% of children with typical CAE evolve to the life-long dis-order of juvenile myoclonic epilepsy (16). As argued earlier, a syndrome that can be defined as “benign” only in retrospect is of limited clinical value. Fourth, the social outcome of young adults who had CAE is unfavorable in many, including an astonishing rate of 30% inadvertent pregnancy in the girls (16).

Therefore, CAE may have significant effects on the child’s development. The associated cognitive problems are very important; the epilepsy does not always remit, and social outcome may be unsatisfactory.

Other absence epilepsies

In several other childhood-onset epilepsies, the absence seizures predominate, but there are special features that differ from CAE despite identical EEG findings. Three of the most perplexing are micturitional absence, myoclonic absence, and absence with eyelid myoclonia. The clinical attack in micturitional absence is the same as in typical absence except it is associated with a powerful bladder detrusor contraction with urination (17). Because the attacks are frequent and often very resistant to medication, this disorder is very socially problematic—the children are constantly wet. The evolution of this disorder is not well described, but it appears to have a significant remission rate. Our personal experience includes only three patients with micturitional absence, and all have eventually remitted, but only after multiple AED trials. The seizures been resistant to the usual absence medications, and the social issues around the frequent seizures have been major.

Myoclonic absence is a very specific seizure type (18). The EEG shows typical 3-Hz spike-and-wave. During the seizure, the child stops suddenly, and the arms extend and “ratchet” upward with a jerking, 3-Hz, motion. Seizures are frequent, but the children do not fall, and there is no postictal confusion, as in typical absence. Almost all children with this disorder are mentally handicapped, and the epilepsy is very resistant to treatment, even to the newer medications. Eventually myoclonic absence may “die down,” but other generalized seizure types continue.

Absence with eyelid myoclonia is recognized by the marked eyelid and upper facial jerking during the seizures (19). This disorder often appears to be inherited as an autosomal dominant and is typically very resistant to conventional treatment.

Cryptogenic partial seizures starting in childhood

Many otherwise normal children have partial epilepsy that has no known cause and proceeds with a benign course (20). Unfortunately, it is not easy to characterize accurately those destined to have a benign clinical course, compared with those who will have persistent epilepsy. In our population-based series from Nova Scotia of 504 children with epilepsies characterized by partial or generalized tonic–clonic seizures, there were 132 children (aged 2–12 years) with cryptogenic partial sei-
zures (21). The cause of the epilepsy was truly unknown based on history and computed tomography (CT) scans [this series was gathered in the pre–magnetic resonance imaging (MRI) era]. All had normal intelligence and neurologic examinations. Over a follow-up period that averaged 88 ± 31 months, 67% entered remission—they were seizure free and no longer received daily medication. Sixty (45%) of these children had smooth-sailing epilepsy—they started daily treatment with an AED after at least two seizures, became instantly seizure free, discontinued medication after a few years, and remained seizure free—truly a benign epileptic disorder. Yet none of these children fit into a current, well-defined, specific benign focal epilepsy syndrome. It appears that ~50% of children with cryptogenic partial epilepsy have a remarkably benign disorder.

**Generalized epilepsy with febrile seizures plus (GEFS+)**

GEFS+ is a fascinating disorder in which understanding the gene defect has allowed a confident expansion of the phenotype (22,23). The disorder is autosomal dominant with very high penetrance (possibly 80%) and is caused by a defect in the neuronal voltage-gated sodium channel. To date at least three separate mutations have been identified (23). In its simplest form, the children have ordinary febrile seizures that continue to an older age than usual. In adolescence there are generalized tonic–clonic seizures with eventual remission. However, ~30% of those carrying the gene have other epilepsy syndromes with different seizure types including absence, myoclonus, and akinetic. There has been a suggestion that severe myoclonic epilepsy of Infancy may be part of GEFS+ (24). It seems likely that GEFS+ deserves the phrase “more common than previously recognized.”

**CATASTROPHIC EPILEPSIES OF CHILDHOOD**

**Continuous spike–wave in slow sleep (CSWS)**

This disorder is generally restricted to the childhood years. There are no large case series, and the clinical profile of the disorder has been elusive. The most classic presentation is a child with partial seizures who begins to show some cognitive deterioration (25). A sleep EEG shows that generalized spike–wave discharges occupy >85% of slow-wave sleep. The awake EEG may show focal spikes or some irregular generalized spike–wave. The severity and type of cognitive dysfunction appears very variable, and the clinically apparent seizures may be few or even nonexistent.

The cause of CSWS remains mysterious, although there is concern that carbamazepine (CBZ) may play a role in precipitating this disorder in some children. A progressive brain disorder is not typically noted, and the few studies with serial psychometric testing have not typically described progressive deterioration. Treatment with AEDs may or may not be successful. The EEG abnormality may persist for many years or stop unexpectedly. The cognitive problems may resolve or persist! Treatment recommendations have nearly always been to stop CBZ and substitute VPA or a benzodiazepine (BZD). The history of one of our patients is illustrative.

TG is now 16 years old. Up until age 3 years, there were no concerns about her development. At that time she had her first seizure—a 90-min focal clonic attack during sleep. CBZ was started, and the dose was gradually increased because she had four more seizures. At age 5 years at school entry, it was noted that she seemed cognitively less capable than other children. Psychometric testing indicated mild global mental handicap. A sleep EEG showed CSWS. Her medication was switched to CLB, and over the next 3 years, she had four overnight EEGs, which continued to show CSWS. There were no further recognized seizures, and medication was stopped at age 12 years when the sleep EEG had normalized. She continues to have serious learning difficulties, and there was no clear improvement, either when her EEG normalized or when medication was stopped.

Therefore, there is a great deal of variability in CSWS. Its relation to LKS is unclear. LKS is clearly more severe in most cases than CSWS, and the localization of LKS to the temporal lobes is very different from the generalized pattern of CSWS. We consider these two disorders very different from each other.

**Landau–Kleffner syndrome**

In 1957, Landau and Kleffner (26) described a specific syndrome in childhood that has been an enormous source of controversy. Previously normal children between ages 1 and 8 years who already have developed speech experience a frightening language regression with verbal and often complete auditory agnosia. Often speech stops completely, and the child’s behavior deteriorates even to the point of psychosis. There are a few seizures but not many. These are usually focal clonic or generalized tonic–clonic, although complex partial seizures also are noted. The sleep EEG shows high-frequency, sometimes continuous, bilateral spikes typically over the posterior temporal regions that tended to abate in rapid-eye-motion (REM) sleep. The institution of AEDs stops the seizures but makes little difference to the aphasia and behavior problems. Years later with intensive language and scholastic therapy, some of the children improve, although a normal outcome is thought to be uncommon. Since the original description of this disorder, >300 cases have been described. Others have suggested that steroids [adrenocorticotrophic hormone (ACTH) or prednisone] seem to help, and the late Frank Morrell (27) suggested that subpial transactions in the left temporal lobe could be curative.

This disorder in its pure form is exceedingly rare. It is
an unusual catastrophic epilepsy because overt seizures are not much of a problem and remit by the mid-teenage years. The problem is the deterioration in language and behavior. At least 50% of children with this disorder have a life-long severe language and/or mental handicap, suggesting that there has been damage to the language circuits in the brain at a critical stage in development. The cause remains unknown, and the neuropathology is usually normal. “LKS therefore represents an age-dependent functional disruption of language induced by a localized paroxysmal EEG disturbance” (28).

Some of the children with LKS resemble children with autistic regression. In autism, there is often a regression of language and social skills, typically between ages 1 and 2 years. This parallel evolution has lead to intensive, long-term EEG studies in children with autism. Some autistic children were shown to have spike discharge, usually without clinical seizures (29). The spikes were typically low frequency, unlike those with LKS or CSWS. Treatment with VPA and/or prednisone has been associated with improvement in some patients. Subpial transactions have been advocated, especially when magnetoencephalogram (MEG) abnormalities are present (30). However, it is known that major improvements are possible in children with autism without such interventions. Therefore, there is an enormous need for randomized trials of intervention in children with autistic regression and epileptic discharge on EEG. The relationship between LKS and autism remains controversial.

**Lennox–Gastaut syndrome**

The Lennox–Gastaut syndrome has broad defining characteristics and even though the disorder is well known, it is quite uncommon (31,32). The diagnosis is often used loosely to diagnose virtually any person with secondary generalized epilepsy; however, a core group of symptoms defines the syndrome, despite multiple etiologies. The onset is nearly always during the childhood years and rarely begins in adolescence. The classic triad was akinetic seizures, slow generalized spike-and-wave discharges on EEG, and mental handicap. There has been a gradual shift in the definition to replace akinetic with mixed generalized seizures, although drop attacks are nearly always present. Some authorities have insisted that a *sine qua non* is nocturnal tonic seizures associated with a generalized electrodecremental event on EEG (33). All authorities have retained in the definition, the EEG findings of interictal slow spike wave. There are a few children with Lennox–Gastaut (<10%) who have remained intellectually normal.

The disorder is typically catastrophic from all points of view. Seizures are intractable and physically damaging. Intellectual development stagnates, and social consequences are profound. The akinetic seizures cause frequent face and mouth injuries. Even the most attentive parent cannot prevent injury. It is difficult to insist that the child wear a helmet with a facemask; however, no other protective gear is effective. There are often long periods of nonconvulsive status, which one group of investigators has deemed to have the greatest effect on the child’s development (34). When there is a large amount of slow spike–wave on EEG, the nonconvulsive status may be difficult to recognize—the child has decreased responsiveness, ataxia, and does not interact properly with toys or people. Clearly intellectual development does not occur at this time. The nocturnal tonic seizures are exceedingly difficult to suppress and usually not “treatable.” The seizure disorder persists for years, with complete remission rare.

It is unclear whether children with Lennox–Gastaut actually regress (i.e., become demented). Most children with this disorder are not intellectually normal when the seizures start (35). Most have a symptomatic etiology, especially preexisting West syndrome; however, a small number of children appear to be completely normal before the onset of seizures. When the seizures are frequent, development stagnates. If the seizures come under control, typically there is developmental progress. To the best of our knowledge, there are no published cases with careful psychometric testing before seizures and then later after the seizures have been controlled. Nonetheless, there is a large clinical suspicion that there is actual deterioration. In addition, many of the children become restless with impulsiveness, poor sense of danger, and hyperactivity.

Little is written about the social consequences of Lennox–Gastaut; however, our clinical experience suggests that they are profound. In addition to the stigma of mental handicap, child care becomes very complex. It is difficult to persuade even close family members to care for a child with frequent drop attacks. The hyperkinesia is especially challenging. The nocturnal seizures keep exhausted parents on edge all night.

So Lennox–Gastaut syndrome is truly catastrophic and interferes with all aspects of the child’s intellectual and social development. The pathophysiology is unclear. The amount of spike–wave on EEG is large but not larger than in some children with severe CAE or CSWS. It is difficult to understand why low-frequency spike–wave complexes should be associated with so much greater brain dysfunction than 3-Hz spike and wave. The underlying mechanism must be different.

**Myoclonic–astatic epilepsy**

The boundaries between myoclonic–astatic epilepsy (MAS) and Lennox–Gastaut syndrome are unclear (36). MAS is said to usually begin in normal children between ages 1 and 8 years. The most prominent seizure type is a drop attack, which may be preceded by a little series of myoclonic jerks; however, other seizure types usually
occur, including the full gambit of generalized seizure types. Nocturnal tonic seizures with electroderecremental events are said to be very uncommon. The EEG shows paroxysmal 4-Hz theta bursts, plus generalized spike–wave, which usually has a higher frequency than 2.5 Hz and often is photosensitive. In many cases, the epilepsy is controllable and resolves; however, cases have been described that evolve to be indistinguishable with Lennox–Gastaut syndrome. Is there a spectrum of disorders that links MAS with Lennox–Gastaut? Are they all variations on the same theme?

The disorder is usually considered as catastrophic because the astatic seizures are so often associated with injury, and if the MAS is severe, it becomes indistinguishable from the Lennox–Gastaut syndrome.

CONCLUSION

Most children in whom epilepsy develops between ages 2 and 12 years have a relatively benign course, especially those with benign rolandic epilepsy. Cryptogenic partial epilepsy often has little consequence. Absence epilepsies may be benign, although a substantial proportion of these children have persistent epilepsy with cognitive and social difficulties. The catastrophic epilepsies of childhood include CSWS, LKS, and Lennox–Gastaut with important disruptions in both cognitive and social development.

REFERENCES


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