Epileptic Encephalopathy of Late Childhood

Landau-Kleffner Syndrome and the Syndrome of Continuous Spikes and Waves During Slow-Wave Sleep

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Landau-Kleffner syndrome (LKS) and the syndrome of continuous spikes and waves during slow wave sleep (CSWS) are two points on the spectrum of functional childhood epileptic encephalopathies. They are characterized by a severe paroxysmal EEG disturbance that may permanently alter the critical synaptogenesis by strengthening synaptic contacts that should have been naturally "pruned." The much more common benign epilepsy with centrotemporal spikes is also related to LKS and CSWS by a common pathophysiology. Although prognosis in LKS and CSWS for seizure control is good, cognitive function declines and permanent neuropsychologic dysfunction is seen in many cases. This permanent damage is most evident in those patients who had early-onset EEG abnormality and a prolonged active phase of continuous spike-and-wave discharges during sleep. If the active phase of paroxysmal activity persists for over 2 to 3 years, even successful treatment does not resolve neuropsychologic sequelae. In LKS, the paroxysmal activity permanently affects the posterior temporal area and results in auditory agnosia and language deficits; in CSWS, the frontal lobes are more involved and other cognitive disturbances predominate. Aggressive treatment should include high-dose antiepileptic drugs, corticosteroids, and surgery in specific cases. Key Words: Landau-Kleffner syndrome—Continuous spikes and waves during slow-wave sleep—Age-dependent epileptic encephalopathy—Epileptic aphasia—Electroencephalography—Epilepsy in children.

HISTORICAL BACKGROUND

The LKS is named appropriately for William Landau and Frank Kleffner, who together in 1957 reported six children with a syndrome characterized as a convulsive disorder, along with acquired aphasia (Landau and Klef-
Landau-Kleffner syndrome is a functional disorder of childhood characterized by the following: (1) seizures that are relatively easy to treat and self-limited, (2) acquired aphasia, (3) an EEG showing epileptiform discharges, usually over one or both temporal regions, and (4) no definitive brain pathology that can explain the behavioral symptoms and some degree of improvement when the epileptic condition resolves (Deonna and Roulet, 1995; Morrell, 1995; Morrell et al., 1995).

One of the terms that have been challenged in recent reports is “acquired aphasia.” Rapin et al. (1977) have argued that the condition is not aphasia but rather a verbal agnosia. Even more recent evidence implies that it might be an auditory agnosia (Morrell et al., 1995). The difference in terminology stems from the fact that the term acquired aphasia suggests a demonstrable age-appropriate language before the onset of paroxysmal EEG and/or seizures. It is possible that an early onset of the condition could prevent language development, but the strict diagnosis of LKS is not possible in a child in whom language never developed, unless the aphasia is reversed by halting the epileptic process.

The EEG that shows predominantly bitemporal abnormalities is markedly activated in slow-wave sleep, when it may show continuous spike-wave discharges, persisting for an extended period of time (Morrell, 1995). Clinical seizures are not always reported or can be present in a very subtle form (Deonna and Roulet, 1995; Morrell et al., 1995).

All patients improve in language function when the active phase of spike-and-wave discharges dissipates, but permanent language deficits and other neuropsychologic sequelae persist, particularly if the paroxysmal EEG has begun early in childhood (Bishop, 1985) and continues during the critical period of language development (Morrell, 1995; Morrell et al., 1995).

Continuous spike and wave in slow-wave sleep is also a functional childhood disorder. Its characteristics include (1) a severe paroxysmal EEG disturbance with spike waves occupying >85% of the sleep recording, (2) self-limited clinical seizures, (3) behavioral and cognitive deterioration with or without premorbid developmental disturbances, and (4) no brain pathology sufficient enough to explain this behavioral deterioration and improvement once the epileptiform activity is stopped or is resolved (Bureau, 1995a; Tassinari et al., 1992).

The above-mentioned characteristics are not, however, totally agreed upon by all. Tassinari et al. (1992) require a sleep index of 85%, which 85% or more of slow-wave sleep shows continuous paroxysmal activity in the EEG. However, the ILAE (1989) classification of epilepsies and epileptic syndrome does not require it. There is variability in the amount of paroxysmal EEG activity if seizures are eventually changed to electrical status epilepticus during sleep in six children, 7 to 12 years of age, who displayed seizures, cognitive decline, and language dysfunction (Patry et al., 1971). All had almost continuous spike-and-wave during nonrapid eye movement (NREM) sleep. They had atonic, generalized tonic-clonic, convulsive, clonic, and atypical absence seizures. Two failed to acquire language, and five were mentally retarded. The degree of mental retardation was directly related to the age of onset. The authors believed that the syndrome was a form of encephalopathy secondary to a focal or multifocal brain lesions and that the marked sleep activation of the paroxysmal activity was due to a particularly active synchronizing system during slow-wave sleep.

The earlier terms “subclinical electrical status epilepticus” and “electrical status epilepticus during sleep” were eventually changed to “continuous spike and wave during slow sleep” (CSWS) because clinical seizures did not accompany spike-and-wave discharges in the EEG. Tassinari et al. (1985) thought that the persistent continuous spike-and-wave discharges over years were responsible for the complex and severe neurologic impairments that developed in the patients.

**NOSOLOGY**

Although there are similarities, LKS and CSWS are not presently considered as interchangeable disorders. Landau-Kleffner syndrome is a functional disorder of childhood characterized by the following: (1) seizures that are relatively easy to treat and self-limited, (2) acquired aphasia, (3) an EEG showing epileptiform discharges, usually over one or both temporal regions, and (4) no definitive brain pathology that can explain the behavioral symptoms and some degree of improvement...
clinical seizure but do not necessarily eliminate the paroxysmal EEG abnormality.

By the midteen years, there is spontaneous resolution of the epileptiform discharges, and often the behavioral and/or neuropsychologic deficits stabilize or improve. However, as in LKS, there are behavioral, cognitive, and permanent language sequelae; the severity depends on the age of onset and the duration of the active phase of paroxysmal activity.

**UNDERLYING CAUSE AND BASIC MECHANISMS OF ACTION**

The syndromes of LKS and CSWS are considered to have a common pathophysiologic mechanism (De Negri, 1995; Gordon, 1997; Hirsch et al., 1990; Maquet et al., 1995; Morrell, 1995; Morrell et al., 1995; Rossi et al., 1999; Tassinari et al., 2000). As noted earlier, both functional disorders begin during the time of cortical synaptogenesis when the elemental functional circuitry is being established in the brain—between the ages of 1 and 8 years. In the process of synaptogenesis there is abundant axonal sprouting that results in a doubling in the number of axonal process and synaptic contact (Huttenlocher et al., 1982; Huttenlocher and de Courten, 1987; Purves, 1988; Purves and Lichtman, 1980). The major factors that determine which of these synapses will be strengthened and which will be discarded or “pruned” are the neuronal activity or synaptic use (Huttenlocher and de Courten, 1987; Purves, 1988). More than the genetic programming, environment is the crucial role-player in the establishment of permanent synaptic contacts. If a paroxysmal disturbance of a great magnitude develops during this time of high axonal sprouting and synapse formation, the epileptic activity can act to strengthen synaptic contacts that normally would be pruned for the neuronal aggregates to mediate normal behavior (Morrell et al., 1995). In LKS, the paroxysmal activity reinforces these contacts in the developing temporoparietal cortex, producing the permanent language dysfunction (Morrell et al., 1995). The disturbance must have a bilateral effect to prevent the transfer of function to the contralateral homotopic cortex. In CSWS, the most prominent paroxysmal activity appears to be in the frontal area and the prefrontal cortex, which disrupts the higher cognitive and executive functioning before damaging language function.

One of the major difficulties in our understanding of the spectrum of these age-related encephalopathies is the low incidence of both LKS and CSWS. One hundred three cases were reported at the Venice colloquium (Beaumanoir et al., 1995), and from that number, 71 seemed to fit the criteria of CSWS and 31 were LKS. One case remained unclassified. The overall data suggest a definite overlap between the two syndromes. Differences seen in the seizure type, clinical presentations, and the sequelae—both neuropsychologic and behavioral—could be ascribed primarily to the initial cortical area involved, age of onset of the EEG abnormalities relative to age-dependent synaptogenesis, length of time the paroxysmal EEG was present, and persistence of the continuous spike-and-wave discharges during sleep. It is the conclusion of this study that LKS is a subtype of CSWS.

Because the functional disruptions caused by the spread of the paroxysmal EEG activity can encompass large cortical regions, the two clinical syndrome disorders tend to become more similar as the disease progresses. They may produce severe cognitive, behavioral, and, ultimately, social dysfunction, mimicking a child with severe autism. The proposed pathophysiologic mechanism also explains that children who are at greatest risk for permanent and irreversible damage are those with early onset of the disorder and a prolonged active phase.

The underlying cause may be any pathology capable of generating an epileptic condition. The literature contains examples of neuronal migration abnormalities, encephalitis, vasculitis, subpial gliosis, and cysticercosis (Cole et al., 1988), all being associated with either LKS or CSWS. In one surgical series of 14 patients with LKS, 13 patients in whom biopsy specimens were taken from the temporal pole revealed some form of pathologic abnormality (Smith et al., 1992).

**EPIDEMIOLOGY**

The incidence of LKS cannot be estimated accurately at this time. If one uses the strict narrow diagnostic criteria, LKS is indeed a rare disorder of children. Since 1957, 198 cases have been published; 81 cases were reported between 1957 and 1980, but 117 were reported in the decade between 1980 and 1990 (Beaumanoir, 1995). In a Paris psychiatric clinic, Dugas and his colleagues (1976) reported one new case each year. The proposed pathophysiologic mechanism also explains that children who are at greatest risk for permanent and irreversible damage are those with early onset of the disorder and a prolonged active phase.

The frequency of CSWS is also uncertain. When using the strict criteria that include the continuous spike-and-wave discharge occurring during 85% of sleep and recognizable cognitive and behavioral decline, it is also a rare disorder. Between 1971 and 1984, there were 19 cases reported by Tassinari et al. (1985) and an additional 25 from the medical literature. Since 1984, 10 new cases have been seen at the Center St. Paul, a rate of one to two per year (Tassinari et al., 1992). Boys are affected.
more commonly than girls, with the peak onset occurring between 5 and 7 years of age (Bureau, 1995b).

**CLINICAL PRESENTATION**

**Landau-Kleffner Syndrome**

The disorder typically presents with speech disturbance between the ages of 3 and 8 years in a child who has already developed age-appropriate language production. The onset can be subacute, steady, or stuttering and initially consists of a loss of understanding of spoken language. Eventually, and sooner rather than later, speech output is disrupted and paraphasias and phonologic errors begin to appear. In severe instances, the child becomes entirely mute and does not respond to nonverbal sounds as well. This is quite noticeable, as the child who up to this point has acknowledged the ringing of the telephone, knocking on the door, and noises outside the home will not respond now to these stimuli. The child will commonly begin to display hyperactivity and an attention deficit. There is a rare progression to severe disinhibition or psychosis (Beaumanoir, 1995; Morrell, 1995; Morrell et al., 1995).

The language disorder is probably a verbal auditory agnosia, that is, difficulty or loss of verbal comprehension, which may be mistaken as acquired deafness, at least early in the course of the illness. It is then followed by gradual deterioration also in verbal production and, finally, mutism and failure to respond to nonverbal sounds.

The most common seizures include episodes of eye blinking or ocular deviation, head drops, and minor automatisms, sometimes with secondary generalization. They have a variable relation to the language deficit, and 20% to 30% do not exhibit behavioral seizures at all (Beaumanoir, 1985). Characteristically, the seizures have a benign course—they respond well to anticonvulsant medication and usually resolve on their own by the midteen years. Prognosis is not as good for the language function. If the aphasia exists for more than 1 to 2 years, complete linguistic recovery is seldom seen, and such patients continue to have a lifelong language dysfunction (Bishop, 1985; Morrell, 1995; Morrell et al., 1995).

EEG is abnormal in most patients with LKS and shows predominantly bilateral temporal (mainly posterior temporal) spikes or spike-wave discharges that are activated by sleep. On prolonged sleep recordings, subcontinuous 1.5- to 5-Hz spike-and-wave discharges may be seen during slow-wave sleep that disappear or fragment during rapid eye movement sleep (Marescaux et al., 1990; Morrell, 1995; Morrell et al., 1995) (Fig. 1). It is this common EEG feature that links both LKS and CSWS into a single entity. Most patients do not demonstrate a sleep index of 85% characteristic of slow-wave sleep in CSWS. However, it has been thought that this condition was met at some point during the course of the disorder and simply not documented by an EEG recording because of sampling error (Morrell, 1995). Background activity during wakefulness is usually normal. With the use of the methohexital suppression test and intracarotid amobarbital and EEG dipole mapping (Morrell, 1989; Smith et al., 1989), it can be shown that many patients have a unilateral primary epileptogenic region (Morrell, 1995; Morrell et al., 1995). This can involve either side, since the contralateral propagation of paroxysmal discharges creates bilateral dysfunction that disrupts normal language development.

**Syndrome of Continuous Spike Waves During Slow-Wave Sleep**

Onset is usually in the first decade, with mean age of onset at 4 to 5 years. The EEG during wakefulness may show focal or bilaterally synchronous spike-wave discharges over the anterior hemisphere and generalized spike wave (1.5 to 3.0 cps), with the spike-wave index being <25%. There is a highly characteristic activation during non-REM sleep. Almost continuous generalized 1- to 3-cps spike waves are recorded in the EEG during non-REM sleep, with a spike-wave index of >85%. The paroxysmal activity during REM sleep is very similar to that of wakefulness, with focal or bilateral paroxysmal discharges over the frontocentral region.
Seizures are usually present although not invariable. They are commonly nocturnal. The seizures are focal motor, complex partial, absence, and secondary generalized tonic-clonic or hemiclonic type. Tonic seizures, a frequent component of other frontal lobe syndromes, do not occur. Compared with LKS, the seizures are more frequent in CSWS, but, like LKS, they tend to respond to anticonvulsant therapy.

Most patients have normal neuropsychologic function before the onset of EEG changes, but some do have prior abnormal development. All children have cognitive decline during the period of paroxysmal EEG. Reduced attention span, hyperactivity, abnormal behavior, apraxias, and apraxias can all occur as the result of prefrontal dysfunction, leading to extensive cognitive decline described as mental retardation or dementia (Bureau, 1995a; Tassinari et al., 1992). Although the seizures respond very well to antiepileptic drug therapy, it does not improve the paroxysmal discharges or cognitive signs and symptoms. EEG changes are self-limited and generally disappear by the midteen years, but focal spikes may continue in the frontal region. Seizures also remit by the midteens with some improvement of neuropsychologic status, although recovery to normal is the exception rather than the rule.

Tassinari et al. (1992) identified three types of patients with CSWS based on their seizure types: (1) The first group had orofacial, generalized tonic-clonic, and myoclonic seizures in sleep similar to the patients with benign Rolandic epilepsy. (2) The second group had unilateral partial, generalized tonic-clonic, and absence seizures. Seizures were more frequent and occurred even while awake. (3) The third group had unilateral partial and generalized tonic-clonic seizures in sleep and absence of seizures, absence of status, and atonic seizures with fall while awake.

With respect to the neuropsychologic and psychomotor difficulties, Tassinari et al. (1992) identified two subgroups. The first subgroup had normal development before the onset of the CSWS. During the active phase of epileptiform discharges, a severe decline in IQ, significant reduction in language function, and temporospatial disorientation occurred in the majority. All exhibited behavioral difficulties, which included hyperactivity, aggressiveness, disinhibition, reduced attention span, and difficulty in connecting with the environment. The second subgroup had preexisting abnormalities of psychomotor development. Further deterioration of cognitive function and behavior were noticeable but generally not as prominent from the baseline as that displayed by the first group.

### DIAGNOSTIC EVALUATION

It is most important to document the development and history of language production in a child suspected of having LKS or CSWS. All cognitive, behavioral, neuropsychologic, or school reports are important to establish premorbid baseline. A suspected child should also undergo neuropsychologic testing by a team experienced in both linguistic and nonlinguistic evaluation. It is important to determine if specific deficits exist in cognitive function because one would expect to see deficits in the language domain in LKS, whereas features of frontal dysfunction would be a hallmark of CSWS.

Testing procedures include a routine EEG and prolonged video-EEG monitoring or ambulatory monitoring (Beaumanoir, 1995; Morrell, 1995; Morrell et al., 1995). Neuroimaging tests should include structural and functional procedures. Computerized amplitude mapping of EEG, magnetoencephalography, and intracranial EEG recordings should be considered if surgical therapy is considered (Morrell et al., 1995).

Structural neuroimaging is generally normal in LKS but abnormal in CSWS (Morrell et al., 1995; Tassinari et al., 1992). The abnormalities in CSWS include focal porencephaly, focal pachygyria, diffuse atrophy, and minor white abnormalities, whereas in LKS, the reported abnormalities are focal pachygyria and mild, diffuse atrophy (Bureau, 1995b).

A small number of patients of LKS or CSWS had functional neuroimaging. When interpreting the results, it is important to note whether radionucleotide injection was given and the scan obtained during the active phase of spike and wave were conducted in the awake or asleep state. If scans are performed in the awake state, both single-photon emission computerized tomography and positron emission tomography with 18F-fluorodeoxyglucose show an area of decreased blood flow or glucose utilization. On the other hand, studies done on sedated patients with induced continuous spike-and-wave discharges show a focal area of increased blood flow or glucose utilization (Maquet et al., 1995; Morrell et al., 1995). Hirsch et al. (1995) reported increased glucose metabolism during the active phase of spike and wave during both asleep and awake states. The area of increased metabolism was greater in sleep. It was not known whether the paroxysmal activity was present during the awake scan. The hypermetabolism was restricted to focal or regional cortical association areas and the type of neuropsychologic impairment was in good agreement with the topography of this disturbance. The metabolic abnormalities of the two syndromes displayed significant overlap, suggesting that they represent two
types of the same spectrum of functional disorders of childhood (Hirsch et al., 1995; Maquet et al., 1995). Some patients who underwent positron emission tomography with 18F-fluorodeoxyglucose scans after the resolution of the active phase of spike-and-wave discharges showed persistent hypometabolism in the areas that previously showed hypermetabolism, documenting long-lasting metabolic alterations (Maquet et al., 1995).

Recording of EEG in slow-wave sleep is essential in the diagnosis of LKS and CSWS. Because of the short recording time, a routine EEG study may rarely record sufficient duration of slow-wave or non-REM sleep. Amitriptyline at a dose of 1 to 2 mg/kg followed by a prolonged EEG recording of 3 hours improves the chance of confirming a significant activation of paroxysmal abnormalities during slow-wave sleep. The Venice colloquium provided direct comparison of EEG data in LKS and CSWS. During the active phase of spike-and-wave discharges, more patients with CSWS met the criteria of a sleep index of 85% than those with LKS. The average frequency of the spike and wave was 2 Hz in each disorder. Sleep spindles were absent in 10% of patients, more frequently in the CSWS group than in the LKS group. If a patient had a frontal spike focus, there was more likelihood of having a sleep index of ≥85%, suggesting that intrinsic circuitry and dense callosal connections of the frontal lobe facilitate generalization during sleep. Patients could be divided into two sets, depending on the severity of the EEG abnormality. The first set had a sleep index of ≥85%, frequently disrupted sleep spindles, only rare focal discharges during sleep, and bursts of spike and wave in wakefulness. This EEG pattern was seen in 70% of patients with CSWS and in 40% of those with LKS. The second, less severely affected set showed a sleep index between 50% and 80%, often recognizable sleep spindles, more frequent focal slowing during sleep, and absent or rare spike-and-wave discharges during wakefulness. These EEG findings were seen in 30% of the CSWS group and in 60% of the LKS group. These data again support a significant overlap of EEG findings among LKS and CSWS, although those with CSWS are more likely to have a severely affected EEG (Beaumanoir et al., 1995). In addition, focal spikes tend to be frontal in CSWS and temporoparietal in LKS.

Magnetoeencephalography performed on a small number of patients with LKS revealed a focus of slow waves and epileptiform activity in the posterior temporal area adjacent to the sylvian fissure, supporting an origin in the dorsal surface of the superior temporal gyrus (Morrell et al., 1995) (Fig. 2). Sobel and colleagues (2000) found that 13 of 19 patients with LKS had perisylvian magne-

toencephalographic spikes. Computerized amplitude and polarity mapping has also been performed in a few patients with LKS and CSWS. In LKS, isolated unilateral spikes during the methohexital suppression test or the first spike in a burst of spike and wave display a tangential dipole with suprasylvian negativity and infrasylvian positivity, indicating the origin, again, in the dorsal surface of the superior temporal gyrus (Hoeppner et al., 1992; Maquet et al., 1995; Paetau et al., 1999). Amplitude mapping of spikes during wakefulness in three cases of CSWS showed two to be predominantly left frontal with temporal spread and one right frontal with frontal and temporal spread. The spikes during sleep appeared to have a more diffuse distribution (Farnarier et al., 1995). Although the number of cases studied is limited, they support differences in cortical areas maximally involved in the two syndromes.

A few children with LKS underwent chronic intracranial electrode and intraoperative recordings in the course of surgical treatment (Morrell et al., 1995). These studies confirmed that the common paroxysmal abnormality is in the area of the posterior temporal lobe, often maximal on the superior temporal gyrus (Fig. 3). At times, the epileptogenic region is confirmed within the sylvian fissure near the Heschl gyrus (Fig. 4).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis between LKS and CSWS is difficult (Table 1). Landau-Kleffner syndrome tends to affect a slightly younger population, presenting first with language dysfunction and only later with other cognitive
and behavioral deterioration. In CSWS, the affected children tend to be slightly older, presenting with more global neuropsychologic and behavioral deterioration before language dysfunction appears (Bureau, 1995a). The severity of the seizures and EEG abnormality is not as pronounced in LKS as in CSWS. The spike-and-wave discharges are maximal in the centrotemporal or posterior temporal region in LKS and in the frontal head region in CSWS (Beaumanoir et al., 1995).

The disorders most commonly confused with LKS and CSWS are pervasive developmental delay and autism. The most important distinguishing feature is the loss of previously achieved developmental milestones with LKS and CSWS. In contrast to LKS, children with pervasive developmental delay and autism display abnormal, nonverbal intelligence as well as language dysfunction. Children with early-onset and persistent CSWS may deteriorate more globally and begin to mimic autism. Although children with pervasive developmental delay and autism may have paroxysmal EEG abnormalities, they do not have the continuous spike-and-wave discharges during slow-wave sleep.

Mental retardation from a wide variety of causes can occasionally be misdiagnosed as LKS or CSWS. A careful history will usually document that motor and other developmental milestones were not met and that the child was affected from birth. Neurologic examination is often abnormal, demonstrating abnormalities in the motor and other systems. These children may also display EEG abnormalities reflecting the underlying cortical pathology; however, they rarely meet criteria for continuous spike and wave during sleep (Deonna and Roulet, 1995).

Developmental dysphasia is another disorder that may mimic LKS. Children with this condition do not develop language skills in the usual time frame. They often have a normal neurologic examination and nonverbal intelligence. EEG abnormalities are rare, and a continuous spike-and-wave abnormality has not been described (Deonna and Roulet, 1995). If a child presents with developmental dysphasia and shows continuous spike and wave in sleep, early-onset LKS is a distinct possibility.

Once seizures and EEG recordings have indicated the presence of an epileptic disorder, more common epileptic syndromes must be excluded. These include benign childhood epilepsy with centrotemporal spikes (BECT), other idiopathic localization-related epilepsies, and the Lennox-Gastaut syndrome (Bureau, 1995a).

The syndrome of continuous spikes and waves during slow wave sleep and the Lennox-Gastaut syndrome share some common features. These include benign childhood epilepsy with centrotemporal spikes (BECT), other idiopathic localization-related epilepsies, and the Lennox-Gastaut syndrome (Bureau, 1995a).

The idiopathic localization-related epilepsies are more difficult to distinguish pathophysiologically from LKS.
and CSWS, but they are readily separated clinically (Bureau, 1995a). These disorders have less or no effect on cognitive function because the active spike-and-wave activity is less severe or because it involves different, more “silent” cortical areas. Aicardi and Chevrie (1982) reported a syndrome that displayed active spike-and-wave discharges that became continuous with sleep. These children had no detectable cognitive or intellectual deterioration. However, the sleep index and the duration of the active phase of continuous spike and wave were not documented. Deonna et al. (1986) had six similar cases but documented increasing neuropsychologic dysfunction at the time of the EEG deterioration. Polypharmacy may have worsened the clinical status, because all improved on tapering antiepileptic medication. It is probable that this syndrome is a subset of CSWS, with an older onset and a shorter course of the active phase of continuous spike and wave. It may also be that more careful neuropsychologic testing would be able to detect cognitive deficits (Bureau, 1995b).

Benign childhood epilepsy with centrotemporal spikes is easily distinguished from LKS by the absence of acquired aphasia; however, BECT may also be a subset of CSWS. In the three clinical subgroups of CSWS distinguished by Tassinari et al. (1992), one subgroup with orofacial and generalized tonic-clonic seizures in sleep closely mimics BECT. Absence of seizures has also been reported with BECT. There are differences, however, in EEG manifestations. In CSWS, focal abnormalities predominate in the frontal areas, whereas in BECT they are maximal in the centrotemporal regions. There is a clear activation of epileptiform activity in BECT during sleep that at times becomes continuous spike and wave, but the sleep index never reaches 85% (Bureau, 1995a; Caraballo et al., 1989; Massa et al., 2000). There was one reported case of BECT that worsened on carbamazepine therapy; this case reached a sleep index of 85%, had a clinical deterioration with atypical absence and falls, but resolved completely with withdrawal of carbamazepine (Caraballo et al., 1989). Mental retardation and a history of prior neurologic insult are common in CSWS but not in BECT. A family history of epilepsy is reported in 40% with BECT but in only 10% with CSWS (Bureau, 1995a). Despite these clinical differences, it is probable that a child with early-onset and persistent BECT with a high sleep index of spike waves would display cognitive or motor deficits if carefully tested (Deonna, 2000).

**TREATMENT AND OUTCOME**

With the small number of cases and variable natural causes of LKS, no controlled trials of treatment efficacy have been attempted (Rotenberg and Pearl, 2003). The

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**TABLE 1. Comparison of Landau-Kleffner syndrome versus the syndrome of continuous spikes and waves**

<table>
<thead>
<tr>
<th>Variable</th>
<th>LKS</th>
<th>CSWS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>68% male</td>
<td>63% male</td>
</tr>
<tr>
<td>Antecedent history</td>
<td>3% encephalopathy</td>
<td>31%; 36% cerebral palsy; 36% encephalopathy</td>
</tr>
<tr>
<td>Family history of epilepsy</td>
<td>3%</td>
<td>10%</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Peak, 5–7; 5% after 9 years of age</td>
<td>Peak, 5–7; 20% after 9 years of age</td>
</tr>
<tr>
<td>First symptom</td>
<td>Seizure, 60%</td>
<td>Seizure, 80%</td>
</tr>
<tr>
<td>Second symptom</td>
<td>Neuropsychological, 40%</td>
<td>Neuropsychological, 40%</td>
</tr>
<tr>
<td>Seizure types</td>
<td>GTC seizure, 35%; unilateral, 26%; unilateral status, 6%</td>
<td>Unilateral, 50%; unilateral status, 6%; absence, GTC, CPS</td>
</tr>
<tr>
<td>During active phase of spike-and-wave</td>
<td>(−) atonic seizure, no significant ↑</td>
<td></td>
</tr>
<tr>
<td>After active phase of spike-and-wave</td>
<td>19% rare seizure; 81% seizure-free</td>
<td>16% rare seizure, 84% seizure-free</td>
</tr>
<tr>
<td>Neuroimaging</td>
<td>13% abnormal</td>
<td>78%</td>
</tr>
<tr>
<td>Meet criteria for 85% spike-and-wave in sleep</td>
<td>Less than 50%</td>
<td></td>
</tr>
<tr>
<td>Frequency of spike-and-wave</td>
<td>2 Hz</td>
<td>2 Hz</td>
</tr>
<tr>
<td>Ictal discharge awake</td>
<td>26%</td>
<td>67%</td>
</tr>
<tr>
<td>Focal discharges</td>
<td>Centrotemporal/parietal, 60%</td>
<td>Frontal, 60%</td>
</tr>
<tr>
<td>Regional predominance of continuous spike-and-wave during sleep</td>
<td>Posterior</td>
<td>Anterior</td>
</tr>
</tbody>
</table>

Table adapted from Beaumanoir, 1995 and Carabello et al., 1989.

n = 103; CSWS = 71; LKS = 31.

LKS, Landau-Kleffner syndrome; CSWS, syndrome of continuous spikes and waves; FH, family history; GTC, generalized tonic-clonic convulsions; CPS, complex partial seizures.
clinical seizures in LKS and CSWS, as with the other idiopathic localization-related epilepsies, are, for the majority, not severe and are easy to control (Bureau, 1995b; Maquet et al. 1995; Morrell, 1995; Morrell et al., 1995). One important exception to this is in the subgroup of CSWS with daily atypical absences and drop attacks (Tassinari et al., 1992). In this group, clinical seizures are severe and at times are difficult to treat. The clinical seizures in both LKS and CSWS are self-limited, with only rare seizures in approximately 20% of both groups once the active phase of spike and wave has resolved (Bureau, 1995b).

All available antiepileptic drugs have been used individually and in combination for the treatment of LKS and CSWS. Efficacy is difficult to ascertain because all antiepileptic drugs effectively control the clinical seizures. However, there is little effect on the paroxysmal discharges in the EEG. As mentioned above, carbamazepine may cause a worsening of seizures; hence, it should be avoided. Valproate alone or in combination with a benzodiazepine appears to be the treatment of choice (Dulac, 2001).

Corticosteroid therapy or adrenocorticotropic hormone appears to have favorable and long-lasting effects (Van Lierde 1995), and some authors suggest that steroids should be the treatment of choice, especially in new-onset disease in a young patient (Deonna and Roulet, 1991; Hirsch et al. 1990; Lerman et al., 1991). Lerman et al. (1991) recommended a high dose for a prolonged period of time (adrenocorticotropic hormone 80 IU/d with a 3-month taper; prednisone 60 mg/d with a 3-month taper). They noted that there may be relapses with steroid reduction and that some children may need to take steroids for months to years. It appears that the earlier the treatment is initiated, the shorter is the duration for which steroid is required and the better is the ultimate outcome (Lerman et al., 1991).

The current recommendation is to initially treat with valproate with or without benzodiazepine. If the epileptiform EEG abnormality and cognitive dysfunction persists despite high therapeutic antiepileptic drug levels, a several-month course of prednisone with careful follow-up is indicated.

Morrell and colleagues (1989, 1995) reported on the surgical treatment by multiple subpial transaction of 14 children with LKS (see also Grote et al., 1999). All children had been unable to use language meaningfully for more than 2 years and displayed continuous spike-and-wave discharges that were demonstrated to arise unilaterally in the superior temporal gyrus and surrounding perisylvian cortex (Fig. 5). With resolution of the paroxysmal EEG abnormality after multiple subpial transaction, there was marked improvement in language function over time, with 50% recovering age-appropriate language and returning to regular classroom school and 29% showing a marked improvement in language function but still undergoing speech therapy. They concluded that success in recovery of language function depended on proper selection of patients and resolution of the severe epileptiform EEG abnormality (Morrell et al., 1995). Other surgical centers have reported similar efficacy of multiple subpial transaction in LKS. Presurgical evaluation requires delineation of an epileptogenic region involving a unilateral posterior temporal lobe thorough sophisticated electrophysiologic and neuropharmacologic tests that include the methohexital suppression test, intracarotid amobarbital test, electrical dipole mapping, and magnetoencephalographic source mapping. The goal in the treatment of LKS and CSWS is the complete elimination of the paroxysmal EEG disturbance, preferably within the first 2 years to prevent serious neuropsychologic sequelae (Maquet et al., 1995; Morrell, 1995; Robinson et al., 2001; Tassinari, 1995).

LONG-TERM PROGNOSIS

Long-term prognosis for seizure disorder in both conditions is good, with <20% having persistent, usually rare, seizures (Bureau, 1995b). However, the long-term neuropsychologic consequences are not benign (Deonna and Roulet, 1995). The majority of patients who have either disorder have some permanent sequelae that limit their activities. Those with the earliest onset of spike-and-wave discharges and longer persistence of the active
phase of CSWS have the worse neuropsychologic sequelae (Rossi et al., 1999).

In 1980, Mantovani and Landau reviewed the long-term prognosis of 9 patients with LKS followed for 10 to 28 years after onset (1980). They discovered that the overall clinical status and language were normal in <50%. Other studies also report that some form of aphasia persists in the majority (Beaumanoir, 1995; Deonna et al., 1989; Dugas et al., 1976). Only half of the patients with a history of LKS are able to live a normal life (Maquet et al., 1995; Morrell et al., 1995). The prognosis for language is usually dependent on the age of onset and the severity of the epileptic disturbance, the bilateral anatomic location, and the length of the active phase (Deonna, 1991; Hirsch et al. 1995; Maquet et al., 1995; Robinson et al., 2001). These factors also determine the severity of other neuropsychologic sequelae.

The long-term outcome of patients with CSWS is also poor (Morikawa et al. 1992). Like LKS, the age of onset and duration of the active phase of spike-and-wave discharges seem to be the two characteristics that correlate with persistent sequelae. Although there is a global improvement in all intellectual areas after resolution of CSWS, complete restoration of function, especially in verbal ability and attention, is rare (Morikawa et al., 1995). Persistent sequelae include a short attention span, hyperactivity, affective symptoms, and language dysfunctions, as well as intellectual impairment.

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