

Landau Kleffner Syndrome : Electroclinical and Etiopathogenic Heterogeneity

M.B. Singh, J. Kalita, U.K. Misra

Department of Neurology
Sanjay Gandhi Postgraduate Institute of Medical Sciences,
Lucknow - 226 023, India.

Summary

Landau – Kleffner syndrome is a rare, functional, age-related epilepsy with aphasia and epileptiform discharges on EEG. The heterogeneity of clinical presentations, course, long-term outcome and response to treatment suggests multiple underlying etiologies. Normal children abruptly develop deterioration of language functions along with spike and wave discharges on EEG. Clinical seizures may or may not be present. The aphasia responds poorly to most drugs. Valproic acid and benzodiazepines are most effective. Steroids and intravenous immunoglobulins have shown a variable response. Long-term outcome of aphasia is variable, many patients persist with residual impairment. Important questions regarding etiopathogenesis are unanswered.

Key words : Landau-Kleffner syndrome, Aphasia, Spike and wave.

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Introduction

In 1957 Landau and Kleffner first published the association of acquired aphasia and a convulsive disorder in six children.¹ At present Landau – Kleffner syndrome (LKS) is considered to be a functional, age-related epilepsy in a child with variable disruption of acquired language and epileptiform discharges on EEG.² Clinical seizures and behavioural abnormalities may be present. LKS is classified in the category of epilepsies and syndromes undetermined as to whether they are focal or generalised.³

Correspondence to : Dr. U.K. Misra, Professor and Head, Department of Neurology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Raebareilly Road, Lucknow- 226023, India.
E-mail : ukmisra@indiatimes.com

Epidemiology

LKS is a rare disorder with 198 published cases since 1957.⁴ However, reported incidence may be less than the actual occurrence of the syndrome. The highest incidence is in children between 5 and 7 years; boys outnumbering the girls.⁵ There are two reports of LKS in siblings.^{1,6} No geographical or ethnic clustering exists. The apparent rarity of LKS may be due to several factors; firstly, the diverse modes of onset may cause diagnostic delay or error. A verbal or auditory agnosia may be interpreted as deafness while prominent early seizures may camouflage minor language abnormalities. Interestingly, the first description of the syndrome was from inmates of the Central Institute for the Deaf at St. Louis, Missouri.²

Secondly, short recording time of routine EEG studies rarely includes slow-wave sleep. Characteristic EEG abnormalities may be missed in such records. Thirdly, prolonged periods of remission regularly punctuate the course of LKS. The abruptness with which a child may return to near or total normalcy from being a bewildered, jargon-speaking person may delay seeking medical attention. Lastly, the syndrome may be truly very rare and that may be the reason for the scarcity of any large series of patients reported in literature.

Etiopathogenesis

LKS is a syndrome with diverse underlying neuropathological substrates. Even in the presence of a focal pathology, the lesion is inadequate to explain the entire clinical picture. Presence of an abnormality can not be taken as proof of causality because prolonged epileptic discharges are known to cause irreversible damage.⁷ The acquired aphasia develops during a period of cortical synaptogenesis, when basic functional circuitry is evolving. It is presumed to be an inevitable consequence of persistent electrical activity in discrete regions of the brain which comprise the temporo-parietal language network.¹ Normal age-dependent acquisition of language prior to onset of symptoms and temporal correlation of aphasia with clinical or electroencephalographic seizures are proof of the above hypothesis.⁸ Outcome of acquired aphasia in young children is good if aphasia is caused by stroke, trauma or some other unilateral disease of the dominant hemisphere. This, however, is not true for children with LKS, even if the EEG abnormality is strictly unilateral.⁹ The mechanism proposed to explain this difference is that the potential of neuronal plasticity and a contralateral assumption of language functions is hampered by the same ongoing epileptic activity which causes aphasia in the first place. The language deficit in LKS was originally described as an acquired aphasia. Subsequently it was classified as a verbal agnosia and more recently as an auditory agnosia.^{10,11} The onset of LKS although may be with receptive component of speech, expressive function too suffers eventually. In an extended follow-up of 4 patients over 20-30 years, was the first symptom disability in understanding spoken words followed by inarticulation and a decreased amount of speech.¹² There may, therefore, be a sequential and perhaps hierarchical language disorder beginning with sensory aphasia, followed by auditory agnosia and finally word deafness. A recent study has verified a permanent dysfunction in the associative auditory cortex in 5 children with LKS with unilateral voltage

reduction of late auditory evoked potentials.¹³ This may explain a persistent short-term phonological memory deficit.¹⁴

A child with LKS may be left with variable degrees of language impairment permanently depending on the age of onset of the disorder. A child afflicted very early in life with a rudimentary use of language is likely to be more severely impaired than an older child whose language had more time to develop before disease onset.¹⁵ Disintegration of language functions, seizures and EEG abnormalities are often observed in LKS. However the relationship between these features is not always predictable.¹⁶ This raises doubts about a unified etiopathogenesis of LKS. It is possible that the initiation of the sequence of events is caused by a common mechanism, which is later modified by other genetic or environmental factors.

Many non-specific pathologic abnormalities have been linked to LKS which include i) subcortical astrocytosis, ii) encephalitis, iii) demyelination, iv) slow viral infection, v) cerebral arteritis, vi) neurocysticercosis, vii) arterio-venous malformation, viii) neuronal migration defect, ix) toxoplasmosis, x) temporal lobe tumor.¹⁷⁻²⁵ The role of underlying CNS infection is suggested due to frequent fluctuations in the course of LKS. Demonstration of serum autoantibodies to central and peripheral nervous tissue along with intrathecal synthesis of antibodies during relapses makes an autoimmune etiology attractive.²⁶⁻²⁸ Remission of the illness with manipulation of the immunological milieu lends further support to the immune hypothesis atleast in some patient with LKS. The immunological mechanisms may be crucial and warrant further studies.

Clinical Presentation

Children, most often 3-7 years old, with no illness in the past develop LKS either acutely or subacutely. A history of perinatal insult, delay in acquisition of milestones and communication disorders in the family are generally absent. Family history of epilepsy has been reported in 12% of all patients, but only in 5% of nonepileptic cases.²⁹ Inability to comprehend verbal sounds earliest speech deficit is the, which may progress to involve non-verbal sounds as well. Eventually the child becomes totally unresponsive to all auditory stimuli. Verbal output is variably reduced and may consist of garbled, paraphasic, neologistic speech. Occasionally telegraphic speech with word-finding difficulties may be prominent. Hearing is always normal. Symptomatic period of the language

disorder may be as brief as a day to a protracted course over several months.¹ Clinical seizures may antedate, accompany or follow aphasia. Seizures are absent in about 30% of the affected children in spite of the EEG always being abnormal.³⁰ Seizures occur as a single seizure or episode of status epilepticus, mostly at onset, in about one third of the children with seizures.²⁹ Infrequent seizures between 5 and 10 years of age occur in the remaining patients.²⁹ Only 20% patients continue to experience seizures after 10 years of age. The rare seizures which persist are frequently nocturnal and respond well to anticonvulsants. Seizures are of various types; most often eye-blinking or brief ocular deviation, head drop and minor automatisms with occasional secondary generalisation.⁸ Complex partial seizures are strikingly rare.²⁹ Intellectual impairment in LKS is mild and rare but psychomotor disturbances, especially hyperkinesia and attention - deficit are frequently reported. Severe disinhibition and psychosis are rare.³¹

Diagnostic Evaluation

Language and neuropsychiatric abnormalities appearing in a child with epilepsy are not uncommon, but not all of them suffer from LKS. Misapplying the diagnosis of LKS to developmentally disabled children who never had a normal language invariably results in misdiagnosis. A thorough evaluation of every child with a speech disorder and an abnormal EEG is therefore important. Clinical evaluation should include obtaining a detailed account of birth events, early development and family history of neurocognitive illnesses and performance of the child both on verbal and non-verbal IQ scales. This poses practical problems in small, almost illiterate children. Neurocognitive testing should include testing for apraxias and agnosias. Audiometry or evoked potentials are useful to rule out a hearing deficit. It is necessary to exclude secondary causes by appropriate tests on serum and cerebrospinal fluid. Structural and functional imaging may be needed to exclude other causes. Detailed EEG evaluation is needed in every patient. In surgical candidates, more sophisticated investigations are undertaken.¹¹

Neuroimaging generally does not reveal any structural abnormality in LKS. One explanation may be related to the time during the course of the illness when imaging is performed. The initial abnormality may be functional and it may lead to structural changes only late in the course of illness. Recently MRI volumetric analysis revealed asymmetric volume reduction in the

left temporal lobe including Heschl's gyrus, planum temporale and superior temporal gyrus.³² This atrophy in the Wernicke's area is consistent with neuronal loss, gliosis and a poor prognosis for language recovery.

Functional imaging by single-photon emission computed tomography (SPECT) and positron emission tomography with ¹⁸F -flurodeoxyglucose (FDG-PET) have consistently revealed a predictable pattern of abnormalities in LKS. Several SPECT studies in patients with LKS are available and reported abnormalities conform to asymmetric increased or decreased temporoparietal perfusion depending on the timing of the study.^{33,35} Basic metabolic characteristics defined by FDG - PET in LKS are a higher metabolism of the cortical mantle as opposed to subcortical structures such as thalami and abnormalities restricted to focal regions -primarily associative cortices.³⁶ In spite of significant cortical asymmetries, glucose metabolism in thalamic nuclei remains symmetrical. This would suggest that either cortico -thalamic neurons do not participate in spike - and - wave generation or that these are inhibited by the disease process.³⁷ The lower subcortical metabolic rates may be related to immaturity of the CNS in children. Abnormal cerebral glucose metabolism has been demonstrated during sleep in patients with LKS.³⁸

Abnormalities on SPECT and PET depend on whether the study has been performed during the active phase of spike-and-wave or during a quiescent period.^{39,40} Similarly studies during wakefulness should be interpreted differently from studies done on sedated patients with induced spike-and-wave. Cerebral blood flow and metabolism increases during clinical seizures and declines interictally.³¹ During electroencephalographic seizures without overt manifestations, the cerebral blood flow and metabolism may increase or decrease. This is possibly related to the stage of evolution or the severity of the disorder. Transformation of a previously hypermetabolic area to one of hypometabolism suggests enduring damage in the affected region. EEG during wakefulness is non-specific with normal background activity most often. Use of amitriptyline and a prolonged record of at least 3 hours increases likelihood of observing slow wave sleep. Percentage of the sleep record demonstrating spike and wave is the sleep index (SI). Repetitive high amplitude spikes and spike waves of 1-3 Hz with varying focalisation are usual. These may be unilateral or bilateral, preferentially located over the temporal or

temporoparietal regions. Paroxysmal discharges (PD) are activated by sleep, especially by sleep onset and it is this non-REM presence of PD which blurs the frontiers between LKS and continuous spikes and waves during slow sleep (CSWS).^{41,42} However there are several electroencephalographic differences between LKS and CSWS. A SI of 85% or more is found in about 78% patients of CSWS where as it is present in less than half of the patients of LKS. The characteristic spike and waves occurring during sleep are posteriorly located in LKS while they are more anterior in CSWS. The frequency of spike and wave discharges is 2 Hz in both conditions and a 60% incidence of focal discharges is also common to both. Ictal discharges may be detected in awake records in both conditions, but are about twice as common in CSWS than in LKS.^{4,5} Course and prognosis of the language disorder are suggested to have a consistent relationship with frequency and severity of seizures and EEG abnormalities by few authors, while others have an opposing view.^{43,44} Opinion is also divided as to whether the EEG abnormality in LKS is the cause or effect of the speech abnormality.⁴⁵

Few authors are of the opinion that CSWS is an EEG pattern encountered in various clinical syndromes, one of which is the CSWS syndrome.⁴⁶ Clinically, patients with LKS tend to be younger and manifest language dysfunction prominently much before displaying deterioration of cognition and behaviour. On the other hand children affected with CSWS are older and show global neuropsychological and behavioural impairment before any language dysfunction. Severity of seizures and EEG abnormalities in CSWS also tend to be more in comparison to LKS.⁴⁷ Autism and pervasive developmental delay (PDD) are commonly confused with LKS and CSWS. The abnormal nonverbal intelligence in addition to the language dysfunction in cases of autism and PDD is an important differentiating feature. Additionally, these children have never achieved developmental milestones as in LKS or CSWS. Mentally retarded children will have a history of being affected from birth with a delay in motor development. They are generally abnormal on neurological examination and EEG abnormalities if present are very different from those of LKS. In another disorder called developmental dysphasia, the neurological examination and non-verbal intelligence are normal inspite of delayed language milestones. The EEG in developmental dysphasia is generally normal.

Severe epileptiform activity of any etiology may

inevitably result in progressive cognitive dysfunction. It is therefore important to distinguish LKS and CSWS from other childhood epilepsies, which are associated with subnormal cognition. The chronology of events and determining whether the epilepsy came before cognitive impairment or vice-versa, is crucial. Atypical absence and atonic seizures are common to CSWS and the Lennox-Gastaut syndrome (LGS). Slow spike and wave EEG activated by sleep may also be present in LGS but not to the extent as in CSWS. In LGS, polyspike and wave and bursts of rhythmic fast activity are present. This is not so in LKS or CSWS. Prominent tonic seizures of LGS also separate it from LKS and CSWS.

Idiopathic localisation-related epilepsies such as benign childhood epilepsy with centrotemporal spikes (BECT) also needs to be distinguished from LKS and CSWS. In BECT the cognitive function is relatively unaffected inspite of a similar pathophysiology because the active spike and wave activity is less severe and involves different, relatively 'silent' cortical areas. Absence of an acquired aphasia in BECT along with prominence of focal EEG abnormalities in the frontal areas rather than in the centrotemporal also differentiates it from LKS. There is some sleep related activation of epileptiform activity in BECT also but it never reaches 85%. A family history of epilepsy is more common in BECT rather than in LKS or CSWS. It is however possible that a child with early onset and persistent BECT with a high sleep index would display cognitive or motor deficits on careful clinical evaluation.

Treatment

An immediate and dramatic but transient beneficial effect of intravenous diazepam on EEG abnormalities and language forms the basis of antiepileptic drug (AED) use in LKS.⁴³ If a correlation is observed among seizures, aphasia and EEG changes, the use of AEDs seems reasonable; the absence of such a correlation, especially when clinical seizures are absent makes the decision more difficult. A successful treatment should terminate the active phase of spike wave discharges and significantly reduce residual neuropsychological sequelae. Judging efficacy of individual drugs is made difficult due to frequent use of polypharmacy in the active phase of the disease. Furthermore, EEG and clinical abnormalities may fluctuate in the absence of any treatment and even remit spontaneously after some years.^{45,48} The effect of treatment must therefore be assessed at short intervals to avoid errors of interpretation.

All available AEDs have been used individually and in combination for the treatment of LKS. The largest series reports. The result of AED in 88 patients at the time of resolution of CSWS revealed that seven patients were on no medication at the time of resolution of CSWS. Of the remaining 81 patients, 55 were taking valproate (VPA) –either alone or in combination. Benzodiazepines (BDZs) most commonly clobazam, were being taken by 39 patients. Phenobarbital (PB), vigabatrin, ethosuximide (ESM) and carbamazepine (CBZ) were being taken by few patients. In the final assessment VPA alone or in combination with a BDZ was considered the drug of choice.⁴⁹ Another small study of five patients evaluated efficacies of several AEDS after at least one month of treatment at an effective dose. All drugs were given alone except ESM with VPA in two patients and BDZs and VPA in another two. The authors concluded that VPA, ESM and the BDZs were effective partially or transiently or both. Phenytoin, CBZ and PB were found to aggravate symptoms to various degrees.⁵⁰ Similar worsening and appearance of CSWS has been demonstrated in patients who were taking PB or CBZ in another study.⁴⁶ Replacement of PB or CBZ with VPA or BDZs led to improvement in the EEG. Several other authors also believe that PB or CBZ may enhance generalised EEG discharges and facilitate appearance of the diffuse pattern during sleep.⁵¹⁻⁵³ Use of VPA and BDZs may not be effective in patients who do not have clinical seizures.²⁸

In spite of a trial of several anticonvulsants, many patients of LKS remain refractory to treatment. Other options including the use of corticosteroids, intravenous immunoglobulins (IVIg) and surgery have been tried in such patients. Several authors feel that new onset disease in young patients is better treated with ACTH or corticosteroids.^{45,54,55} The problem of toxicity with chronic steroid use in children is especially prominent as high doses are recommended for prolonged periods. Short therapies or abrupt reduction in doses often result in a relapse.^{49,55} Early steroid use may shorten treatment duration and also improve the final outcome.⁵⁵ The first report of successful IVIG use in a case of LKS appeared in 1997.²⁸ Subsequently IVIG use has been reported in two more patients.^{56,57} In the last reported case IVIG was used as first-line therapy without a prior trial of anticonvulsants or corticosteroids and good clinical and electroencephalographic response was observed.⁵⁷ However at present this form of treatment can best be described as experimental and needs evaluation in larger clinical trials.

Neurophysiological outcome, especially of language functions often remains unsatisfactory after medical treatment of LKS. Surgery therefore becomes a desperate option in some of these patients. The most common epilepsy surgery is brain resection. However resection of eloquent cortical areas as are involved in LKS would lead to unacceptable deficits. Morrell and colleagues innovated a technique known as multiple subpial transection (MST) for patients with epileptogenic foci in unresectable areas.⁵⁸ MST involves severing horizontal intracortical fibres responsible for spread of epileptiform discharges while preserving the normal vertically aligned neuronal connections. This reduces synchronised discharge from the epileptic focus and also limits its spread. Cortical functions remain normal and major postoperative deficits do not occur. Most series have reported substantial recovery of speech in patients of LKS following MST.^{11,59,60} Superiority of surgery over medical treatment can be established only if comparable patients are randomly allocated to either of the two modalities. Till such a study can be undertaken, surgical options are justified only in the medically refractory patients of LKS. Receptive vocabulary is most likely to improve in those patients who have had shorter periods of language impairment prior to surgery.⁶⁰

Conclusion

Almost half a century after the original description of LKS, it still remains an enigma. Gaps in knowledge are evident from the very beginning with its ambiguous placement in the ILAE classification and controversy whether LKS and CSWS are different nosological entities or different points on the spectrum of a common disorder. Etiological leads available are inconclusive. Currently an immunological basis seems to be a contender atleast in some patients warranting further studies. Demonstration of elevated intrathecal antibodies during relapses needs evaluation as a diagnostic tool. A genetic susceptibility predisposing to epileptic discharges in specific neuronal circuits during a period of neuronal immaturity can not be denied. Of the almost 200 reported cases so far, 4 children were siblings – was that only chance or an etiological clue?

Another question raised from LKS is about the other localisation-related epilepsies of childhood. Are these epilepsies such as BECT truly benign or do they also cause neuropsychological impairment which is not picked up by routine clinical evaluation. There are too many unsolved questions and the disease too rare with

very few patients who may provide the answers. It is time for large collaborative efforts if the mystery surrounding LKS has to be cleared. Till such a time, LKS will continue to remain, as in the words of Landau, an eponymic badge of ignorance.⁶¹

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