Landau–Kleffner syndrome

Abdelkarim A. Al-Qudah, *MD, ABCN.*

ABSTRACT

Landau-Kleffner syndrome is one of several language disorders associated with epilepsy or epileptiform abnormalities on EEG. Ultimately, these patients understand little or nothing of what they hear. Two thirds have behavioral abnormalities and close to 75% have seizures. Brain computerized tomography and MRI are normal, EEG changes show characteristic epileptiform changes. Antiepileptic drugs can easily control seizures, but language recovery is more difficult. Autoimmune etiology is considered likely and long-term prognosis remains variable.

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In 1957 Landau and Kleffner described 6 children with a syndrome of acquired aphasia with convulsive disorder.[1] Landau-Kleffner syndrome (LKS) is characterized by acute or subacute deterioration in language skills in children with previously normal expressive and receptive language development in association with epileptiform EEG abnormalities.[1-5] Approximately two thirds of patients have clinical seizures and behavioral changes.[1,2] Electrical status epilepticus of sleep (ESES) and LKS are classified separately by the Commission on Classification and Terminology of the International League Against Epilepsy under the heading of epilepsies and syndromes undetermined whether focal or generalized.[5] The syndromes have many common features and may represent different manifestations of the same underlying pathology. Both involve a regression of cognitive function in association with an epileptiform EEG. Focal EEG discharges tend to be more centrotemporal in LKS, and those in ESES more frontal or frontotemporal.[4] Seizures are present in the majority of ESES cases and often predate the onset of ESES while seizures are present in approximately 70% of cases of LKS.[2] Clinical seizures are similar, as is the natural history with disappearance of EEG abnormalities in adolescence.[2] A number of language disorders have been associated with epilepsy or EEG epileptiform abnormalities which are very important to consider in the differential diagnosis of LKS.[1-6] These include acquired epileptic aphasia (LKS), developmental dysphasias, ESES and possibly autism.[1-6] Electroencephalogram changes in partial epilepsies may look like LKS, particularly, benign rolandic epilepsy.[7-8] Landau-Kleffner syndrome is a rare disorder with unknown prevalence. In a study of 440 pediatric epileptic patients, 0.2% had LKS.[9] Male to female ratio is 2:1. Age of onset is variable ranging from 1.5-13 years with peak age of 4-7 years.[1-7]

Language impairment. Receptive language dysfunction seems to dominate the early stage of LKS. Ultimately, the clearer picture of verbal auditory agnosia (VAA) in which children understand little or nothing of what they hear, namely, cortical deafness and are essentially mute, becomes apparent. Verbal auditory agnosia is the most common language abnormality in LKS.[2,8,10] Expressive language deficits develop later in most cases. Approximately 10% of the aphasia is initially mainly expressive.[7] The clinical course of LKS is usually gradual evolving over weeks or months, although at times it is abrupt. Reading and writing as well as the use of sign language may be relatively spared. However, reading and spelling deficits are not uncommon at follow up.[8]

From the Division of Pediatrics and Pediatric Neurology, Jordan University Hospital and Faculty of Medicine, Jordan University, Amman, *Jordan*.

Address correspondence and reprint request to: Prof. Abdelkarim A. Al-Qudah, Pediatric Department, Jordan University Hospital, PO Box 13407 Amman, *Jordan*. Tel. +962 79566067. Fax. +962 65353388. E-mail: dr_qudah@hotmail.com

Behavioral impairment. Two thirds of LKS patients develop some behavioral disturbances,[6-7,11] including rage, aggressive behavior and hyperactivity as the usual behavioral clinical features. Other behavioral changes include ritualistic behavior, loss of initiative and sleep disorders. Extreme discrepancy between their performance and verbal abilities is also noted. Behavioral disturbances are thought to be secondary to the primary language dysfunction.[6] Many of the behavioral abnormalities described in LKS are similar to those seen in autistic children.[6-8,10-12]

Seizures. Clinical seizures occur in approximately 70% of the cases. Both partial, partial with secondary generalization and generalized seizures are reported. Eyelid blinking, atypical absences, head drops and automatisms are frequently reported.[1-13] Seizures proceed aphasia in one third of the patients[7] and usually disappear before adulthood. Seizures are usually easily controlled with antiepileptic drugs such as benzodiazepines, valproate, sulthiame, ethosuximide and phenobarbitone. Carbamazepine, and phenytoin have been reported to be ineffective or even harmful.[1-13]

Diagnosis. Diagnostic workup should include clinical assessment, neuropsychological evaluation to determine the nature of the language disorder and the level of intelligence[14] and ancillary investigations such as EEG, neuroimaging and others.[15,16]

1. EEG. The EEG changes are variable, and there is no constant relationship between the frequency of the clinical seizures, the intensity of the EEG abnormalities, or both, and the severity of the language dysfunction.[17] During wakefulness background is usually normal and EEG changes include generalized spike-and-wave discharges, bitemporal, independent or synchronous spikes and multifocal spikes. Unilateral temporal or central-temporal spikes often similar in morphology and localization to those seen in benign rolandic epilepsy are also documented.[1-6] The EEG changes are often considerably augmented by slow wave sleep, resembling changes seen in a) the syndrome of continuous spikes and waves during slow sleep appearing as continuous 1,5-5 HZ spike and wave discharges that may be seen in approximately 85% of the record[6-7] and b) atypical partial epilepsy of childhood.[18] A striking feature in most cases is the variability of the EEG pathology in time and intensity. Cole et al in a review of 95 cases reported that 12% had strictly unilateral discharges.[17] As mentioned earlier, ESES and LKS are classified separately.[5] However, the 2 syndromes have many common features clinically and by EEG. The association of ESES with LKS is well known.[19-21] Focal discharges in LKS tend to be centrotemporal and those in ESES, are more frontal and frontotemporal.[4] The correlation between EEG abnormalities and language outcome is variable ranging from no correlation to good correlation.[19-23]

2. Neuroimaging. Brain CT and brain MRI are generally normal.[1-6] Positron emission tomography studies have shown unilateral temporal, or bitemporal abnormalities manifested either as decreased or increased glucose utilization.[15] A study by Guerreiro et al on single photon emission computed tomography scan demonstrated abnormal perfusion in the left temporal lobe in 4 children with LKS.[16]

Other investigations. Magnetoencephalogram can help in detecting the source of epileptiform activity aiding presurgical localization of epileptiform activity in LKS.[24] The study of auditory evoked response showed normal function of ear and brainstem auditory relays, while amplitude of the middle latency and late cortical responses were decreased.[25] Event related potential study has shown that some children with LKS can process speech input.[26]

Etiology and pathogenesis. The exact cause behind epileptic aphasia is unknown.[27,28] The dysfunction could be related to the epileptic process in an obscure way. Gascon et al believed that EEG abnormalities represented cortical manifestation of subcortical de-afferentation process.[23] Ansink et al suggested that most disturbances might be located in the supramodal cortex in the region of hippocampus or gyrus parahippocampi influencing the integration of gnostic processing from different afferent information.[29]

Landau-Kleffner syndrome has been linked to multiple etiologies such as neurocysticercosis, Haemophilus influenza type B meningitis, temporal lobe tumors, demyelinating disorders and cerebral arteritis.[30-34] The autoimmune etiology is considered likely based on findings of autoantibodies to myelin in affected LKS patients[35] and well supported by many studies reporting high serum IgG antibodies to brain endothelial cells,[35] high IgG index,[20-21] good response to intravenous immunoglubolins (IVIGs)[20-21,36,37] and encouraging language improvement in LKS to treatment with adrenocorticotropic hormone (ACTH) or oral steroids.[6-12]

Treatment. Several treatment modalities have been tried in LKS including antiepileptic drugs,[38] corticosteroids,[37-39] ketogenic diet,[40] subpial resections[41] and vagal nerve stimulation.[42] The clinical seizures are usually well controlled by antiepileptic drugs, but the effect of these drugs on the language recovery is uncertain.[6] Bergqvist et al reported 3 cases of LKS with good response to ketogenic diet.[40] Irwin et al reported 5 children with LKS whose seizures improved dramatically after multiple subpial transection (MST). Improvement in language occurred, but none improved to an

age-appropriate level.[41] In another study on 3 LKS cases using MST substantial recovery of language was noted.[43] Four recent studies, 3 of them case reports, have shown significant response of LKS patients to IVIGs.[20-21,36-37] Intravenous immunoglobulins were given in a dose of 0.4-0.5g/Kg/day for variable periods of time. Therapy with corticosteroids appears to be most effective early in the course of LKS.[38] Oral steroids or ACTH have been used.[39] Lagee et al reported a case who responded to steroids after first and second relapse and to IVIG after third relapse.[37] Tsuru et al reported effectiveness of high dose IV methyl prednisolone (20 mg/Kg) in LKS as first line treatment modality.[12] No doubt that larger controlled studies are required for establishing treatment guidelines in LKS. Speech therapy is also, an important supportive modality.

Prognosis. Long term prognosis in LKS is variable. Bishop reported 45 cases followed for at least 12 years. Patients who had age of onset of LKS before age of 5 years had worse prognosis than later onset.[44] Deonna et al reported 7 LKS patients 13-28 years after the onset of aphasia.[45] One recovered completely, one had good oral language but persisting dyslexia, one recovered normal verbal comprehension but had severe expressive language difficulties and 4 had absent language comprehension. Robinson et al reported 18 children with LKS at a mean length of follow up of 67 months. Three out of 18 had language outcome within normal range. No child with ESES lasting more than 36 months had normal language outcome.[46] Erdem et al reported a 6-year old LKS patient who had multiple exacerbations despite use of immunoglobulins and corticosteroids in a 4-year follow-up period.[47] The relationship between the outcome of the aphasia and the type of seizure or between the aphasia and topographic distribution of the EEG paroxysms remains uncertain.[6]

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