Landau-Kleffner syndrome

Landau-Kleffner syndrome is a rare childhood-onset epileptic encephalopathy. The condition should be suspected if a child with normal development shows a fairly abrupt loss of established language skills. Such children should be referred to a regional department of paediatric medicine or the National Centre for Epilepsy for a broad interdisciplinary work-up. An EEG examination during wakefulness and sleep is essential for diagnosis.

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MAIN POINTS

Landau-Kleffner syndrome is a rare epileptic encephalopathy that usually affects children aged 3–8 years with previously normal development

The main symptom is acute or subacute loss of language

The language impairments are due to epileptic activity in the brain's language areas, which is particularly pronounced during deep sleep

Landau-Kleffner syndrome is an epileptic encephalopathy that usually manifests itself in children aged 3–8 years with previously normal development (1). The main symptoms are acute or subacute aphasia with inability to recognise, process or interpret verbal and/or non-verbal sounds (1). Nocturnal epileptic activity impedes access to the child's previously established receptive and expressive language (1). The prognosis for the aphasia varies. In a small Norwegian study, in which 11 patients were followed for more than ten years, approximately one third regained normal or virtually normal language function, roughly a third were left with moderate long-term language difficulties, while a third ended up with no functional language, either receptive or expressive (2). In ICD-10 the disorder is referred to as Landau-Kleffner syndrome or Acquired aphasia with epilepsy (F80.3).

In contrast to other childhood epileptic encephalopathies, such as Lennox-Gastaut syndrome, Landau-Kleffner syndrome is the result of age-dependent epileptic activity that occurs primarily in deep sleep. The condition belongs to a spectrum of related disorders, including benign childhood epilepsy with centrotemporal spikes (BECTS) and continuous spikes and waves during slow-wave sleep (CSWS) (1).

Epidemiology

Landau & Kleffner described six children with the condition in 1957 (3). Since then, more than 350 children with the syndrome have been described worldwide. In Norway the National Centre for Rare Epilepsy-Related Disorders has a record of 28 persons with this diagnosis in 2015. The true incidence and prevalence are unknown; however, boys are affected more often than girls. Onset is usually between 3–8 years of age, but has been reported as early as two years of age and as late as 14 years (4).

Aetiology and basic mechanisms

The cause of Landau-Kleffner syndrome is unknown. The results of brain imaging are usually normal. There is no clear genetic basis, but families with mutations in the *GRIN2A* gene have been described, in which some members have Landau-Kleffner syndrome while others have BECTS or CSWS (5).

Landau-Kleffner syndrome is defined as an epileptic encephalopathy. This means that the epileptic activity per se causes the language decline, either partially or completely. The fact that steroids are very effective in some children (6) but ineffective in others suggests that autoimmune or inflammatory processes may contribute to the pathogenesis in some individuals.

Several studies have shown increased levels of autoantibodies directed against brain-derived neurotrophic factor (BDNF) in patients with Landau-Kleffner syndrome compared with healthy controls. A study of affected children showed an autoimmune reaction against central and peripheral myelin during episodes of symptom exacerbation. Autoantibodies against other brain antigens have been detected in a limited number of patients with CSWS (6). Intravenous immunoglobulin therapy was clinically effective in some patients and also reduced previously elevated IgG in cerebrospinal fluid. In our view, this strengthens the hypothesis that antibodies *may* be involved (6).

However, strong epileptic activity can itself activate inflammatory processes which are dampened by steroid treatment. Steroid efficacy is consequently not synonymous with an autoimmune aetiology (7). The variable efficacy of steroids in these children suggests that the epileptic activity may have multiple underlying causes.

Cerebrospinal fluid is not routinely screened for neuronal antibodies before the initiation of steroid treatment for children with Landau-Kleffner syndrome. The National Centre for Epilepsy has chosen to test serum for neuronal antibodies prior to treatment initiation. However, there is no international consensus on this.

The language impairments are caused by

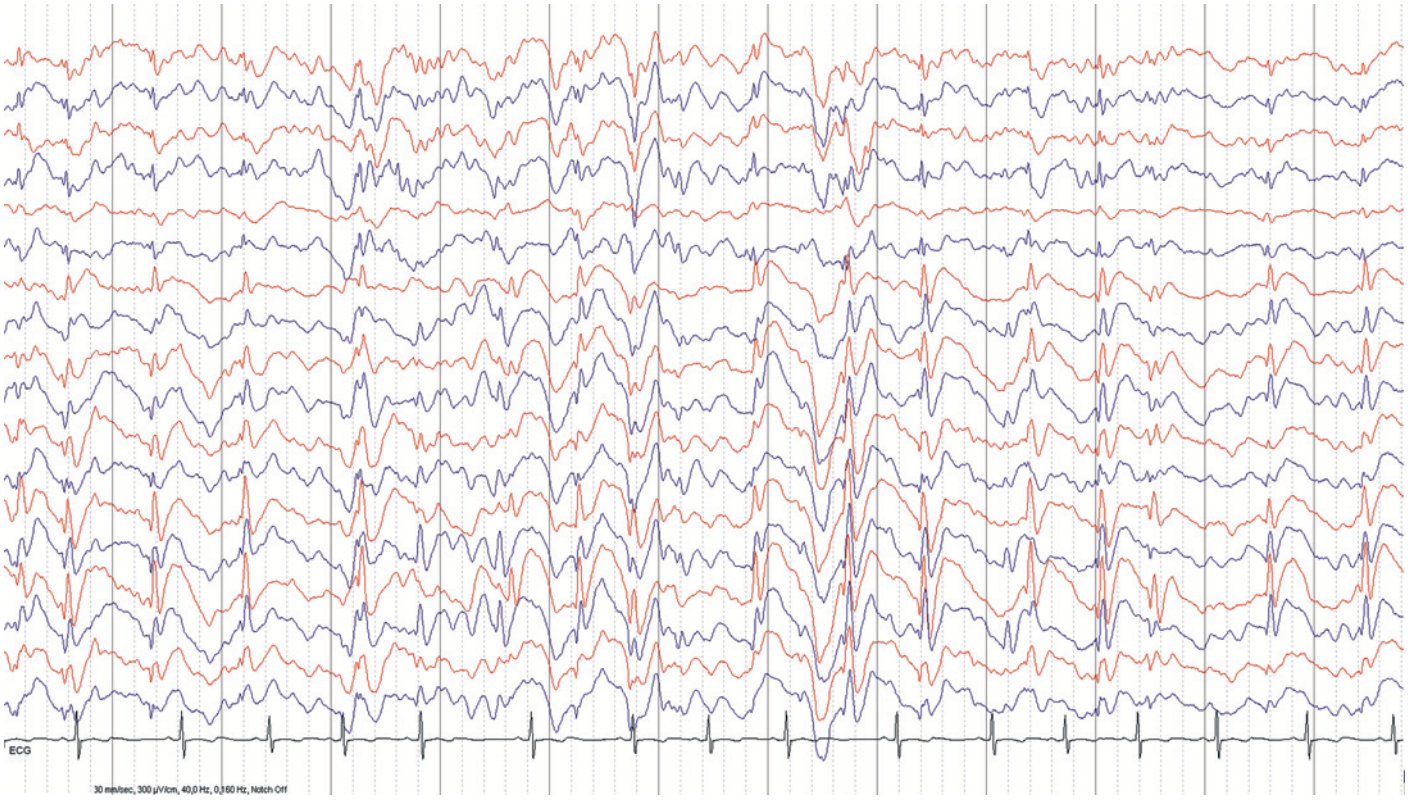

Figure 1 *EEG recorded during non-REM sleep. There is an intense increase in epileptic activity, with left hemispheric dominance (red)*

epileptiform abnormalities localised to the areas around the Sylvian fissure, i.e. areas important for language processing (8, 9). It has been suggested that when such abnormalities occur during a phase of neural development associated with active cortical synaptogenesis and the establishing of long-term functional networks, the result may be abnormal synaptogenesis in these regions with persistent language impairments as a consequence (4).

Clinical presentation

Landau-Kleffner syndrome should be suspected in all children with normal development who, at the age of 2–14 years, show a fairly sudden loss of language. In the course of days, weeks or months, they develop verbal and/or auditory agnosia, i.e. a complete or partial inability to recognise, process and interpret verbal and/or non-verbal sounds. Peripheral hearing is normal, but the child does not understand what s/he hears. This affects the child's language comprehension. Speech production is also affected. Typical signs are difficulties with articulation, fluency and word retrieval. Other symptoms include babbling, neologisms, verbal perseveration or mutism. Around 10 % have primarily expressive difficulties, but a combination of receptive and expressive difficulties is the most common (8). Language function shows substantial individual variation, often varying over time and seemingly independent of seizure tendency. Children with Landau-Kleffner syndrome without seizures may have severe language impairments, indicating that it is the epileptic activity and not the seizures that causes the language difficulties. Many are hypersensitive to sound (2, 8).

In 70–80 % of patients, seizures of different types occur: absence seizures, focal seizures or generalised tonic-clonic seizures (8). Seizure frequency is generally low. EEG abnormalities are usually most pronounced over posterior temporal regions around the Sylvian fissure, unilaterally or bilaterally (9).

During non-REM sleep, epileptic activity can develop into an almost continuous spike wave pattern, usually with a frequency of 1.5 to 2.5 spikes per second (Fig. 1). The degree of EEG abnormality depends upon the disease stage and is greatest around disease onset. Background activity and sleep macro-architecture are usually normal. During REM sleep, epileptic activity partially or completely ceases. Standard EEG *may* also be normal.

Attention and inhibition difficulties, hyperactivity, aggression, social withdrawal, emotional lability, anxiety and depression are relatively common comorbid traits, as are sleep disorders. Working memory is usually impaired, whereas long-term memory remains intact (8).

ADHD and behavioural disorders may be suspected in these children before their language difficulties are detected. There are probably multiple explanations for the children's challenging behaviour, but their language difficulties are likely to be the main cause. Some children with Landau-Kleffner syndrome have autism-like difficulties (8).

Landau-Kleffner syndrome is a clinical diagnosis that requires an interdisciplinary assessment with thorough anamnesis, as well as neurological, speech- and language therapeutic, and neuropsychological assessments, and EEG tests.

Differential diagnoses

Continuous spikes and waves during slow-wave sleep (CSWS)

In 1971, a report was published describing children with a characteristic sleep EEG: electrical status epilepticus induced by sleep (ESES) (10). The clinical correlates of ESES are poorly defined, but many affected children develop language and learning difficulties, cognitive impairments and behavioural problems. Most also have epileptic seizures of various types. In 1985 the syndrome was named 'continuous spikes and waves during slow-wave sleep' (CSWS) (11). This condi-

tion differs from Landau-Kleffner syndrome in that the epileptic abnormalities in the EEG have a more frontal localisation and often imply more general cognitive impairments (1). Moreover, a morphological neural substrate, such as polymicrogyria, is detectable in some children with CSWS. Around 0.5 % of all children with epileptic seizures have CSWS.

Intellectual disability

According to ICD-10, normal premorbid general intelligence is a prerequisite for a diagnosis of Landau-Kleffner syndrome. We raise the question, however, of whether this criterion should be revised. With delays in diagnosis, treatment and pedagogical-psychological interventions, a child can end up with reduced cognitive abilities. In rare cases, it is therefore appropriate to make the diagnosis even if the child has a mild intellectual disability. Moreover, there is nothing to suggest that this condition only affects children of normal intelligence. In children with early onset, it can be difficult to evaluate premorbid language and cognitive development. Furthermore, it is not easy for those close to the child to recall her/his language development retrospectively.

Autism spectrum disorders

Children with Landau-Kleffner syndrome can be misdiagnosed as having autism spectrum disorders, most often infantile autism or regressive forms. As in Landau-Kleffner syndrome, children with regressive forms of autism lose acquired language and social skills. Regression in autism spectrum disorders is often more general, with cognitive impairments in multiple domains. Difficulties with how language is used in social contexts are also more pronounced. Many of these children have epileptic activity in the EEG (12).

Other conditions with language impairments

All types of acquired aphasia (for example, due to brain injuries, tumours or infections), mutism, learning disabilities and hearing loss are potential differential diagnoses (13).

Treatment

There is no international consensus regarding treatment of Landau-Kleffner syndrome. Rapid initiation of drug therapy has proven to be important for the prognosis (9). A long duration of epileptic activity worsens the prognosis and appears to be of greater significance than age of onset (9). The aim of treatment is primarily to restore language skills, and to achieve seizure freedom. The seizures are generally mild and infrequent, and usually respond well to antiepileptic drugs. However, the epileptic activity in the EEG and the language deficits tend to persist (9).

Valproate, clobazam (or other benzodiazepines), levetiracetam, ethosuximide and sulthiame are the most frequently used antiepileptic drugs (14). Ethosuximide and sulthiame are not licensed in Norway. If the epileptic activity and language impairments persist with antiepileptic drugs in the course of a few weeks, initiation of steroid therapy is recommended (9).

At the National Centre for Epilepsy patients are treated with prednisolone orally 2 mg/kg/day for at least three months before gradual tapering. Some require treatment over longer periods. Balancing the efficacy of steroid therapy against long-term adverse effects can be difficult. Repeated prednisolone treatment may be tried in the event of relapse.

Intravenous immunoglobulin therapy has yielded varying results (14). Such therapy may nevertheless be considered in patients who are refractory to antiepileptic drugs or steroids, or in whom language impairments recur upon steroid withdrawal.

Surgery in the form of multiple subpial transections has been performed on a limited number of the most severely affected children. Improvement in individual cases has been described (15). The surgeon transects the horizontal corticocortical fibres, while sparing the vertical corticosubcortical fibres. The aim is to prevent the spread of epileptiform activity (15).

In children with Landau-Kleffner syndrome who also have ADHD, central stimulating drugs may be appropriate.

Maintaining communication is crucial for the child's interaction with family, peers etc. The same applies for behavioural and psychosocial functioning. This requires early establishment of alternative and augmentative communication strategies. Visual language (sign language or Norwegian with sign support) or other forms of alternative communication with simultaneous aural training can provide valuable intellectual stimulation (16). Language interventions should be continuously evaluated and adjusted because the situation can change quickly. Lingual improvements in the teenage years necessitate the use of other measures, such as increasing verbal interventions. Language interventions should also be intensified when the EEG improves. Treatment and interventions should also target comorbid difficulties.

Prognosis

The epilepsy in Landau-Kleffner syndrome has a good prognosis, and most patients become seizure free with antiepileptic drugs. As a rule, both the epileptic abnormalities in the EEG and the seizure tendency decrease or disappear by 15 years of age. General intelligence is usually preserved.

The prognosis for the language impairments varies. From adolescence, some individuals achieve normal or almost normal language function, some have moderate long-term language difficulties, whereas others are left with non-functional language, both receptive and expressive (2). For the latter group, it is important to establish alternative and augmentative communication strategies as soon as possible.

Early age of onset and a long history of epileptic EEG activity are poor prognostic factors. Fluctuations in the disease course indicate a better prognosis (7).

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Litteratur

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