Austin Journal of Autism & Related Disabilities

Open Access

Austin Publishing Group

Review Article

Landau-Kleffner Syndrome and Autistic Regression

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Received: August 19, 2016; **Accepted:** September 28, 2016; **Published:** September 29, 2016

Abstract

We reviewed the clinical aspect of the Landau-Kleffner syndrome and autistic regression. A subgroup of children with autism after initially normal developmental (autistic regression) is of particular interest.

Landau-Kleffner syndrome is a rare syndrome of unknown etiology. Most patients appeared normal before the onset of the syndrome. The syndrome consists of two main symptoms: acquired aphasia in previously normal children, and an abnormal electroencephalographic pattern with spike and spike wave activity more frequently located in the temporal region. Among children with autism at least 30% develop normally. The association of EEG abnormalities and autistic regression is evident. It is important to differentiate between, these two clinical entities. Treatment and prognosis is different in both clinical entities. It need more research and studies to achieve definitive and effective treatment for this pathology.

Keywords: Landau-Kleffner syndrome; Autistic Regression; Aphasia; Epilepsy

Introduction

Autism Spectrum Disorders (ASD), neurodevelopment disorders are including a group of processes that occur as common characteristic impaired social interaction, process verbal and nonverbal language and existence of repetitive behaviors (stereotypes), with limited activities and interests [1].

Autism is frequently combined with other symptoms of neurological dysfunction, such as epilepsy, disorders motors, hyperactivity, including abnormal Electroencephalograms (EEGs).

A subgroup of children who develop the impairments of autism after initially normal development ("autistic regression") is of particular interest [2]. Progressive loss of previously acquired language and cognitive skills associated with social and affective withdrawal are noted during the second year of life in most cases. The aetiology of the deterioration usually remains unknown neither neurometabolic and neurodegenerative nor infectious diseases of the central nervous system are usually identified [2].

These children have an increased incidence of abnormal EEGs similar to those found in children with Landau-Kleffner [2]. Special consideration for Landau-Kleffner syndrome characterized for an acquired aphasia and encephalographic disorders that can reach electric slow status during sleep in children previously normal. It is the children may occur with autistic traits, like how disruptive behavior, the tendency to "kicking tantrum" stereotypes and then we may lead to think about autism, discarding other pathologies such as epilepsy and eventual association with dysfunction mitochondrial [3].

It is very important to differentiate between these two clinical entities, for the autistic regression side and on the other side the Landau-Kleffner syndrome, which are handled and treated differently and are of very different prognosis. The sufficient cannot be stressed on the importance of this clinical differentiation.

Epileptiform patterns, spikes and sharp waves, occur as interictal epileptiform discharges which are generally prolonged and clinically silent. The pattern, frequency and localization vary considerably among individuals with clinical epilepsy and without manifest seizures. Abnormal EEG findings, with focal and multifocal epileptiform activity increasing during sleep; have been detected in a considerable percentage of children with autistic regression, especially when evaluated through prolonged sleep EEG [2].

At least 3% of normally developing children, 10% of children with migraine and 15% with autism without epilepsy have spikes on their EEGs. Although often asymptomatic, interictal epileptiform discharges have also been associated with transient cognitive impairment, and developmental regression. Interictal epileptiform discharges have been associated with developmental regression in a number of childhood epilepsies. In addition to Landau Kleffner syndrome, other regressive syndromes such as infantile spasm, Lennox-Gastaut syndrome and others [2,4].

Landau-Kleffner Syndrome

Landau-Kleffner syndrome is the prototype of disorders with epileptiform regression. In 1957, Williams Landau and Frank Kleffner described a syndrome in six children that showed, as fundamental characteristics, the existence of acquired aphasia that was usually of the receptive type, and convulsive disorders accompanied by encephalographic alterations.

The Landau-Kleffner syndrome shows two main symptoms: 1. Acute or sub-acute acquired aphasia in previously normal children and 2. An abnormal spike and wave paroxysmal encephalographic pattern more frequently located in the temporal region that may reach electrical status epilepticus during slow sleep if this activity covers 85% of the encephalographic pattern [4].

Although aphasia is present in all patients, it constitutes the first manifestation in only half. Its onset may be abrupt or progressive

Citation: Guevara-Campos J, Guevara-González J and Dimas-Rendón I. Landau-Kleffner Syndrome and Autistic Regression. Austin J Autism & Relat Disabil. 2016; 2(5): 1031.

over several days or weeks [2,4]. Typically, the aphasia is receptive; the child begins to have difficulty-understanding language to the point that deafness may be suspected. The capacity for oral expression gets impaired quickly; mutism is frequent. Writing is preserved in older children [4-6].

The course of the aphasia found in the Landau Kleffner syndrome is one of its most disconcerting characteristics. A relationship between the age of onset and the long-term results has been reported: the younger the child the worse the prognosis for the recuperation of speech. The effects are devastating in young child that have not yet developed linguistic abilities since the cortical mechanisms to, process speech cannot develop. In older children, and the effects are less serious because they have already learned language [4].

Epileptic seizures constitute the first manifestation in approximately half of the cases of Landau-Kleffner syndrome. In more than 16% of the cases the seizure were not detected until the electrical status epilepticus was discovered during slow sleep [7].

Seizures occur chiefly during the night, and partial seizures are more frequent, followed by generalized tonic-clonic seizure, atypical absences and rarely, mioclonic absences [6].

Most researchers support the hypothesis that paroxysmal activity produces a functional disconnection of the cortical areas related to speech. Paroxysms have been shows to be located in the depths of the Sylvian fissure through dipole modeling [4].

In most of the patients, no close relationship is established between the frequency of the seizure and the degree of aphasia, which can be serious even in absence of seizure. Seizures almost always disappear in adulthood, although rare cases have been reported in the literature of refractory epilepsy that persists until adulthood [4,6].

The behavioral and cognitive alterations characteristic of the patient with Landau-Kleffner syndrome are believed to be secondary to epilepsy rather than structural damage to the central nervous system. This affirmation is based on the fact that frequent and intense epileptic discharges are focally located in language areas important for speech and the fact that recovery, either spontaneous or induced by treatment, is always associated with disappearance of EEG paroxysmal activity [4].

Encephalographic abnormalities are present in all patients. The background rhythms are usually normal, but theta slowing is occasionally present in the same regions as the spikes. Spike paroxysms or spike and wave complexes can be unilateral or bilateral and may be focal, multifocal or diffuse. Discharges are bitemporal in 50% of the patients and in the parietal-occipital regions in 30% of the patients. Discharges are usually activated by sleep. Paroxysms are frequently similar to those found in Benign Rolandic Epilepsy. There is a clear activation of epileptiform activity in Rolandic epilepsy during sleep that can transform into continuous spike and wave [4,6,7].

Bilateral foci are frequent, they tend to increase by more than 85% during sleep and can transform into continuous spike and wave during slow wave sleep or electrical status epileptic during slow sleep [6,7]. The language impairments are caused by epileptiform abnormalities localized to the areas around the Sylvian fissure. 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 [8].

Table 1: Characteristics of Landau-Kleffner Syndrome and Autistic Regression.

	Landau-Kleffner Syndrome	Autistic Regression
Neurodevelopmental	Normal	Normal
Epilepsy	Yes	No
Electrical status (EEG)	Yes	No
Mutations	Yes-GRIN2A	No

It has been long debated in the epilepsy literature whether interictal epileptiform abnormalities, in the absence of clinical seizure, might affect cognitive development [9], or lead to behavioral regression [2,7,9] (Table 1).

Autistic Regression

Among children with autism at least 30% develop normally or nearly normally during the first year or two of life before developmental skills regress [2]. In most cases, no cause of the regression can be identified, although several rare metabolic and degenerative disorders may also occur in this age group [2]. Children with autistic regression lose previously acquired speech and verbal understanding, withdraw from social contact, and lose their interest in toys.

The association of EEG abnormalities and autistic regression was particularly evident when EEG features were located over the temporal areas; conversely, posterior EEG abnormalities were associated with a no regressive onset of the disorder [4,9].

The correlation between localization of EEG changes and risk of regression are novel in the literature. The association of regression with temporal EEG abnormalities was particularly strong in individuals with epileptiform-autism Phenotype and macrocephaly [9].

The association between autism, epilepsy and mitochondrial disease is uncommon, but in the group of children with autism regression or which are accompanied by signs of neurological involvement such as mental retardation, hypotonic, ophthalmoplegia, dysmorphic features, this possibility should be considered [3].

Epilepsy-aphasia syndromes are a group of rare, severe epileptic encephalopathies with characteristic electroencephalogram pattern and developmental regression particularly affecting language and pathogenic deletions that include GRIN2A have been implicated [10].

It is essential to distinguish the two neurological disorders to better treatment and prognosis patients affected.

Undoubtedly it needed more research and studies to achieve definitive and effective treatment for this pathology.

Conclusion

Landau Kleffner syndrome and autistic regression are rare diseases in neuropediatrics. It is very important to differentiate between them by having different treatment and prognosis for children. More studies and research for better understanding of these entities and realization of effective treatment are necessary.

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