Landau Kleffner Syndrome, Electrical Status Epilepticus in Sleep and Autistic Regression: An Overview of Literature

Özalp Ekinci[1], Uğur Işık[2], İsmet Melek[3]

[1]Child and Adolescent Psychiatrist, Antakya Obstetrics and Child Care Hospital, Child Psyhiatry Clinic, Hatay - Turkey
[2]Assist. Prof. Dr., Acıbadem University, Faculty of Medicine, Pediatric Neurology, İstanbul -Turkey,
[3]Assoc. Prof. Dr., Mustafa Kemal University, Faculty of Medicine, Department of Neurology, Hatay - Turkey

ABSTRACT

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Language regression in children is a challenging condition for clinicians since the diagnostic and therapeutic algorithms are not well established. Landau Kleffner syndrome (LKS), Electrical Status Epilepticus in Sleep (ESES) and Autistic Regression (AR) are three rare clinical entities in which langauage regression is present. LKS and ESES appear to be two points on the spectrum of epileptic syndromes characterized by severe paroxysmal EEG disturbance in sleep and regression. However, the available literature indicates that AR has many distinct features than LKS and ESES. For all of these three conditions, early recognition and treatment is crucial for favorable outcomes. Overnight EEG has an important diagnostic role for LKS and ESES. In this review, the clinical features, prognosis and treatment options of LKS, ESES and AR will be discussed.

Key words: Landau Kleffner syndrome, electrical status epilepticus in sleep, autistic regression, language regression

ÖZET

Landau kleffner sendromu, uykuda elektriksel status epileptikus ve otistik regresyon: Literatüre bir bakış

Çocuklarda dil regresyonu, tanı ve tedavi yaklaşımları ile ilgili yeterli düzeyde araştırma yapılmamış olması nedeniyle, klinisyenler için zorlayıcı bir durumdur. Landau Kleffner sendromu (LKS), uykuda elektriksel status epilepticus (ESES) ve otistik regresyon (AR) nadir görülen ve dil regresyonun eşlik ettiği klinik durumlar arasında yer almaktadır. LKS ve ESES, aynı epileptik sendrom spektrumu içinde yer alan, uykuda aktive olan paroksismal EEG aktivitesi ve regresyonun olduğu iki klinik antite olarak değerlendirilmektedir. Ancak yapılan araştırmalar, AR'nin LKS ve ESES'den birçok açıdan farklılıklar gösterdiğini ortaya koymuştur. Her üç klinik durumda da, prognoz için en önemli faktörler arasında erken tanı ve tedavi kaçınılmaz görülmektedir. Uyku EEG'si LKS ve ESES için önemli bir tanısal değer taşımaktadır. Bu derleme yazısında, LKS, ESES ve AR'nin klinik özellikleri, prognozları ve tedavi yaklaşımları tartışılacaktır.

Anahtar kelimeler: Landau Kleffner sendromu, uykuda elektriksel status epilepticus, otistik regresyon, dil regresyonu

INTRODUCTION

One of the most annoying conditions which parents can face in their children is the regression or loss of the previously developed cognitive functions and especially language skills. Language regression can occur in children with previously normal language development or may be in the form of a deterioration of the previously abnormal or delayed language skills (1,2).

Broadly, two types of language regression is defined in clinical studies:

- If language regression occur in the context of autistic regression (AR), it is termed as autistic language regression (ALR) (3,4).

- If language regression is not accompanied by autism or autistic spectrum disorder (ASD) symptoms, then it is called isolated language regression (5).

In both types, congitive and behavioral regression may be present.

The loss of language skills after acquiring more than five-word vocabulary is a commonly used definition of language regression in clinical studies (5). In some of these children who regress, language and/or cognitive regression is associated with an epileptiform electroencephalogram (EEG) and/or clinical epilepsy (6). Landau Kleffner syndrome (LKS) and electrical status epilepticus in sleep (ESES) or continuous spike and wave during slow wave sleep syndrome (CSWS)

are the two rare conditions in which the language regression is associated with either an epileptiform EEG or clinical seizures (6-8).

The background of this review article is as follows:

- Either with effect of the increased awareness or other unknown factors, there appears to be a rising prevalence of diagnosed autism and ASD: Prevalance of ASD was 6.6 per 1000 at the age of 8 years according to Centers for Disease Control and Prevention, 2007 (9).
- ALR, especially if the patient has epileptiform abnormalities on EEG, is usually compared with LKS and ESES.
- Acquired epileptic aphasia (LKS, CSWS) may respond to anti-epileptic drugs/ steroids or surgery.
- Prolonged EEG recordings are being ordered to look for ESES or sleep activated epileptiform abnormalities in children with a history of regression.

Landau Kleffner Syndrome

Historical Information

In 1957, William L. Landau and Frank R. Kleffner (8) described six children who developed an acquired receptive aphasia in conjunction with an epileptic disorder. The EEGs demonstrated severe paroxysmal changes, which appeared parallel to the course of language impairment. They termed this clinical condition "syndrome of acquired aphasia with convulsive disorder in children". This syndrome of acquired aphasia, seizures, and an epileptic electroencephalogram has become known as the Landau- Kleffner syndrome. The mechanism is thought to result from a functional interference with the posterior temporal language areas secondary to persistent epileptic discharges.

Clinical Features

Children with LKS or acquired epileptic aphasia have prior normal, age- appropriate language and otherwise normal cognitive development. LKS patients experience a language regression between the age of 2 to 8 years. Peak age is 4-5 years. This regression is characteristically accompanied by epileptiform EEG abnormalities and/ or clinical seizures (10).

The language disturbance of LKS patients in the early course is severe receptive language deficits referred to as: verbal auditory agnosia "loss of the ability to comprehend a spoken word" (6,7,11). Language regression may be acute or subacute. Word deafness is the core language disturbance. In extreme cases, perceiving non-verbal sounds such as sirens or ringing of the telephone can be disturbed (10). LKS patients may be eveealuated to find out if they are not really deaf. Probably as a consequence of auditory agnosia, affected children develop expressive language deficits with disrupted speech production. Language in these children may regress to complete mutism unless they have the true diagnosis and early treatment (7).

EEG in LKS

The main feature of the LKS syndrome is the EEG abnormalities associated with language regression. The EEG of the children with LKS shows frequent sleep activated epileptiform activity maximally over the posterior temporal areas, unilaterally or bilaterally, with a dominance in the perisylvian or intrasylvian cortex (6,12-14). Centro-temporal spikes in the intraperisylvian region which have a characteristic vertical dipole are also reported
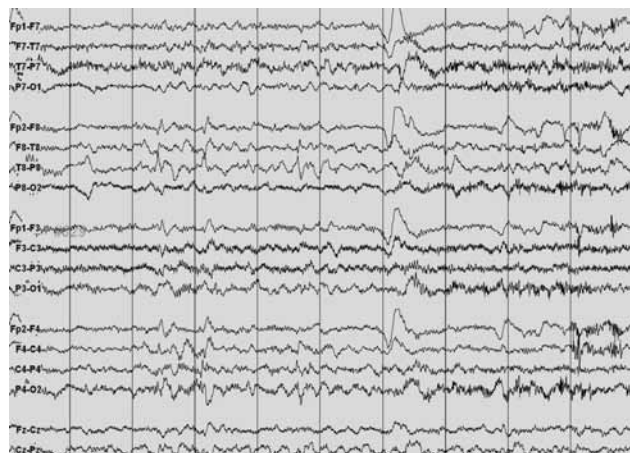

Figure 1: EEG of a 8 year-old boy diagnosed with LKS who had language regression and nocturnel seizures. Right centro-temporal epileptiform abnormalities are present.

in these patients (12,15). Some clinicians consider the presence of continuous spike and wave during slow wave sleep throughout the period of language regression, as a requirement for the diagnosis (16).

Seizures and screening in LKS

Although the presence of seizures is not needed for the diagnosis, 70-80% of LKS patients have clinical seizures (10,13,17). Patients tend to have partial onset seizures with eye deviation, eye blinking and head drops or complex partial seizures with secondarily generalization may be seen (7). Atypical absence seizures also have been reported (11). In LKS, structural brain abnormality is uncommon. Both computed tomography and MRI are usually normal (13,18-22).

Psychiatric symptoms in LKS

LKS patients may present psychiatric symptoms including: hyperactivity, inattentiveness, impulsivity and aggression (usually as a reaction to the loss of understanding language) (11). In case reports, psychotic symptoms (18,23,24), sleep and eating problems (24) were also reported.

Generally, children with LKS do not loose reciprocal social interaction skills and the understanding of social cues, in contrast to ASD with regression (7). They also do not have repetitive and restricted interests or behaviors. However, especially in severe and refractory LKS cases, clinicans may observe abnormal social behaviors resembling autistic symptoms. Most of these behaviors are mainly based on social withdrawal or unwillingness of the child to sociability. As a reaction to the unexpected loss of understanding spoken language, children with LKS may present with withdrawal to their own world. In a child psychiatric point of view, we suggest that, this social withdrawal may be termed as "the symptom of autism" secondary to a medical condition, or a depressive adjustment disorder.

Clinical Course

In the course of the syndrome, clinical seizures tend to resolve spontaneously with or without treatment by mid-adolescence. The EEG abnormalities also may resolve by adulthood. However, language deficits usually persist; sometimes correlated with the epileptiform EEG, although this is not the case for all LKS patients (7,10). Total recovery to normal language functioning is rare, a few number of patients are reported to have spontaneous remissions (8,11,25).

Treatment

Treatment algorithms are mainly based on expert consensus guidelines. Only case reports or case series are available as evidence for the efficacy of treatment options (26). Lagae (26), in his recent review indicated the use of antiepileptic drugs (AEDs) as the first-line treatment, including VPA and ethosuximide. However, a number of reports have shown that the early use of steroids, including prednisone, methylprednisolone and/or andrenocorticotropic hormone (ACTH) are effective in improving both the EEG abnormality and language (18,27-31). Series published to date used very different schemes of steroid treatment, different dosing and time course, making comparisons difficult. It is generally suggested that steroids should be given in high doses as soon as this diagnosis is established, followed by maintenance doses for several months to years (10,31). High-dose diazepam was also reported to be effective in some studies (32,33). Intravenous immunoglobulin also has been found successful in arresting LKS (34,35). Taken together, it appears that controlled studies are needed for evidence-based pharmacotherapy alghoritms.

In children with LKS who are resistant to pharmacotherapy, surgery as multiple subpial transections may be considered (10,12). Despite the reported generally favorable results for surgery on the short term, long-term outcome remains uncertain (36-38).

Electrical Status Epilepticus in Sleep

Electrical Status epilepticus in Sleep (ESES) or continuous spike wave during slow wave sleep (CSWS)

is an epileptic disorder characterized by specific EEG abnormalities which is associated with language, cognitive and behavioral regression in children (6,7,10). Children with ESES/CSWS often present with global regression in cognitive and/or motor skills. The clinical picture of the syndrome is variable but generally multisystem cognitive decline is seen.

Historical Information

After 14 years from the first introduction of LKS, Patry et al. (39), in 1971, reported 6 children with nearly continuous activation of epileptiform EEG abnormalities which began with sleep onset, continued throughout the night, and resolved when the children awakened. These EEG findings were originally termed "electrical status epilepticus''. In 1977, Tassinari et al. introduced the term electrical status epilepticus during slow sleep (ESES) for this EEG phenomenon (40,41). In 1989, the Commission on Classification and Terminology of the International League Against Epilepsy (ILAE) introduced the more descriptive term continuous spikes and waves during slow sleep (CSWS) for the clinical syndrome associated with ESES.

EEG criteria

The percentage of epileptiform activity during sleep can be expressed as spike-wave index (SWI). The SWI is defined as the total number of minutes of all spike and slow-wave abnormalities multiplied by 100 and divided by the total non-rapid eye movement sleep minutes (20). Various SWI criteria are proposed by different authors for ESES: 85% (42), 50% (43), 90% (22), 60% (33), 25% (44). The commonly used definition in clinic studies is "bilateral secondarily generalized 1.5 to 4.5 Hz spike-waves occuring during greater than 85% of slow wave sleep" (6,7).

The distribution of epileptiform activity in the EEG during the awake stage and during the whole sleep in patients with an ESES can be focal, multifocal, unilateral, asymmetric/symmetric bilateral, diffuse, or more restricted. The ESES/CSWS pattern may be continuous, fragmented, or periodic (14).
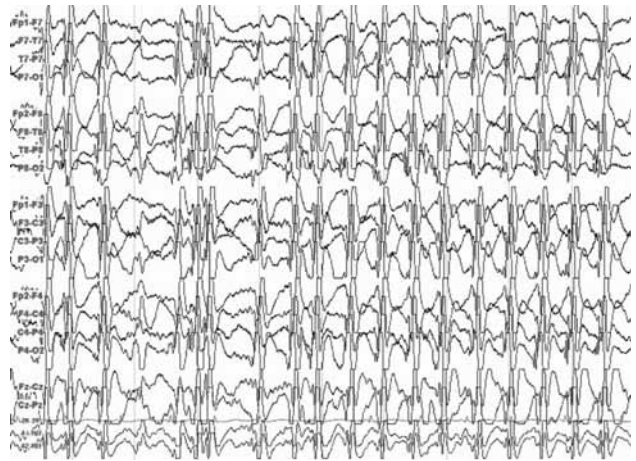

Figure 2: EEG of a 10 year-old girl with rare seizures and poor school performance. ESES (generalized spike and waves comprising most of non-REM sleep) pattern is evident.

Clinical Features

ESES is seen in children between the age of 3 to 14 years with a peak age of 5 to 7 years (45-47). Patients may have have a previously normal language and cognitive development or preexisting developmental and congitive delay (6,7,20,45). Up to one third of children with CSWS have a preceding neurologic condition, such as meningitis or neonatal encephalopathy (39,48).

Global regression

Cognitive regression: Severe decline in IQ, short term memory deficits and poor reasoning is demonstrated in ESES/CSWS patients. (6,7,20,42,49-51).

Language regression: The language impairment in ESES/CSWS includes an expressive aphasia as well as difficulties with lexical and syntactic skills. Comprehension is generally spared (7,20,42,49-51).

Behavioral regression: Reduced attention, hyperactivity, disinhibition and aggression are reported in several studies (6,7,42,50,51).

Motor symptoms: Motor deficits and apraxia, ataxia, dystonia, dyspraxia also have been reported

which may be unilateral (7,42). Disturbances with temporal-spatial organization can also be seen (6,7,42).

Seizures and screening

Seizures are the presenting symptom in 80% of children with ESES/CSWS (10). Seizures can present in many types; partial onset or secondarily generalized seziures are more common (7). Typical absence and atypical absence seizures also may be seen (20,52,53). Although the seizures associated with ESES may be more severe and harder to control with AED than in LKS, they tend to remit in mid-teen years as in LKS patients (6,7,10,42). Focal MRI abnormalities have been reported in patients with ESES (6). Various neuroimaging abnormalities including pachygyria and perisylvian polymicrogyria have been described in CSWS (44). Van Hirtum-Das et al. (44) found MRI abnormalities in almost half of their patients with ESES.

Treatment

As in LKS, treatments are mainly based on expert consensus guidelines and small uncontrolled series. It is suggested that the amelioration of the continuous epileptiform discharge on EEG is directly associated with the improvement in neuropsychological outcome (10). Among the treatment options, corticosteroids seem to offer better efficacy and more long-lasting effect (10,33,54,55). However, large series are needed for an evidence-based treatment algorithm. Moroever, there is no consensus on the dosing and duration of steroid treatment altough using high doses for prolonged periods generally is recommended (10).

Although phenytoin, carbamazepine, and barbiturates may reduce seizures, they are contraindicated in ESES because they may worsen the EEG discharges (31-57). Among the other conventional AEDs, the single or combined uses of valproic acid and ethosuximide have been reported to be beneficial in some studies. (33,58,59) However, some authors hold the view that the conventional AEDs play only a minimal role and the response of patients is incomplete and transitory (10,54). Response to treatment by short-term, high dose diazepam cycles was reported (32). Various other combination threapies and different algorithms were also suggested (33).

Levetiracetam and clobazam were also found to be effective in a recent study (60). Sulthiame, a drug that is very efficacious in benign rolandic epilepsy of childhood, has also been reported to be helpful in isolated cases of ESES with marked improvement or resolution of epileptiform discharge (60-62).

Case reports have suggested that intravenous gammaglobulin may benefit some children with ESES (35,60,63). Surgery is also suggested for the resistant cases to medication options. In a small series of 5 children with ESES undergoing multiple subpial transections in the United Kingdom, all showed improvements in behavior, language and seizure frequency (64). Unilateral congenital or early-acquired brain lesions may present with refractory seizures and ESES. In the study of Loddenkemper et al. (65), of 8 patients presenting with medically refractory epilepsy, hemiparesis and developmental delay, six patients underwent hemispherectomy and 2 patients underwent focal resection. Postoperative EEG demonstrated resolution of generalized interictal discharges and ESES in all. In a more recent study, 50% (16 patients) of children with ESES were resistant to medical treatment. Of these patients, 8 had surgery; five patients had callosotomy, one patient hemispherotomy, one parietooccipital resection, and one multiple subpial transection. The authors of this study suggested that surgical treatment options should be considered early in drug-resistant symptomatic ESES cases (58).

For the control of behavioral symptoms, psyhotropic medications may be needed. An atypical antipsychotic agent risperidone, which is commonly used in the treatment of aggresion in children, has been reported to be generally safe and effective also in children with epilepsy (66). However, no previous study investigated the use of risperidone in children with ESES. For the treatment of attention deficits and hyperactivity, only a case series studied the use of methylphenidate in children with ESES. Four of the 5 children showed favorable improvements (67). The available literature indicates that methylphenidate appears to be an

effective and safe treatment of ADHD in children with epilepsy, especially when the seizures are controlled (68). Large scale open-label and randomized controlled studies are needed to evaluate the safety and efficacy of psychotropic agents in children with ESES.

Prognosis in LKS and ESES/CSWS

In the majority of both ESES/CSWS and LKS cases, the seizures and EEG abnormalities tend to resolve by adolesence and/or adulthood (7,10,50). However, long-term neuropsychological outcome is poorer. Overall, the rate of reaching normal language and congitive level is reported between 10% and 44% (22,69,70). The prognosis in LKS and ESES depend on the interaction of different factors. The earlier onset of ESES and longer duration of untreated EEG abnormalities appears to be the major predictors of poor outcome in both conditions (22,52,54,69). If the paroxysmal activity on EEG persists for over 2 to 3 years, even successful treatment does not resolve neuropsychological sequelae and permanent language dysfunction may develop (22,52). A handful of studies reported partial or full recovery of language skills when effective treatment is initiated early (22,27,55,71). Thus, when suspicious of these syndromes, initiating prompt and effective treatment is of vital importance for language recovery. In both LKS and CSWS, referrals of the patients to overnight EEG recordings are the 'gold standard' for the early diagnosis of EEG abnormalities and successful treatment.

Controversy about the presence of LKS and CSWS as two separate clinical entities

While some researchers suggest that there is not sufficient evidence to warrant considering LKS and CSWS as two separate entities (46), the significant clinical differences between two conditions are still argued by others (10). The argument to state LKS and CSWS as different spectra of the same syndrome partly arise from the view that the two conditions are atypical variants of benign childhood epilepsy with centrotemporal spikes (BCECTS) (60,62). Although BCECTS shares the EEG finding activation of

epileptiform abnormalities during sleep, the clinical features, prognose and the treatment of BCECTS is different from LKS and CSWS (10,60).

Autistic Regression

Autism is a developmental disorder characterized by qualitative deficits in social interaction and in language, in association with restricted, repetitive behaviors and interests (DSM-IV). Diagnosis is made before the age of 3 (72). Parents of children with autism usually have concerns about their child's basic social and language development in the first 2 years of life (9,73-75). Even in the first birthday, the children who later will be diagnosed with autism have clues of ASD in social and emotional reciprocity (75,76). These observations are mainly demonstrated by retrospective home video analyses (75,76).

Approximetely 1/3 of the parents (%20-56) of autistic children report an early regression in their children (1,3,77-82). This regression takes place before 3 years of age, commonly between 18-24 months when the child was in the stage of 3–5 words vocabulary (73,78,83,84). Autistic regression (AR) includes regression in language, sociability, play, behavior and sometimes cognition as well (3,4,83). The children who regressed may be reported to be normal prior to the regression or have had some preexisting autistic features, which clearly to be worsened by regression (3,80). Almost half of the parents of children who experience AR report abnormalities in sociability, communication and/or cognitive development before the loss of skills (73,81,85,86). These findings underlie the controversy about the presence of an entirely normal phase before the regression. Siperstein and Volkmar (81) indicated that the parents of children with autism were more likely than parents of children with other developmental disorders to report any regression of developmental skills. Most of the published literature on AR was derived from retrospective parent reports, which is subject to recall bias.

Vaccinations, especially MMR, were previously reported to be related to AR (78,80). However, many large sample-sized, subsequent studies focused on this topic, and the results clearly indicated that there is no evidence

of a link between AR and the vaccinations (86-89).

The number of studies on AR is limited. Moreover, the available studies used different methodologies, different definitions, heterogeneity in patient recruitment and retrospective parental reports. Thus the specific features of AR are largely unknown. Wiggins et al. (73), in their recent study based on record-review surveillance data, found that boys were more likely to have regression than girls, and regression is more likely to be associated with a documented ASD diagnosis and more cognitive impairment.

Childhood disintegrative disorder

Childhood disintegrative disorder (CDD) is a global regressive syndrome accompanied with autistic regression. CDD emerges after a normal development of 2 years of age and involves regression in multiple areas of functioning (71,90). CDD includes motor regression and loss of bowel and bladder use (71,90-94). In comparison with autism, EEG abnormalities and epilepsy are significantly much more common in those with CDD (95,96).

Epilepsy in autism

The frequency of epilepsy in autism ranges from 4-42% according to different studies (3,82,97-100). It is also known that a significant majority of autism patients without seizures have interictal epileptiform EEG abnormalities (IIEA) on routine EEG studies (98-100). The general incidence of IIEA within autistic individuals is found to be between 6-74% (7,98-102).

Risk factors of epilepsy in autism include the presence and the degree of mental retardation, the presence of cerebral palsy and motor deficits and; two peaks, in infancy before the age of one and in adolescent years (4,7,98,100).

Controversy about epilepsy/EEG abnormalities in Autistic Regression

Some studies, especially the older reports, demonstrated higher rates of epilepsy in autistic children

with a history of regression versus the autistic children without regression (79,80,103,104). These results raised the questions if there is a clinically important relation between epileptiform EEG and/or epilepsy and AR as it is shown in ESES or LKS patients. With the hope of finding evidence of a treatable disorder, at least in some cases, physicians throughout the US and Europe refer children with ASD with regression history for 24 hour EEG or EEG-video recordings to look for evidence of ESES or sleep activated epileptiform abnormalities.

However, most of the later studies did not demonstrate such a relation. In 1997, Tuchman and Rapin (3) found no difference in the percentage of epilepsy but found higher ratio of interictal epileptiform EEG abnormalities in autistic children with a history of regression compared to the autistic children who don't have a history of regression. Three recent studies also did not find a relation between AR and epilepsy/EEG abnormalities (5,105,106). More recently, Baird et al. (107) has not found any relationship among autism, epilepsy, and regression.

Autistic regression and ESES

In most of studies that have reported EEG findings in children with AR, the pattern of ESES is not found (1,3,5,106). Tuchman (4), in his latest review, concluded that at the present time the evidence does not support a
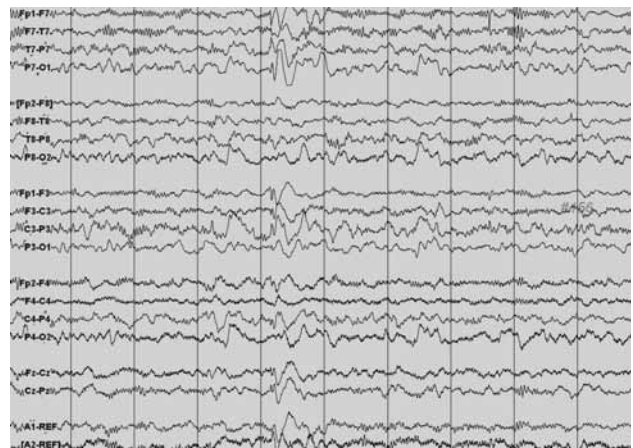

Figure 3: EEG of a 7 year-old boy with a history of autistic regression. Left centro-temporal epileptiform abnormalities are present.

Table 1: Comparison of LKS, CSWS and AR

	Basic type of regression	Features of language regression	EEG and SPECT findings
LKS	Language regression	Loss of previously acquired receptive language: verbal auditory agnosia	Sleep activated epileptiform EEG abnormalities, ESES Postero-temporal, centro-temporal focus
ESES/CSWS	Global regression in various cognitive functions. Language regression	If language regression is present: expressive or expressive/receptive aphasia with difficulties with lexical and syntactic skills	ESES pattern Fronto-central or fronto-temporal focus
Autistic regression	Regression to autism or an ASD diagnosis (or worsening in previous ASD symptoms)	Regression in language accompanied with regression in reciprocal sociability, play and behaviour The emergence of repetitive behavior and interests	ESES too rare Multifocal, independent and infrequent EEG abnormalities

LKS: Landau Kleffner syndrome, ESES: Electrical Status Epilepticus in Sleep, AR: Autistic Regression, CSWS: Slow Wave Sleep Syndrome

Table 2: Comparison of LKS, CSWS and AR

	Onset	Premorbid	Diagnosis, intervention	Treatment
LKS	2-8 years, peak age: 4-5 years	Usually normal language and cognitive development	Early diagnosis is crucial: overnight EEG	1.Medications 2. Surgery in refractory cases 3. Special education
ESES/CSWS	1-14 years, mean 4-8 years	Up to one-third have preexisting developmental delay and/or neurologic abnormality	Early diagnosis is crucial: overnight EEG	1.Medications 2. Surgery in refractory cases 3. Special education
Autistic regression	Before age 3 years, usually:18-24 months	Contraversy, Parental Recall bias, Usually when 3-5 word vocabulary	Early clinical diagnosis is crucial, EEG generally does not have a diagnostic role	1. Special education 2. Medications for behavioral control and additional psychiatric symptoms

LKS: Landau Kleffner syndrome, ESES: Electrical Status Epilepticus in Sleep, AR: Autistic Regression, CSWS: Slow Wave Sleep Syndrome

causal relationship between epilepsy, epileptiform abnormalities or ESES in AR. This view is also supported by two other recent studies (105,108). In contrast to AR, ESES has been reported in CDD (109,110), although the prevalence is unknown (4).

There is more evidence that AR has many distinct features than ESES/LKS. The EEG abnormalities of AR are not spesific as ESES/LKS. Sleep activated abnormalities are not characteristic in AR (4). The EEG abnormalities in AR, if present, are usually multifocal, independent and infrequent in nature (5,7,100,111).

The difference in prevalance of epileptic seizures constitutes another important difference between ESES/LKS and AR. Approximetely 70% of the LKS patients have clinical seizures and the ratio is even higher in patients who have ESES. However, this ratio is much lower in AR. Studies showed that 30% of the children with AR have clinical seizures (6,100,111). Interestingly, seizures in AR are more likely to occur in children who regress in language after age 3 (1,112,113).

With the available data at the present time, the EEG abnormalities in autism with or without regression seem to be an epiphenoma which is the result of the same underlying pathology rather than the EEG abnormalities a cause of the regression (5).

CONCLUSION

LKS and the CSWS are two points on the spectrum of epileptic syndromes which are characterized by severe paroxysmal EEG disturbance in sleep and regression. Regression in language skills without autism

symptoms is another diagnostically important shared feature of these two syndromes. However, available evidence to date indicates that the language regression in the context of AR distinctly differs from these syndromes both in clinical features and the frequency/type of the EEG abnormalities/epilepsy. Moreover, sleep activated epileptiform EEG abnormalities appear to be causally, or at least prognostically, associated with LKS/CSWS, but not with AR. Finally, the children with isolated language regression must be referred to overnight EEG studies of first priority for the early diagnosis and available treatment options.

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