Language impairments and neuroimaging findings of Landau-Kleffner syndrome, continuous spike-waves during sleep and benign epilepsy with centrotemporal spikes

Zaburzenia językowe oraz wyniki neuroobrazowania w przypadku zespołu Landaua-Kleffnera, zespołu ciągłych wyładowań iglica–fala podczas snu wolnofalowego oraz łagodnej padaczki skroniowej z igelcami w okolicy centralno-skroniowej

Bartłomiej Gaworowski
Uniwersytet Jagielloński w Krakowie
Neuropsychiatria i Neuropsychologia 2015; 10, 2: 78–85

Address for correspondence:
mgr Bartłomiej Gaworowski
Uniwersytet Jagielloński
e-mail: bartlomiej.gaworowski@gmail.com

Abstract
Epilepsy is a frequent neurological disease in childhood, characterized by the occurrence of two or more seizures at least 24 hours apart. Child epilepsies are mostly age related, and linguistic, cognitive and behavioural symptoms depend on brain development, the maturation process, genetic factors as well as the focal site of seizures. This article specifies the speech and language deficits discovered so far in Landau-Kleffner syndrome (LKS), continuous spike-waves during sleep (CSWS) and benign epilepsy with centrotemporal spikes (BECTS). Landau-Kleffner syndrome and CSWS are currently considered as synonyms, with the core symptom of acquired aphasia. Regression in CSWS is of global type, whereas in LKS it is of linguistic nature. Benign epilepsy with centrotemporal spikes is mostly accompanied by interictal epileptic discharges resulting in reading disability, such as dyslexia, and speech disorder of phonological nature and oromotor deficits. Continuous spike-waves during sleep, LKS and BECTS are age related, sharing common EEG features, results from PET studies, long-term prognosis and therapeutic approaches. There is a need for a new group of syndromes or one syndrome with an epileptic encephalopathy mechanism with regression which is common to all three syndromes or a syndrome of interictal spike and wave discharges. Further research is also needed confirming the type of language disorders in CSWS and BECTS and the severity of language disability in LKS.

Key words: epilepsy, Landau-Kleffner syndrome, aphasia.

Introduction
Language disorders mostly occur as a result of neurological or neurofunctional deficits. There are neurofunctional and neurological impairments where language deficits have been deeply examined, such as aphasia resulting from stroke,
and those where the exact relation between language and neurological deficit is still unknown. An example of the latter is epilepsy with language disorders. Language deficits in epilepsy have so far been seen as secondary, and therefore very little attention has been given to their specifics and potential treatment. The current classification of epilepsy does not take into consideration language deficits, which leads to the situation where language deficits are extremely diverse even within one syndrome or type of epilepsy. The clinical picture and etiology of epilepsy can have various natures. That is one reason why the classification of epilepsy is constantly changing. A typical characteristic of epilepsy is the tendency to repetitive and unprovoked seizures. Epilepsy can be diagnosed when there are at least two seizures at least 24 hours apart. It can be classified based on two factors: origin of seizures and probable cause of seizures. Based on the source of seizures epilepsy has been divided into two groups: partial epilepsy and generalized epilepsy. If we however take the cause of seizures into consideration, we can differentiate between idiopathic, symptomatic and cryptogenic epilepsies. In childhood epilepsy, syndromes help in specifying the etiology of epilepsy, which results in an easier choice of treatment and determination of the prognosis. The syndromes comprise a series of symptoms and additional examination results, including electroencephalography (EEG). Examples of such syndromes are benign childhood epilepsy with centrotemporal spikes (BECTS), also called Rolandic epilepsy (RE), Landau-Kleffner syndrome (LKS) and continuous spike-waves during sleep (CSWS), all three occurring in children.

According to the International League Against Epilepsy, they are all separate syndromes with distinctive features. Yet, they seem to share similar clinical as well as neuroimaging features. Professionals use the terms and concepts of CSWS, LKS, BECTS and even status epilepticus during slow sleep (ESES) heterogeneously, which often leads to confusion. So far, language impairments have been associated mostly with LKS. It turns out that there are other syndromes such as CSWS and BECTS where similar language disturbances might also occur.

This article aims to present clinical manifestations with a special focus on language impairments of each syndrome as well neural correlates corresponding to them. The last part of the article is an attempt to draw conclusions from the comparison of the syndromes and propose a new solution to the problem of terminology.

Landau-Kleffner syndrome

Clinical manifestations

Landau-Kleffner syndrome affects children between 3 and 10 years of age. According to Billard, Fluss and Pinton (2009), LKS is the syndrome with the highest combination of epileptic disability and language impairment. The syndrome was first described in 1957 by William L. Landau and Frank R. Kleffner as a “syndrome of acquired aphasia with convulsive disorder in children” (Landau and Kleffner 1957 in Van Bogaert and Paquier 2009). Aphasia means that the language disorder originated as a result of brain dysfunction, here epilepsy, and corresponds to severe disorder in auditory comprehension leading to complete muteness as the child no longer can hear his/her own words. The term “acquired” corresponds to the fact that the language dysfunction occurred after the child had already begun to develop language skills. Billard et al. (2009) note that developmental aphasia could also account for LKS. Developmental aphasia (the term ‘developmental’ refers to children) has been studied by Echenne et al. (1992 in Billard et al. 2009), who found a higher incidence of abnormal EEG in aphasic children than expected, mainly during night recordings. According to the authors, the physiopathology of language disturbances in aphasic children might be identical to Landau-Kleffner syndrome. Landau-Kleffner syndrome may be a link between epilepsy and language disorders, including aphasia. Unfortunately, detailed analysis of the types, forms and degree of language impairments in LKS is still missing.

Auditory agnosia (inability to recognise differences between sounds) or “word deafness” is often a foreground of neuropsychological diagnosis for LKS (De Tiège et al. 2013). Children often start failing to respond to the commands of their parents, even with raised voices. The disability extends to familiar sounds such as phone rings, bells, etc. The language disorder can be progressive or incremental, with either remissions or exacerbations (Pearl et al. 2001). Word deafness can also lead to telegraphic speech, fluent jargon and finally to mutism. The child is then restricted to a sign system and gestures. It is stipulated that the “subsequent decline of speech expression in LKS might result from defective auditory analysis of the patient’s own speech” (Metz-Lutz 2009, p. 73). The poor analysis then leads to receptive auditory agnosia (inability to understand music). Further observation lead to
the conclusion that the type of aphasia may be less severe than auditory verbal agnosia and that language impairment may occur without any clinical seizure (Paquier et al. 1992).

Bishop et al. (2008) underline a relationship between age of onset and the prognosis in LKS, suggesting that LKS is a disorder of higher-level auditory processing. The younger the child affected with LKS, the more devastating the outcome. The most devastating regression occurs in children at the age of 5 and lower. Often, language acquisition is blocked as of the onset of LKS, leaving the child only with what has been acquired so far. This is linked with the critical period for language development. Writing skills are not mastered due to the age of presentation, and in older children they may even be lost. Spared writing skills positively influence the prognosis in the re-education phase (Pearl et al. 2001). LKS is therefore an age-dependant functional disruption of language. Also, the duration of ESES plays a crucial role in the language outcome. Robinson et al. (2001) report that full language recovery is possible with children who have suffered from ESES for less than 3 years.

Neuroimaging findings

Both Gordon (1990) and Lanzi et al. (1994) found a relationship between language and epileptic representations. Landau and Kleffner first correlated the occurrence of language disturbances with focal interictal abnormalities in temporoparietal regions. Later research demonstrated that the spikes are extremely variable and can be temporal, centrotemporal, parietooccipital and even bilateral synchronous (Paetau 2009). Background activity is often normal. Sleep onset activates epileptiform discharges, which continue during non-REM sleep. The majority of patients have spike-and-wave discharges, but some experience focal ones, restricted to the temporoparietal region (Pearl et al. 2001). It is currently stipulated that interictal discharges might interfere with maturational processes by reducing axonal pruning and creating inappropriate connectivity. A single spike-wave discharge can also disturb auditory sensory processing (Seri et al. 1998). Picard et al. (1998) suggested a parallel in LKS “between the intensity of language disorders and the presence of bilateral PA” (paroxysmal anomalies) (p. 598). Paetau (2009) found in his study that 80% of patients have the onset of epileptic discharges in the auditory or language-related perisylvian cortex. Receptive language dysfunction in LKS has been proven to occur also as a result of focal epilepsy of the auditory related cortex (Paetau 2009).

Experience with the use of MST (multiple sub-pial transections) for treatment of LKS supports the theory of Morrel (1995) “that one primary focus in the sylvian cortex may activate secondary spikes in the contralateral homotopic area, causing serious developmental consequences” (Paetau 2009, p. 54), including language disorders. On the other hand, recent experiments using EEG triggered functional magnetic resonance imaging (fMRI) have shown that language impairments are not only restricted to the epileptic focus but might also be related to cortical or subcortical structures; for example, they might result from an increased blood oxygenation level dependent (BOLD) response in the primary and associative auditory cortex (Seri et al. 2009). This provides supporting evidence for the existence of language disorders in LKS or in other epileptic syndromes, such as CSWS or BECTS.

Interestingly enough, LKS provides supporting evidence for the theory that sleep is involved in brain plasticity and synaptic homeostasis (Mascetti et al. 2009). Specifically, paroxysmal activity during non-rapid eye movement (NREM) sleep is enhanced, suggesting that paroxysmal activity is influenced by neural mechanisms initiating and maintaining normal NREM (Masotti et al. 2009). Maquet et al. (2003 in Mascetti et al. 2009) demonstrated that sleep positively affects declarative and procedural memory. This brings more insight into the understanding of the effect of epileptic discharges on language functions.

Continuous spike-waves during sleep

The story of CSWS begins with electrical status epilepticus during slow sleep (ESES) and specifically when Tassinari and his colleagues proposed this notion. It is characterised by an EEG pattern of diffuse spike-waves lasting for at least one month and during a minimum of 85% of slow sleep (Tassinari et al. 2002). The children examined by Tassinari and his colleagues had partial or generalised seizures accompanied by a global cognitive regression resulting in severe mental retardation. Some of them experienced language problems typical of LKS, indicating a clear overlap. Despite this factor, the International League Against Epilepsy has decided to classify this syndrome under the name of CSWS.

Clinical manifestations

Continuous spike-waves during sleep are considered a prototype of the epileptic encephalopa-
theties. They are both age related and occur almost exclusively during sleep. Continuous spike-waves during sleep mostly occur in children around 3 years old and continue until they reach 15. The outcome of the patient depends on the location, duration, age of onset of CSWS as well as the individual neuropsychological profile of a child. Patients with a global regression experience more problems with treatment (Seri et al. 2009). Researchers are still not consistent with the etiology of CSWS. Some think it is because of psychomotor regression (Aldenkamp and Arends 2004 in De Tiège et al. 2009), whereas others claim it is because of brain pathology (de Tiège et al. 2009). Research has shown that the results of the epileptic activity during sleep are homogeneous and heterogeneous metabolic abnormalities in the awake state (de Tiège et al. 2013). There can be one or many sites of spike-wave discharges that are related to metabolic changes. If epileptiform abnormalities affect frontal lobe structures, such symptoms as autistic and psychotic behaviour, memory and executive function deficits often prevail. Epileptic encephalopathy occurs only during non-REM (rapid eye movement) sleep. The guidelines for diagnosing CSWS based on the level of activation of epileptiform activity of EEG vary among researchers and clinicians (Scheltens-de Boer 2009).

It is difficult to completely isolate and describe language deficits in CSWS separately from LKS, mainly because in the literature speech and auditory impairments in CSWS have been examined in LKS. Auditory dysfunctions have so far been considered as an aphasic receptive disorder or an auditory verbal agnosia, suggesting a clear overlap with LKS (Metz-Lutz 2009). Echenne et al. (1992) conducted a study in which more than 30% of cases with receptive aphasia had CSWS (Billard et al. 2009). Cognitive deficits in CSWS might account for potential language deficits, including dyslexia, apraxia, dysarthria, decreased speech output, visual agnosia, severe oral motor dysfunction, and also autism and learning arrest (Bogaert et al. 2006). The association between cognitive functions and epileptiform EEG activity has been determined by the fact that deficits disappear after EEG normalises. Seri et al. (1998) found in their research that a single spike-wave discharge can interfere with low-level auditory sensory processing. The presence of language disorders in CSWS is explained as a result of a “bilateralization of discharges and the generalisation in CSWS covering almost 80-90% of slow-wave sleep time; the hematopic temporal cortex in the opposite hemisphere is no more available as a functional area for auditory and verbal processing” (Metz-Lutz 2009, p. 74).

Neuroimaging findings

The focal or generalised origins of CSWS still remain undetermined (Paquier et al. 2009). Interestingly, it has been observed by [18F]-fluorodeoxyglucose [FDG-PET] studies by De Tiège et al. (2009) and Van Bogaert et al. (2011) that the inhibition of neurons often occurs in areas unrelated to the epileptic network, in distant brain areas and in the awake state. The authors claim that cognitive and behavioural regression might result from the violation of neurophysiological processes through the sleep-wake cycle. This concerns both on-site and distant, unconnected, brain areas (De Tiège et al. 2009). The neurological regression is hence connected not only with neuronal deficits at the site of epileptic discharges but also the neurophysiological changes in the distant brain areas. Again, this is supporting evidence for common deficits for LKS, CSWS and BECTS. De Tiège et al. (2013) tried to describe the neurophysiological mechanisms behind regional cerebral glucose metabolism in an awake state. The results of their research showed that the onsets of spike-wave discharges (SWDs), typical of CSWS, are related to hypermetabolism in the awake state in all patients, which, apart from hypometabolism and isometabolism, stems from the intense epileptiform activity during CSWS. Hypermetabolism has been observed in different brain areas in LKS and BECTS. In LKS, abnormal metabolism has been registered at the superior temporal gyri (a region often affected in aphasia), but in BECTS in centro-parietal regions. This could help explain the neuropsychological changes occurring with each syndrome (De Tiège et al. 2013).

Benign epilepsy with centrotemporal spikes

Clinical manifestations

Benign epilepsy with centrotemporal spikes is often called Rolandoic epilepsy (RE). The name “Rolandoic” comes from the fact that the seizures begin in the area of the brain called the Rolando area. “Benign” (also in the case of benign Rolandoic epilepsy – BRE) means that the patients affected with this syndrome often overcome it completely at the physical, behavioural and cognitive level. Benign epilepsy with centrotemporal spikes is the common epilepsy
syndrome in childhood. It mostly affects boys and girls equally below 15 years of age and accounts for almost 20% of epilepsy syndromes of that group.

Benign epilepsy with centrotemporal spikes begins with short duration seizures related to sleep accompanied by suggestive orofacial motor signs (Fejerman 2009). The child feels tingling on one side of the mouth or throat. Consequently, various speech problems occur, including heterogeneous cognitive deficits affecting language and memory functions. They are mostly associated with the intensity of interictal spiking and disappear after EEG normalisation (Van Bogaert et al. 2011).

Similarly to LKS and CSWS, receptive language impairments seem to dominate the clinical picture of BECTS. Since 1997, there has been growing evidence that neurocognitive impairments in speech, language, memory dysfunctions and especially auditory processing difficulties are in fact key factors in BECTS (Smith et al. 2012) BECTS can even lead to status epilepticus generating dysarthria (poor articulation of phonemes), speech arrest or orofacial apraxia (inability to carry out facial and lip movements). Speech and language deficits may result in developmental problems such as reading disability or speech sound disorder that might affect the future academic performance of a child (Clarke et al. 2007). Families with BECTS have increased risk of reading disabilities and speech disorders (Bali et al. 2007; Clarke et al. 2007 in Fejerman 2009). What is interesting is that susceptibility to the key comorbidities in BECTS, such as speech sound disorder or reading disability, does not result from recurrent seizures but is in fact inherited (Smith et al. 2012). Deonna et al. (1993 in Fejerman 2009) reported speech deficits of a phonological nature together with oromotor deficits in BECTS. Staden et al. (1998 in Fejerman 2009) confirmed a consistent pattern of language disturbances in children with BECTS, suggesting interictal dysfunction of perisylvian language areas.

As the seizures in BECTS disappear in the second decade of life, the cognitive effects of them can prevail. Monjauxe et al. (2005) demonstrated that BECTS is not benign in terms of linguistic deficits, which can persist in remission later in life. It can even happen that patients affected with BECTS without seizures suffer from reading and speech sound disabilities (Clarke et al. 2007).

For a long time the neuropsychological performance of children with (B)RE was considered normal. What is interesting, BRE was proven to include more learning and behavioural disabilities than typical Rolandic epilepsy (Verotti et al. 2002 in Fejerman 2009). There is indeed a relation between neuropsychological and neurocognitive difficulties and EEG activity. Massa et al. (2001 in Fejerman 2009) in a study of 35 children with BRE correlated neuropsychological impairments with EEG patterns. Picielli et al. (2008 in Fejerman, 2009) associated increased epileptiform discharges during sleep with specific learning disabilities.

Neuromaging findings

Electroencephalography is generally normal except for centrotemporal areas where interictal epileptic discharges are observed (Archer et al. 2003). Nicolai et al. (2007 in Fejerman, 2009) associated slow-wave focus during wakefulness, high number of spikes in the first hour of sleep, and asynchronous spike-wave foci with educational deficits.

Datta et al. (2013) examined a very interesting case of BECTS evolving to LKS and back by subsequent recovery. Before treatment the child suffered from verbal agnosia with poor verbal but surprisingly good performance functions. The reading network was left-hemispheric but with sentence generation failure. Post-treatment functional magnetic resonance imaging (fMRI) showed language task reorganisation from left hemispheric to right hemispheric but with right hemispheric non-verbal function decrease, presumably due to the crowding-out mechanism. Very rare left hemispheric centro-temporal spikes remained.

Conclusions

Despite the fact that the International League Against Epilepsy decided to classify LKS, CSWS and BECTS as separate concepts, there are similarities between them leading to the hypothesis of not only the same origin but also of the same character. Continuous spike-waves during sleep, LKS and BECTS are age related and share common EEG features, results from PET studies, long-term prognosis and therapeutic approaches (Tassinari et al. 2000). Spike-wave (SW) discharges mostly disappear after the adolescence period, suggesting that all three epileptic syndromes occur during the brain maturation period. Doose et al. (1996) proposed the concept of hereditary impairment of brain maturation supported by PET findings of increased cortical metabolism in children with CSWS and LKS. Continuous spike-waves during
sleep and BECTS display common EEG features suggesting a common pathophysiological background (Aicardi and Chevrie 1982; De Negri 1997). This leads to a hypothesis of a common genetic basis where epileptic syndromes occur on a continuum. Continuous spike-waves during sleep tends to lie on the more severe end of the clinical spectrum, whereas BECTS lies on the milder end. Benign epilepsy with centroparietal spikes with cognitive and learning disorders is regarded as BECTS+. The deficits have been proven by longitudinal EEG and neuropsychological studies and likely result from EEG epileptic interictal discharges (EIDs) due to the fact that they disappear after EEG normalisation. The research has shown transient cognitive impairments as well as verbal task deficits with left and right sided discharges (Billard et al. 2009).

Benign epilepsy with centrotemporal spikes can also have atypical features such as early age of onset and high SW or spikes. In that case neuropsychological deficits might occur, leading to atypical evolution and neuropsychological impairments and consequently to CSWS.

Regression in CSWS is of a global type whereas in LKS it is of linguistic nature. Aphasia in LKS tends to improve around puberty, which is similar to CSWS. In both cases cognitive and language impairment is not always subject to disappearance, which is mostly connected with the duration of ESES. In the majority of cases, language functions and social development increase after EEG pattern improvement. Holmes et al. (1981) stated that epiphenomena of underlying pathology of the cortex concerned with speech cause EEG abnormalities rather than aphasia. Electroencephalography change may not necessarily lead to a change in aphasia, and aphasia may continue in adulthood despite normalisation of EEG (Hirsch et al. 1990). Surprisingly enough, in some patients aphasia improves after the disappearance of continuous spike waves (Li et al. 1996). Improvement of LKS might occur either by the loss of epileptic activity or reorganisation of the motor and sensory cortex. Hence, the improvement of aphasia can take place with sustained epileptic activity.

A recent survey in North America showed that the use of concepts in ESES and CSWS is far from homogeneous. It has even been stated that CSWS is a vague synonym of ESES (Tassinari et al. 2012). There is indeed a lack of clarity in terminology which is progressing.

Both LKS and CSWS seem to share the same pathophysiological mechanism. They develop during synaptogenesis, which occurs between the age of 1 and 8. It involves a great increase in the number of synaptic connections and axonal processes to become twice as high compared to the number present in the adult. Environment plays a crucial role in determining which synaptic connection will be strengthened and which deteriorated. Electroencephalography disturbance acts as a strengthening mechanism where synaptic contacts should degenerate in order for neuronal aggregates to generate normal processes. As a result, in the case of LKS, paroxysmal activity leads to bilaterally faulty connections in temporoparietal regions, causing language impairments, whereas in CSWS the negatively formed connections occur in frontal regions, resulting in executive, attention and later language disturbances. Due to the spread of paroxysmal activity to other regions, the syndromes of LKS and CSWS merge and cause severe cognitive, behavioural and linguistic disability as in autism.

All three syndromes seem to represent different clinical expressions of one pathological entity. Brazzo et al. (2012) regard the three syndromes as clinical variants associated with the EEG pattern of ESES/CSWS. Epilepticus during slow sleep and CSWS are currently considered synonyms and LKS is a “particular presentation of epilepsy with CSWS in which acquired aphasia is the core symptom” (Buzatu et al. 2009, p. 69). They belong therefore to a common spectrum of epileptic syndromes. Taking into consideration the above and the similarities between CSWS, LKS and BECTS, I propose to introduce a new group of syndromes or one syndrome with the epileptic encephalopathy mechanism with regression, which is common to all three syndromes, or a syndrome of interictal spike and wave discharges. This would bring some clarity and support clinical studies and treatment.

Unfortunately, there is still insufficient evidence to confirm the type of language disorders in CSWS and BECTS and the severity of language disability in LKS. Research on the types, forms and severity of speech/language impairments is also missing. The situation does not look better in terms of the efficacies of any modes of therapy (Kleffner and Landau 2009). It also remains unknown how epileptiform EEG corresponds to language disability. Detailed examination of epileptiform EEG activity and language deficits could potentially reveal an interesting correlation but also a common deficit typical for all three epileptic syndromes and improve future treatment. Comparing the epileptiform and non-epileptiform EEG activity and langu-
age impairments in the three syndromes could bring us closer to understanding the relation between the deviant EEG activity and language impairments. That could also be a huge asset in creating a continuum of language deficits in epilepsy and consequently a better classification of epilepsy as well as treatment.

References


