RESEARCH ARTICLE

ACTA Vol. 12, No. 4, 2014, 401-416
NEUROPSYCHOLOGICA

Received: 12.09.2014
Accepted: 20.12.2014

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

DOI:10.5604/17307503.1132368

LANDAU-KLEFFNER-TYPE SYNDROME IN CHILDREN WITH DRUG-RESISTANT SYMPTOMATIC EPILEPSY

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SUMMARY

Background: To compare the severity and features of language disorders with the localization of brain lesions in children with epilepsy-inducing cortical dysplasias.

Material and methods: The cognitive performance of 20 children with cortical dysplasias of different localization was evaluated. All patients also underwent EEG and MRI studies. The severity of language disorders depends on the age of seizures-onset and its frequency.

Results: Losses of language in children occur regardless of the side and localization of the epileptogenic focus. The language functions are intact if the epilepsy-onset was at school-going age and if the seizures are rare. The loss of language or its retrogression can be observed in preschoolers that have daily repeated seizures with secondary generalization. This disorder resembles Landau-Kleffner syndrome, but cannot be classified as aphasia. In the case of severe seizure frequency, language deterioration is accompanied by an executive function deficit.

Conclusions: The "youngest" cognitive functions in phylogenesis and ontogenesis (language and executive functions) are the most vulnerable in children with drug-resistant epilepsies. We assume that severe language impairments in children with Landau-kleffner-type syndrome induced by focal cortical dysplasias are not aphasia as a localization-related disturbance associated with focal brain lesion. They are related to aberrant reorganization in the whole language dynamic system. We suggest that the proper way to call observed language disorders is not an "acquired epileptic aphasia" or "total aphasia", but "retrogression of language development"..

Key words: epileptic encephalopathy, cortical dysplasia, drug-resistant symptomatic epilepsy, Landau-Kleffner syndrome, language development

Epilepsy leads to the deterioration of cognitive functions in every fourth child, 37% patients with severe epileptic syndromes perform mental retardation (O'Leary et al, 2006; Berg et al, 2008; Garsia- Penas J.J., 2011; Epilepsii i sudorozhnye sindromy u detey, 1999).

The aim of this study is to emphasize the impact of seizure onset and seizure frequency on mental deterioration in children with epilepsy and to underline that the localization of the epileptogenic lesions does not significantly influence cognitive functioning in children with localization-related symptomatic epilepsy.

We evaluate the cognitive functions in children with cortical dysplasias associated with drug-resistant focal epilepsy. Special attention was paid to language development in this cohort of patients.

Language impairments often accompany drug-resistant symptomatic focal epilepsy, especially in early-onset epilepsies. In general it can be subdivided into two groups: transient disturbances (ictal or postictal) and permanent, often progressive, disturbances associated with interictal epileptogenic activity. The second type of disturbances occurs more often in children than in adult patients. However, it is not yet clear whether there are specific mechanisms underlying language disturbances in symptomatic epilepsy with a different localization of the epileptogenic lesion. Usually researchers attempt to establish linkage between language impairments and the localization of the epileptogenic zone or brain lesion. Thereby Landau-Kleffner syndrome is prominent and still current with regard to this issue.

Landau-Kleffner syndrome (LKS) is traditionally associated with the dysfunction of temporal lobes. In some way it is the most vivid example of the correlation between language disorders and epilepsy (Rapin et al., 1977; Aleksandrova, 2004; Hirsch et al., 2006; Troitskaya, 2006; Zenkov, 2007; Duran et al., 2009; Mikati et al., 2009; Steinlein, 2009). LKS was described by W. Landau and F. Kleffner in 1957 as a syndrome of an «acquired aphasia with convulsive disorders» in children. In recent years it has been called «acquired aphasia with epilepsy (Landau-Kleffner syndrome)» (F80.3 in ICD). Some researchers also call it «aphasia-epilepsy», «childhood aphasia», «receptive aphasia», «Wernicke's aphasia». 30-50% of patients display language disorders as the first and sometimes even the only symptom of the disease. The language disorders may occur acutely or gradually in the age range of three to eight years old. There may be no developmental disorders preceding LKS and developmental milestones are usually normal in such children.

For the most part researchers note that the most frequent and obvious impairment in LKS is loss of receptive language skills. Children become unresponsive to words and sounds ("word deafness"), they develop a progressive lack of attention to language. In more severe cases children with LKS fail to react even to environmental sounds and loud noises (Pearl et al., 2001). At the same time we can observe a progressive loss of vocabulary, paraphasias and difficulties in articulation. The degree of these disturbances may vary, in the most severe cases children may appear to be deaf mutes. Language disorders are accompanied

by non-linguistic cognitive functions. Children who develop the syndrome also display behavior problems, hyperactivity, deficits in selective attention, cognitive deterioration, absent-mindedness, aggressiveness, social dysadaptation (Aicardi, 1999; Ballaban-Gil and Tuchman, 2000; Pearl et al., 2001). There might be difficulties to distinguish the clinical symptoms of LKS from other epileptic syndromes associated with language disorders such as epilepsy with autistic symptoms and ESES (epileptic status epilepticus induced by sleep) (Lewin et al., 1999; Rossi et al., 1999; Ballaban-Gil and Tuchman, 2000; McVicar and Shinnar, 2004). Some researchers suggest joining LKS and ESES; for ESES is considered to be the EEG-base of language deterioration in LKS (Ermolenko et al, 2008).

Language impairments can precede seizures, seizures are infrequent; these may occur only once or twice in a lifetime. This is often of a focal motor type, secondary generalized or atypical absences. Myoclonic tonic seizures are rare. But there are always abnormal specific EEG-patterns that we can observe in LKS. Epileptiform activity is observed in uni- or bilateral derivations, abnormal EEG-activity predominates in the temporal regions in 85% patients (Lewin et al., 1999; Zenkov, 2007; Paetau, 2009). It can also arise from the parieto-occipital region (Pearl et al., 2001). The specific EEG-disorders of LKS persist, occurring one by one spikes and waves and sharp-slow waves. The discharges are multifocal or generalized. We can observe continuous spikes and waves in slow-wave stages of sleep (CSWS) in up to 70-85% of patients (McVicar and Shinnar, 2004; Zenkov, 2007). Thus the EEG focus is suggested to be a bilateral temporal focus, whereas there is a large subgroup of LKS children whose EEG disorder is generalized.

Temporal lobe focus is traditionally associated with language symptoms, and the primary disorders are administrated in comprehension and receptive skills. Nevertheless, there are also the subgroups of children with LKS that demonstrate language impairments but there is no primary temporal focus recorded in EEG. So what kind of explanations can we afford for the language disorders associated with a non-left-temporal EEG-focus in children with LKS and Landau-Kleffner-like syndromes?

The morphological features of the epileptogenic zone in LKS are different. Originally it was suggested to be a cryptogenic epilepsy, i.e. there were found no specific epileptogenic lesions and its etiology was unknown. Though in recent years it has been shown that LKS can be observed in children with brain lesions of different etiology: left temporal cortical dysplasia, astrocytoma, gliosis, toxoplasmosis, meningitis or encephalitis with no focal lesions (Pearl et al., 2001; Aleksandrova, 2004; Mikati et al., 2009). The common feature for the cognitive epilepsy-induced disorders above is the abnormal EEG-activity that is frequently generalized and reflects the prominent disturbances of brain activity.

Some authors have reported children with diagnosis of LKS associated with brain lesions in the non-language areas of the left hemisphere and lesions in the right hemisphere. M.A.Mikati et al. (2009) report the case of a 7-year-old girl with ganglioglioma in the right temporal lobe who developed LKS. The developmental milestones were normal. The first seizure occurred when she was 1 year 4 month.

She suffered from rare versive seizures. When she was 4-years-old she started to have the language impairments followed after a series of seizures that persistently ocurred during 2 months. She behaved as if a deaf girl and demonstrated autistic behavior – the girl avoided eye contact. Parents noticed her regression in motor and social skills. The epileptogenic zone was in the right temporal region and there was also a secondary EEG-focus in the left temporal lobe (ESES). After tumor resection and EEG normalization the girl began to imitate speech but there were observed no significant improvements in behavior and motor and social skills. Thus, the behavior and language symptoms resemble the LKS symptoms (acquired epileptic aphasia (AEA)) except for the localization of a epileptogenic lesion in the right temporal lobe. M.A.Mikati et al. (2009) report other cases of children who have developed a language deficit similar to LKS and Landau-Kleffner-like syndromes and have had epileptogenic lesions in non-language areas. We can also find similar case reports of AEA in children with EEG-focus in the right hemisphere (Zenkov, 2007).

Therefore children with a different localization of the epileptogenic focus may display similar prominent language disorders to those which are reported and discussed in the subject literature as AEA. **The goal of our research is to compare the severity and features of language disorders with the localization of the brain lesion in children with epilepsy-inducing focal cortical dysplasias.**

MATERIAL AND METHODS

Research participants included 20 patients with refractory symptomatic epilepsy induced by cortical dysplasias, aged 2.2–15 years. All children were observed at the pediatric department of the N.N.Burdenko Neurosurgery Institute and were candidates for epilepsy surgery. All the children underwent an MRI to verify the localization of cortical dysplasia. Cortical dysplasias were diagnosed in all patients: 14 patients had cortical dysplasias (type 1 and 2); more diffused dysplasias were diagnosed in 6 children; 2 children had “double-cortex” syndrome. Brain lesions predominated in the right hemisphere (n=11), in the left hemisphere (n=6), or were bilateral (n=3). Frontal lobe lesions were observed in 6 patients, a temporal lobe lesion was observed in 1 patient, occipital brain lesions were observed in 3 patients, an insula lesion was reported in 1 case. We have also observed brain lesions in the fronto-temporal and parieto-occipital regions. Bilateral diffused cortical dysplasia was diagnosed in 3 patients. 11 boys and 9 girls participated in the current research.

The epilepsy onset varied from birth to the age of 7 years old. One child had a seizure remission of 7 years. The duration of epilepsy is varied: from 2 years to 10 years. The semiology of epileptic seizures was mainly of complex motor seizures, dialeptic seizures and secondary generalized seizures with the versive component.

Evaluated was the cognitive performance of 20 children. Used were a neuropsychological assessment by A.R. Luria and a clinical observation of the chil-

dren's speech and behavior (when the neuropsychological test battery was not available). Children had a comprehensive neuropsychological battery administered by A.R. Luria which included clinical measures of language, gnosis, praxis, motor functions, immediate and delayed verbal and visual memory, visio-spatial functions and executive functions (Luria, 1962).

Behavior disorders and the young age of the children often do not allow one to administrate a fully comprehensive neuropsychological test battery. In some cases we observe child's behavior, social skills, way to communicate with his mother, closest persons and researchers, surveys and anamnesis acquisition instead of a comprehensive neuropsychological evaluation. Parents were queried in detail regarding the developmental milestones of the child, the presence, frequency, duration and type of seizures. Medical records especially video-EEG-monitoring and MRI-data were also specifically reviewed for full information.

RESULTS

The severity of disturbances in expressive and receptive language functions differ. Table 1 provides details regarding the language disturbances observed in patients before epilepsy surgery.

There were no language symptoms in 4 children (*Group 1, cases 1-4*). Seizure-onset was early in 2 children (at the age of 1 and 1.8). Seizure frequency was mild or moderate. Seizures occur weekly or monthly. Late seizure-onset was observed in 2 children of this cluster as well. The first seizure occurred when they were 5 and 7 years old, seizure frequency varied. But it was not severe in both cases. We can assume that all the children of this cluster have good enough language skills and this fact is related to the rare seizure frequency and the normal level of language skills preceding epilepsy-onset. We suppose that normative language developmental milestones and rare seizure frequency can predict an absence of acquired epileptic language symptoms. Nevertheless we can observe non-language cognitive impairments and behavior troubles (attention deficit, hyperactivity) in children of this cluster that resemble acquired frontal syndrome. Children had a learning disability and displayed academic underachievement. Children perform disturbances in set maintenance and cognitive load, severe memory deficits, inhibitory control deficits, calculation difficulties and visio-spatial deficits in their comprehensive neuropsychological evaluation. They ignore their errors and do not check results properly, that is evaluate as executive functions disorder. They perform intellectual decline and have moderate troubles in the retelling and interpretation of tales and pictures.

Localization-related language disturbances are demonstrated in the second cluster of patients *(Group 2, 5-10 cases*). Three children demonstrate naming disturbances, 2 patients perform perseverations and echolalias in expressive language, imitative speech. These 2 children had diffused bilateral "double-cortex" syndrome. Severe perseverative disturbance in writing skills was observed in one patient with left frontal lobe cortical dysplasia.

The language performance in the next cohort of patients (*Group 3, cases 11 – 15*) was very similar to the LKS symptoms reported in the subject literature but it had some particularities. They had epileptogenic lesions in the left cingular

Table 1. Performance of children with epilepsy-inducing cortical dysplasias across the receptive and expressive language functions

№	Age	MRI and diagnosis	Age at onset	Seizure frequency	Language deterioration symptoms
1	11 year old	Cortical dysplasia located in insula in the right hemisphere. Symptomatic temporal lobe epilepsy	7 years old	Several times a day, every day	No symptoms. Right-handed.
2	8 year old	Cortical dysplasia located in the left occipital lobe. Symptomatic occipital lobe epilepsy	1year 8 months	Fluctuating (every week, every month)	Retrained left-handed. No symptoms
3	15 year old	Cortical dysplasia located in the right temporal lobe. Symptomatic temporal lobe epilepsy (TLE)	5 years old	3-4 times/month	Right-handed. No symptoms
4	14 year old	Schizencephalia, polymicrogyria, cortical dysplasia located in the right parieto-occipital region	1 year old	From 1 to 10 times a month	Right-handed. No symptoms
5	11 year old	Cortical dysplasia located in the right parieto-occipital region. Symptomatic occipital lobe epilepsy	4 month	Everyday with long-term remissions	Right-handed. Difficulties in object naming, loss of vocabulary, Phonemic or semantic verbal substitutions, «infantile» utterance
6	4 year old	Cortical dysplasia located in the left frontal lobe. Symptomatic frontal lobe epilepsy (FLE)	2 years old	Several times a day, every day	Right-handed. Difficulties in finding names for commonly known objects. Loss of vocabulary
7	9 year old	Cortical dysplasia located in the left frontal lobe	Epilepsy onset in 4th month. Long-term remission. Recurrence at the age of 8	Many times a day, every day	Ambidexterity. Perseverative writing, loss of vocabulary
8	10 year old	Double-cortex syndrome. Diffused bilateral brain lesion. Symptomatic generalized epilepsy	1.5 years old	Weekly	Right-handed. Language development delay. Loss of vocabulary, perseverations
9	13 year old	Cortical dysplasia located in fronto-temporal region. Symptomatic TLE	Seizure onset at 10 months, the next one at the age of 3, the recurrence of seizures at the age of 13	Monthly	Right-handed. The language development delay. Poor vocabulary, naming disorder, deficit of word-finding abilities
10	15 year old	Double-cortex syndrome. Diffused bilateral brain lesion	1 month	Several times a month, sometimes – every day	Right-handed. Language development delay. Loss of vocabulary, perseveration in speech, dysarthria

Table 1 (cont.). Performance of children with epilepsy-inducing cortical dysplasias across the receptive and expressive language functions

11	13 year old	Cortical dysplasia located in the mesial frontal lobe region. Bilateral brain lesion	3 years old	Many times a day, every day	Right-handed. Normal language development till 3 years old. After 3 years old - progressive loss of expressive language skills, regression of language development. «Infantile» utterance
12	10 year old	Cortical dysplasia located in the posterior areas of the left cingalate gyrus. Symptomatic Landau-Kleffner-like syndrome	3 years 10 months	Many times a day, every day	Right-handed. Normal language development till 3 years old. After 3.5 years old — babbling, distortion of sounds pronunciation. Only separated vowel sounds.
13	5 year old	Cortical dysplasia located in the left frontal lobe. Symptomatic FLE	9 months	Many times a day, every day	Right-handed. No language symptoms till the age of 2.5. Then progressive losses in expressive language skills, up to total speech arrest
14	2.2 year old	Cortical dysplasia located in the right occipital lobe	14 months	Every day, frequent seizure series	Right-handed. No language symptoms till seizure onset. After it — total loss of receptive and expressive language function, speech arrest
15	7 year old	Pachygyria in the right fronto-temporal region	Age of 3.5	Many times a day, every day	Right-handed. Arrested language development. Loss of vocabulary. Distortion of sounds pronunciation
16	7 year old	Cortical dysplasia located in the right frontal lobe. Symptomatic FLE	Age of 4 months	Many times a day. Every day	Right-handed. Separated syllables used instead of words. Prominent acquired frontal syndrome
17	5 year old	Cortical dysplasia located in the right fronto-temporal region. Symptomatic FLE	Age of 2 months.	Many times a day. Every day	Retrained left-handed. Separated syllables used as words. Prominent acquired frontal syndrome
18	5 year old	Polymicrogyria in the right occipital lobe.	Age of 1 month.	Daily up to 50-80 seizures a day	Right-handed. Severe arrested language development. The child has never said a word. Very severe frontal syndrome
19	7 year old	Diffused pachygyria of the right hemisphere. Symptomatic FLE	Age of 2 weeks	Several times a day, everyday	Right-handed. The child has never said a word. Severe frontal syndrome with motor stereotypes and perseverations
20	2.2 year old	Cortical dysplasia located in the right fronto-parietal region. Symptomatic FLE	The third day after birth	3-6 times a day, every day	Right-handed. Severe arrested language development. The child has never said a word. Very severe acquired frontal syndrome

gyrus, in the left frontal lobe, in the right occipital lobe and in the frontal lobe bilaterally. Here we would like to report some revealing cases.

Case 1. Epilepsy-inducing dysplasia located in the posterior areas of the left cingular gyrus was diagnosed in a 10-year-old boy. The developmental mile-

stones until he was 3 years 4 months old were normal. He used grammatically complex sentences, learned poems, knew the alphabet and could spell simple words. When he was 3.4 years old, his parents noticed changes in his behavior – he became strange, capricious, malicious. At the same time he developed a progressive lack of attention to language, losses of receptive skills. He also performed poorly in expressive language skills, vocabulary appeared to be more and more limited. The dramatic progressive losses of receptive and expressive language skills occurred during a month. The boy appeared to be mute and deaf, so the parents even decided to have an audiometry performed, but it remained within normal limits. Afterwards the boy performed increasing language skills, but his language development was delayed. The first seizure followed developmental language disorder only in 6 months. For the first time seizures were atypical absences, then they transformed into atonic and secondary generalized seizures with a tonic component in the right side of the face and the right hand. Its frequency at the moment of administration was up to several times a day. After the seizure-onset the language skills decreased up to total speech arrest. According to video-EEG-monitoring, the separated epileptoform discharges arise from the left parietal region, CSWS was observed during EEG-registration of sleep.

Neurologically the child demonstrated mild extrapyramidal disorder. The boy performed severe neurobehavioral and cognitive disorders in neuropsychological administration. He used only several vowels and gestures instead of words to communicate with his mother and others. Attention deficit disorder and hyperactivity were observed. This behavior appeared to be “field-dependent”. If he saw handles, he began to open and close doors, if he saw a pencil, he began to draw and so on. At the same time he performed poor set of maintenance and cognitive load, so his persistent activity did not last long and he gave it up very quickly. He did not play with toys and did not communicate with other children. He rather preferred a limited number of toys and stereotyped games. He did not maintain eye contact. He became very accurate and stubborn and he would watch closely to ensure that everything was in its place. Nevertheless his domestic and social skills were not so poor: he could dress, eat and wash himself.

The language symptoms were interpreted as LKS symptoms before the evidence of cortical dysplasia. The developmental language disorder preceded seizure-onset.

Reporting this case we pay attention to the severe acquired frontal syndrome with autistic component and attention deficit disorder observed in this patient. One can conclude that such a drastic language disorder has developed in a patient with non-language area brain lesion. More crucial in developing language impairment is the CSWS that is evidence of generalized diffused disorder in brain activity.

Case 2. The point of interest in the case is the improved language after its deterioration in a right-handed boy with epilepsy-inducing bilateral dysplasia in the mesial frontal lobe region. The developmental milestones before the age of 3 were normal, the boy’s speech was phrase, he has learned all the letters in

the alphabet, but he could not yet read and write. The first seizure occurred when he was 3 years old, the seizure was dialeptic with hypersalivation, then there followed secondary generalized seizures with versive component . The frequency of seizures quickly became drastic (many times a day), coinciding with a high temperature , and the patient was hospitalized in a resuscitation department under suspicion of meningitis. Subsequently, following treatment the meningitis turned out not to be the case. The patient was discharged from hospital within a month, and the parents noticed at once a cardinal change in the child's behavior – the boy began appear as a „deaf-mute" or an „autist" (according to the mother's words). He preferred to be alone, sat quietly in this room, communicated little and became unresponsive to calls. Audiometry was administrated as there was a suspicion as to the deafness, developed after treatment by gentamycin. However, the child fails to react even to environmental sounds that has led one to the conclusion as to 100% deafness in both ears. After hospital the patient began to take antiepileptic drugs. The seizures occurred in series (up to 20 times a day with remissions of 2-3 weeks). From when the antiepileptic treatment was prescribed, the cognitive functions improved within two weeks. The boy began to react to calls and sounds, his comprehension skills improved, he said individual words. In point of fact all these improvements have coincided with a reduction in the frequency of the seizures. The audiometry conducted then was within normal limits. However, the seizure frequency increased within the course of 1-2 months and a total loss of expressive language and an arrest in speech coincided.

An infantile utterance of speech and infantile way in naming objects appeared within 1-2 months following the period of speech absence. Individual, stereotyped words like "grandma", "dad have remained. As the boy grew up, his way of speaking, social skills and interests haven't changed and they resemble those of younger children.

His behavior remains "infantile", even at the age of 10-13 he likes to watch the cartoons he watched at the age of 3-4 years old. He has lost the acquired social skills, for example, he refused to get dressed and wash himself. During the neuropsychological assessment he constantly keeps close to his mother, makes stereotypic hands movements. The attention deficit disorder and set maintenance deficit are observed in neuropsychological examinations. He does some tasks on kinesthetic praxis with perseverations and then he gives up doing the tasks at all. The pictures he has drawn throughout many pages of a notebook are stereotyped, being always the same strange car. The pencil grasp is labile. The boy can show the most well-known and frequent subjects yet cannot name it. He displays an infantile way in the naming of subjects. He calls an apple a "hum-hum", a cat – "meow-meow", a dog – "bow-wow", the teapot – "sh-sh-sh", etc. At the same time he can recall all the letters he knew at the age of 3, before the disease. Neuropsychological counseling and classes with a speech therapist have been long and unsuccessful. According to EEG-monitoring, there are two epileptogenic foci arising from the right central region and the left parietal lobe.

Thus, all the patients of this cluster demonstrate a prominent combination of language disorders and acquired frontal lobe syndrome with attention deficit disorder, set maintenance troubles and behavioral stereotypes.

We would like to pay attention to the last cluster of patients (*Group 4, cases 16-20*), in which language disorders are associated with brain lesions in the right hemisphere. All the children of this cohort demonstrate severe developmental language disorders. 4 of the 5 patients are right-handed while the other child primarily preferred to manipulate with her right hand but by the age of 5 she almost always preferred to use her left. All 5 children in a semiology of seizures and cognitive evaluation have common features: daily frequent secondary generalized seizures and early seizure-onset (before the age of active language development). They fail to react to calls and speech, they use 1 or 2 syllables in substituting for words and they say them regardless of the situation. Severe attention deficit disorder, hyperactivity, set maintenance disturbance, perseverations and stereotypes in behavior are observed. One can conclude that this group of children demonstrates the most severe acquired frontal syndrome. According to the EEG-data continuous epileptogenic activity arises from the cortical dysplasia area, and it has rapidly tended to be secondary generalized.

The cohort of patients supports the evidence of a close association between Landau-Kleffner-like language symptoms and acquired epileptic frontal syndrome.

DISCUSSION

One can observe different types and severity of language disorders within the four groups of patients. One can conclude that there is a significant relevance between language symptoms and the seizure-onset and seizure frequency. Early seizure-onset (from 0 till 3.5 years old) and the high frequency of secondary generalized seizures (up to several times a day) tend to lead to severe language disorders. Impairments of language development can be observed from birth or it can occur after the normal developmental milestones. The most dramatic language impairments are associated with the epilepsy-onset occurring in preschoolers who suffered from everyday repeated seizures. No significant causal relationship between the localization of a brain lesion and language development was found. Landau-Kleffner-like symptoms are observed in children with epileptogenic brain lesions of different localization. The seizure semiology also supports the evidence of a different localization of the epileptogenic focus. However, there are no significant facts as to the propagation of epileptogenic activity to language areas. Moreover, language disorders are observed in children with lesions in the right hemisphere. This is especially clearly observed in the last reported cohort of children who suffered from severe epilepsy with early seizure-onset and a high seizure frequency. As we have reported, speech in this patient group did not appear at all and they have severe developmental language disorder.

As the majority of our patients had cortical dysplasias in the frontal lobes it is not surprising that they develop disorders associated with frontal lobe lesion –

"acquired epileptic frontal syndrome" as E.Perez et al. have called it (1993). However, this syndrome of different severity has been observed in patients who had non-frontal lobe lesions (brain lesions were localized in occipital and parieto-occipital regions). The severity of acquired frontal syndrome also significantly depends on the seizure frequency and seizure-onset. The most severe frontal syndrome is observed in children with early seizure-onset and daily repeated seizures; in this case language does not even have a to develop. These children did not establish contact (verbal and nonverbal), movements and activity were not purposeful and stereotyped. These facts reveal the evidence that language disorders up to total speech arrest, progressive loss of language ("aphasia-epilepsy") and the acquired frontal syndrome in children with cortical dysplasias and epileptic syndromes can be associated with a different localization of the brain lesion and there is also an increasing evidence that disorder severity depends on the seizure-onset and the duration of the epileptic disorder. Although it is necessary to underline that cortical dysplasia localization and the localization of the epileptogenic focus influence features of revealed impairments. For instance, some patients with frontal lobe lesions perform frontal syndromes that include various primitive behavioral automatisms (licking, sniffing around subjects and people).

It was earlier considered that LKS (AEA) and dramatic loss of language skills had at its base and most prominent symptom temporal lobe epileptogenic foci. Accumulation of clinical and electrophysiological data raises questions as to why the language disturbance called AEA can be observed in patients with non-language areas lesions and whether it is possible to consider these language disturbances as aphasia. Is there any similarity in the underlying mechanisms between LKS language symptoms and the language disorders displayed in patients suffering from early-onset daily seizures associated with brain lesions of different localization including right hemisphere lesions?

In recent literature it has already been noticed that language disturbances in children with epilepsy are not necessarily associated with the epileptogenic focus located in the language area as it is in adult patients (Zenkov, 2007). Two explanations can be suggested: the first one suggests the equipotential brain areas, i.e., equal hemispheric specialization of brain functions in preschool age; the second one suggests an atypical language dominance due to brain plasticity in children.

The hypothesis of equipotential brain regions or the progressive hemispheric specialization of brain functions suggests that the left and right hemisphere equally participate in cortical language distribution at the early stages of development. Further, the left hemisphere gradually begins to dominate in the organization of language functions as the processes of brain maturing occur and training and environment influence the maturation processes. The hypothesis is corroborated by research into children with a congenital pathology of the hemispheres as the language performance in neuropsychological evaluations of children with early brain lesions of the left hemisphere remains within its normal

limits. Additionally many facts contradicting the concept of equipotential brain regions have been reported. These facts convincingly emphasize the evidence of the different contribution of left-sided and right-sided brain lesions to language development. Children with left-sided brain lesions perform significantly lower than children with right-sided lesions and the frequency and severity of language symptoms are significantly higher in patients with left-sided lesions (Hecaen, 1983; Simernitskaya, 1985).

Therefore, it is impossible to explain language disturbance in children with epilepsy associated with a right-sided epileptogenic focus using the hypothesis of the equal cortical representation of functions within the right and left hemispheres.

The possibility of atypical language dominance in patients with epilepsy was observed using fMRI-data. Thus, areas of receptive and expressive language functions can separately transfer to the opposite hemisphere in cases when brain tumors are located in the left temporal and left frontal lobe (Kurthen et al., 1992; Holodny et al., 2002; Petrovich et al., 2004; Kamada et al., 2006; Powell et al., 2007). O.Devinsky et al. (2000) have revealed spread language area using intraoperative electrostimulation in 44 patients with epilepsy with lower full scale IQ, cognitive performance and educational level. All cited data corroborate evidence of a high possibility of compensation for acquired neurocognitive hindrance and brain plasticity. Language areas appear to transfer to healthy cortical areas, but the transfer is limited. So one can conclude that the occurrence of language disorders associated with lesions in non-language areas cannot emanate only from atypical language dominance.

The moot point in discussing language disturbances is still the same: whether children with basic symptoms of AEA such as progressive losses in expressive and receptive language skills demonstrate *aphasia* as a localization-related disturbance associated with the local lesion of language areas as described in adult neuropsychology.

Naturally, it is impossible to deny the fact of acquired aphasia in epilepsy. Possibly, aphasia can be observed when language areas and cortical areas that sustain cortical representation of language functional system are involved in epileptogenic lesions. However, we suggest that global dramatic language impairments, up to its total arrest and retrogression after the period of normal developmental milestones ("patients are like deaf-mutes") associated with aggressive epileptogenic activity cannot be considered as aphasia in its original sense (Luria, 1997). We assume that aberrant reconstructions in the whole language dynamic system is revealed in cases when a regress of language functions is estimated; this comes acutely or gradually, within the course of several months. This aberrant reorganization of language functions due to epileptic encephalopathy can be reversible (if seizures can be medically controlled) or irreversible in cases of intractability of the seizures to medical management or a late decision for epilepsy treatment. In our opinion, the features of these phenomena can speak against its aphasic origin. First, the earlier epilepsy-onset leads to a lower performance in language skills, as the language functional system is still unstable and is not set. Contrarily,

according to the subject literature (Hecaen, 1983; Simernitskaya, 1985; Aleksandrova, 2004), children with early non-epileptogenic brain lesions and injuries demonstrate better compensation for language deficits.

Second, according to Simernitskaya (1985) and H. Hecaen (1983), children with focal brain lesions perform lower in expressive language skills but the receptive language functions remain intact. At the same time, a basic language symptom in LKS marked in a great number of recent research works is "verbal auditory agnosia" up to "word deafness" and the failure to react to environmental sounds. This is not a surprising fact given that the temporal lobe structures are particularly vulnerable to epilepsy and the aberrant cortical reorganization of cognitive functions begins with the receptive language function. D.Bishop (1982) and K. Baynes et al. (1998) considered that receptive language function is impaired due to deficits in the verbal and acoustic processes that are associated with the propagation of epileptogenic activity to the temporal lobes. We note that the very fact of involving the right temporal lobe in the epileptogenic system may explain an absence of reaction to nonverbal sounds in patients with severe LKS. Children become completely inaccessible to any type of contact (not just verbal contact, but also eye contact), they do not use words as a way of communication and their activity tends to be unpurposeful. This fact contradicts the aphasic origins of LKS language symptoms, it alludes to the executive impairment that coincide language disorder.

Third, the severity of AEA strongly depends on the epileptogenic activity and it does not appear to improve without efficient antiepileptic treatment while aphasia in childhood induced by a focal brain lesion appears to be transient due to brain plasticity (Simernitskaya, 1985).

The features of language improvement in the case of adequate epilepsy treatment and comparably good seizure relief are also presumed to indicate that the language symptoms in Landau-Kleffner and Landau-Kleffner-like syndromes are not aphasia in the sense of a localization-related disorder but an aberrant reorganization within the whole functional system. The child starts to react to words and calls, he remembers several words that he had already used, but the vocabulary abilities are still limited and utterance is infantile with sound pronunciation problems. The most evident and essential language disorder is the occurrence of "autonomous child speech". This has been reported by L.S.Vygotskiy, who described it in children with normal developmental milestones at the age of 1-2 years (Rubinstein, 1983; Levina, 2006). Some researchers also call it "child slang" or "imitating language" (Mikati, 2009). Autonomous language represents a natural stage in language development and serves as a bridge connecting the pre-verbal developmental stage and stages of language development. It might be essential that autonomous speech fundamentally differs from normal speech; the phonetic structure and the semantic aspect distinguish it first of all. A phonetic structure usually presents the repeating of syllables like "bow-wow", "meow-meow", "bi-bi" etc., sometimes neologistic jargon resembling "adult" words. The semantic aspect is reflected in its name. As the child uses the same

words for different subjects, its speech is therefore clear only to those closed to him so it is called “autonomous”. The language development is directly related to the development of a child’s thinking (Pachalska et al 2012; Mirski et al 2014).

We have observed “autonomous” or “autonomous”-type speech in several patients. The complete occurrence of autonomous speech is revealed in the 13-year-old child after the period of a total loss of speech. Aberrant reorganization of the language functional system leads to such a severe language disorder. We can find interesting research data in recent subject literature concerning this problem. D.Bishop (1982) describes a cohort of children with AEA who lived and studied in special boarding schools far from their home. While language functions improve they begin to speak in the original dialect accepted at their birthplace even if this dialect essentially differs from that of the boarding school teachers. It is evident that children have restored the earlier language skills instead of learning anew. It might be essential that the severity and extent of the aberrant reorganization of language function can be different and reflects different levels and stages of language development or even pre-verbal development.

Our research data and reports in recent subject literature indicate that language disorder and acquired epileptic frontal syndrome are associated in cases of severely spread epileptogenic activity. It can be identified in all cohorts of patients regardless of the localization of the brain lesion. Frontal lobe lesions cause the most severe acquired frontal syndrome including actualization of primitive behavioral patterns like licking, sniffing around and tasting inedible subjects. The severity of acquired frontal syndrome depends on the “malignancy” of the epileptic activity, the age of epilepsy-onset and the seizure frequency.

We conclude that the most vulnerable cognitive functions are the language functions and executive functions that are the “youngest” ones in phylogenesis and ontogenesis (Brown & Pachalska 2003). The disturbances of these functions present the base for acquired epileptic frontal syndrome. It means that epilepsy-induced cognitive disorders reflect a reciprocal interaction and interference of declines associated with localization-related functional brain areas and remediation of functional systems, especially the “youngest” ones while the “oldest” functional systems appear to remain stable. We suggest that, probably, from this point of view, we can replace in cases of severe language disorders the term “aphasia-epilepsy” or “total aphasia” by the term “regress of language development”, as the brain functioning “returns” to the previous milestones in cognitive development. The severity of the regress can be different depending on the “malignancy” and spreading of epileptogenic activity: from the total losses of expressive and receptive language abilities though the “autonomous” language up to limited vocabulary abilities and stagnation of language development. We suppose that the most severe language disorders and acquired frontal syndrome are observed in children with the earliest epilepsy-onset and a high frequency of secondary generalized seizures, or so our data implies. The language function and executive functions have not even time to be formed in these extremely adverse conditions and in the conditions of a child’s brain immaturity.

Language impairments due to aberrant reorganization of the language functional system make ordinary speech therapy and the processes of neuropsychological intervention already indicated by some authors inefficient (Aleksandrova, 2004). Therefore, the prior goal in overcoming language the deficits of such origins is early and adequate epilepsy treatment including epilepsy surgery.

CONCLUSIONS

We suggest that language disorders in LKS develop due to the global aberrant reorganization of the functional language system (that leads to a recourse of language development) but not localization-related brain lesion (that leads to instant aphasia). Thus, there is a significant relationship between language impairments and the age of the seizure-onset, the seizure frequency and the frequency of secondary generalized seizures. But language deficits are not related to the localization of cortical dysplasia and the epileptogenic focus. The language functional system tends to be undeveloped in cases of early epilepsy-onset and severe seizure frequency (before the crucial periods of language development). Language and executive functions are the most vulnerable to negative epilepsy influence as they are the “youngest” ones in the phylogenesis and ontogenesis and the least “trained” amongst the cognitive functions

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