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Does Electrical Status Epilepticus in Sleep Adversely Affect Language in Self-Limiting Focal Epilepsies of Childhood?

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ABSTRACT

Introduction: The electrical status epilepticus in sleep (ESES) accompanies a wide spectrum of focal and generalized epilepsies, which manifest with cognitive-linguistic regression. Both ESES and language impairment can be seen in self-limited focal epileptic syndromes of childhood (SFEC). The association between the presence of ESES pattern on the EEG and the severity of the language impairment has not been adequately clarified.

Methods: Twenty-eight SFEC cases without intellectual and motor disabilities and 32 healthy children were recruited. Cases with active ESES (A-ESES, n=6) and without ESES pattern on EEG (non-ESES, n=22) were compared in terms of clinical features and linguistic parameters by both standard and descriptive assessment tools.

Results: The only significantly different clinical feature in the A-ESES group was the increased prevalence of polytherapy. While most of the linguistic parameters were impaired in A-ESES and non-ESES groups compared to healthy controls, A-ESES patients differed from non-ESES patients only in terms of decreased complex sentence production, which was assessed by narrative analysis. A-ESES patients also showed trends toward producing lower numbers of words, nouns, verbs, and adverbs during narrative analysis. There were no differences among patients under polytherapy and monotherapy in terms of these language parameters.

Conclusion: Our results show that ESES increases the negative effect of chronic epilepsy on complex sentence and word production. Linguistic distortions that are not reflected in objective tests can be detected by narrative tools. Complex syntactic production obtained by narrative analysis is an important parameter that extensively characterizes language skills in school-age children with epilepsy.

Keywords: Antiepileptic, ESES, language disorder, occipital epilepsy; Rolandic epilepsy

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INTRODUCTION

Electrical status epilepticus in sleep (ESES) is frequently observed in childhood-onset epileptic encephalopathy and is characterized by electroencephalographic spike-wave activity in more than 85% of non-REM sleep and cognitive regression. Although ESES and epilepsy with continuous spike–waves during sleep (CSWS) are used interchangeably; ESES is used for the pattern seen in the electroencephalographic examination, while CSWS is used to describe the clinical picture with cognitive and linguistic regression. Genetic etiology, structural anomalies, and brain damage acquired in early life are among the causes of ESES (1). The electrical status epilepticus in sleep may also accompany idiopathic epilepsies in children with normal development patterns. According to the 2017 classification of the International League Against Epilepsy (ILAE), ESES pattern and language disorder can be seen together in Rolandic epilepsy (RE), and Gastaut type occipital paroxysmal childhood epilepsy (G-ICOE) (2), which are among the self-limited epilepsies of childhood (SFEC) (3,4). It has been reported that ESES has a negative effect on the morphosyntactic, semantic, and pragmatic dimensions of language (5). The electrical status epilepticus in sleep accompanies severe language impairment in Landau-Kleffner Syndrome (LKS), which starts with auditory agnosia and evolves into acquired epileptic aphasia. It has been suggested that SFEC and LKS may be parts of the epilepsy-aphasia spectrum since interictal discharges and language-cognitive problems of varying severity are common features in both (6,7). There are several shared genes associated with LKS, RE, and ESES; and *GRIN2A* mutations are cited as the most common genetic cause detected so far in this spectrum (8).

Treatment goals in children with ESES are stopping epileptic seizures, suppressing abnormal EEG findings and preventing language-cognitive impairment (9). However, the impact of clinical, electrophysiologic, and therapeutic aspects of epilepsy on language functions are largely not understood. The relatively benign and treatment-responsive nature of SFEC may cause the clinical features seen in severe and persistent epilepsies to be overlooked in SFEC. In our previous study, we showed that children with SFEC may develop advanced language impairment independent of EEG findings and seizure activity, and may display subclinical linguistic impairment that is not reflected in standard tests

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Highlights

- **ESES pattern and language impairment can be seen together in SFEC.**
- **Patients with ESES produced fewer complex sentences than those without ESES.**
- **Subclinical language disorders can be detected by narrative analysis.**
- **The prevalence of polytherapy is higher in patients with ESES.**
- **The production of fewer complex sentences in ESES is not related to the number of AEDs.**

(10). In this study, we aimed to investigate the impact of ESES on language disorder in SFEC patients.

METHODS

Participants and Clinical Information

In this study, 28 right-handed children with SFEC (mean age ± standard deviation, 10.4±1.9) without mental and motor developmental impairment and 32 age-gender matched right-handed healthy children (10.7±1.9 year-old) with normal EEG results obtained either asleep or awake were included. Ethical conformation and written consent were obtained from parents. While 19 of the epileptic children had RE (10.7±1.9 year-old), 9 of them had received the diagnosis of G-ICOE (9.9±2.0 year-old) as per relevant criteria of ILAE (2). Cranial imaging was normal in all patients, there were no additional systemic, psychiatric, or neurologic diseases other than epilepsy and no drug use other than anti-epileptic drugs (AED). Family education and monthly income levels of healthy and epileptic children were similar. Demographic and clinical data collected from epileptic cases were gender, age, type of epilepsy, age of epilepsy onset, disease duration (years), follow-up duration (months), the annual frequency of seizures, number of AEDs, and history of febrile convulsions. Parents were interviewed regarding their children's school grades in language and mathematics classes and level of success in school. Failure in school was defined as exhibiting more than 1 standard deviation in grades or repeating a class. Asleep and awake EEG examinations were performed in all patients within the week before the administration of language tests. The cases were divided into 2 groups according to their EEG findings:

1) Non-ESES (n=22): In this group, normal or unilateral/bilateral focal epileptic activities were detected in the EEG obtained within 1 week before the language assessment, and ESES was not observed in any EEGs performed during the patient follow-up, including the last EEG.

2) Active ESES (A-ESES, n=6): In this group, continuous spike slow wave activities were observed in >85% of the non-REM period, but focal epileptic activities were not detected in the EEG obtained within 1 week before language assessment.

Language Assessment

Test of Language Development-Primary-Fourth Edition: Turkish Version (TOLD-P: 4 Turkish) is used to determine the verbal language level of school-age children . It contains six main subtests: picture vocabulary, relational vocabulary, oral vocabulary, sentence comprehension, sentence imitation and morphological completion. Turkish Non-word Repetition Test (TNRT) has 16 words each with 2, 3, 4 or 5 syllables. Because Turkish is an agglutinating language, the impact of derivational and inflectional suffixes on repetition performance is examined through language-like and language-unlike words (11). In order to evaluate the language comprehensively, narrative examples were obtained in addition to the standard language test of TNRT. The Multilingual Assessment Instrument for Narratives which is used to analyze children's narration skills was adapted to Turkish as LITMUS-MAIN-TR (12). It has four parallel stories, which consist of two models and two main stories. In this study, after listening a model story, participants answered comprehension questions about the story and told the main story by looking at pictures. Then participants answered the main story's comprehension questions. Macro-structures and narrative examples were analyzed after transcription of the stories and the story structure (plot, settings, protagonist's goals[G], attempts [A] and outcomes [O]), story complexity (number of total GAOs) scores, and number of terms describing internal state (words like *know, feel, see, hear, hungry, happy,* etc.[IST]) were determined. For micro-structures, mean length of utterances (MLU), number of total words, type-token ratio (TTR), number of different nouns, verbs, adjectives, adverbs, conjunctions, complex sentences (sentences with at least 1 subordinate clauses) and mazes (gap fillers, repetitions, revisions) were counted.

Statistical Analysis

The normality of distribution was assessed by Shapiro-Wilk's and Kolmogorov-Smirnov's tests (p>0.05). Since most of the groups did not have a normal distribution, a non-parametric Mann-Whitney U test was used to determine significant differences between the two groups. The non-parametric Kruskal-Wallis test was used in triple group comparisons and Dunn's test was used for post-hoc analysis. Categorical variables were compared with the chi-square test. Correlation studies were conducted with Spearman's correlation test. A p-value less than 0.05 was considered a significant difference.

RESULTS

Clinical and Demographic Characteristics of Epilepsy Cases

There was no difference between the A-ESES and non-ESES groups in terms of gender, age, epilepsy type, duration of illness, age of epilepsy onset, follow-up duration, the annual number of seizures, history of febrile convulsions, and failure in school. However, the A-ESES group showed a higher number of female patients and G-ICOE patients than the non-ESES group. Prevalence of polytherapy was significantly higher in A-ESES patients, and congruently, A-ESES patients were using a significantly higher number of AEDs than non-ESES patients (Table 1). Moreover, A-ESES and non-ESES groups showed a comparable distribution of anti-epileptic medications (Table 2).

Comparison of Language Parameters Between Study Groups

While verbal language level, TNRT, model story comprehension, main story comprehension, story complexity, story structure, terms describing internal state, MLU, number of complex sentences, and maze parameters were significantly lower in both A-ESES and non-ESES groups compared to healthy controls, there was no difference between the groups in terms of number of total words, TTR, nouns, verbs, adjectives, adverbs, and conjunctions. The only parameter that was significantly different between the A-ESES and non-ESES groups was the number of complex sentences in favor of non-ESES patients (*p*=0.001 by Kruskal-Wallis). Additionally, A-ESES patients also showed trends toward exhibiting reduced story complexity and producing fewer words, nouns, verbs, and adverbs than non-ESES patients during narrative analysis (Table 3).

The Effect of Demographic and Clinical Variables on Complex Sentence Production

The potential The potential impact on complex sentence production of demographic and clinical variables that showed a significant or near-significant trend between A-ESES and non-ESES groups was investigated.

Table 1. Comparison of clinical features between epileptic children with and without ESES

	A- ESES (n=6)	Non-ESES (n=22)	p value
Gender	5F/1M	8F/14M	0.113
Age	11.1±2.7	11.1±2.4	0.496
Type of epilepsy	2RE/4 G-ICOE	17RE/5 G-ICOE	0.121
Age of epilepsy onset	6.9±1.8	7.9±2.1	0.100
Disease duration (years)	4.2±1.5	3.2±2.2	0.111
Follow-up duration (months)	41.4±18.3	32.7±18.9	0.119
Annual number of seizures	5.3±7.9	3.7±9.6	0.317
Number of AEDs	1.8±0.8	1.0±0.5	0.030
Patients with polytherapy	4	2	0.013
History of febrile convulsions	0	5	0.492
School failure	6/6	16/22	0.378

AED: antiepileptic drug; F: female; G-ICOE: Gastaut type occipital paroxysmal childhood epilepsy; M: male; RE: Rolandic epilepsy;

Table 2. Anti-epileptic drug types used by patients during the language tests

		A-ESES (n=6)	Non-ESES (n=22)	p value
Monotherapy (n=22)	VPA	1	9	0.537
	CBZ	1	5	0.748
	LEV	0	3	0.831
	LMT	0	2	0.443
	TPM	0	1	0.595
Polytherapy (n=6)	VPA+LEV	1	1	0.898
	VPA+LMT	1	0	0.478
	CBZ+LEV	1	1	0.898
	VPA+LEV+CLB	1	0	0.478

CBZ: carbamazepine; CLB: clobazam; LEV: levetiracetam; LMT: lamotrigine; TPM: topiramate; VPA: valproic acid.

There was no significant difference among patients under polytherapy (4.3±2.0) and monotherapy (4.8±3.4) in terms of complex sentence production (p=0.307) or any of the investigated language parameters (not shown). Also, there was no significant correlation between the number of AEDs and the number of complex sentences produced during narrative analysis (p=0.294, R=0.191). Since carbamazepine and valproate were the drugs most commonly used in the entire SFEC cohort, children using these drugs were compared in terms of the number of complex sentences. No difference was found between the carbamazepine (n=6, 3.8±2.9) and the valproate group (n=10, 5.6±4.0) in terms of complex sentence production (p=0.126). Likewise, there were no significant differences among carbamazepine and valproate users in terms of other language parameters (not shown). Since the numbers of cases of the other drug groups specified in Table 2 varied between 1 and 3, the necessary statistical power could not be obtained to make comparisons between these antiepileptic groups. Due to the relatively high number of female cases and G-ICOE cases in the A-ESES group, we wondered whether complex sentence production could have been affected by these variables. In epileptic cases, no significant difference was found (p=0.476) by means of complex sentence production between female (4.8±4.3) and male (4.9±2.8) patients. Likewise, as determined in our previous study (10), there was no difference in complex sentence production among RE (5.2±3.8) and G-ICOE cases (4.6±2.1) (p=0.983).

DISCUSSION

In our previous study, we found that language impairment in epilepsy is not limited to severe and generalized epilepsy and can also be seen in patients with SFEC, a relatively benign and treatment-responsive form of epilepsy. Furthermore, we have previously shown that language impairment is not associated with any clinical factors of epilepsy (e.g. seizure frequency and epileptic activity on EEG) (10). In this study, we examined the effect of having SFEC and ESES on morphosyntactic and pragmatic components of language. The SFEC group was specifically selected since the previous ESES-language associations have been studied in epilepsy syndromes (e.g. LKS), with a relatively more severe disease course. Similar to the previous study, we showed that the SFEC group had significantly impaired language functions regardless of the presence of ESES (10). In the current study, patients with ESES produced fewer complex sentences than the non-ESES group. No significant differences were found between SFEC patients with and without ESES in terms of other language parameters. However, several additional parameters of the narrative analysis were relatively lower in the A-ESES group, indicating an overall impairment in the language domain.

In children who perform in the average range, language impairment may be masked only when standard language tests such as TNRT are administered. By using narrative examples, the semantic-pragmatic components of the language that are not reflected in standardized measurements can be more precisely evaluated (12). By analyzing narrative examples, the linguistic skills of children from different ethnic and cultural backgrounds can be elucidated without putting them into standard molds. In this way, the narrative is used both to reveal the nature and limits of language impairment and to plan and implement intervention tools for language impairment (13). The gradual increase of sentence length and syntactic complexity in written and oral expression is accepted as an important indicator of syntactic development in school age children, adolescents and young adults. Complex thought is required

Table 3. Comparisons of language parameters between A-ESES patients (n=6), non-ESES patients (n=22) and healthy controls (n=32)

	Group	Mean ± SD	p (Kruskal-Wallis)	Significant post-hoc comparisons (p<0.05)
Verbal language level	A-ESES (1)	90.33±12.93	0.001	1–3 2–3
	non-ESES (2)	85.04±17.45		
	Healthy (3)	107.94±13.43		
TNRT	A-ESES (1)	6.17±2.64	0.001	1–3 2–3
	non-ESES (2)	6.83±2.57		
	Healthy (3)	12.35±2.27		
Comprehension (model story)	A-ESES (1)	8.33±1.21	0.008	1–3 2–3
	non-ESES (2)	8.43±1.44		
	Healthy (3)	9.32±0.94		
Comprehension (main story)	A-ESES (1)	8.00±0.63	0.014	1–3 2–3
	non-ESES (2)	7.48±1.86		
	Healthy (3)	8.81±1.54		
Story complexity	A-ESES (1)	3.67±1.51	0.002	1–3 2–3
	non-ESES (2)	5.13±3.24		
	Healthy (3)	7.29±1.81		
Story structure	A-ESES (1)	8.33±0.82	0.001	1–3 2–3
	non-ESES (2)	8.52±2.64		
	Healthy (3)	11.61±1.82		
IST	A-ESES (1)	4.33±3.56	0.001	1–3 2–3
	non-ESES (2)	3.96±1.94		
	Healthy (3)	7.10±1.58		
MLU	A-ESES (1)	8.29±1.89	0.001	1–3 2–3
	non-ESES (2)	8.41±2.29		
	Healthy (3)	10.51±2.07		
Number of total words	A-ESES (1)	61.33±17.56	0.413	None
	non-ESES (2)	74.54±26.26		
	Healthy (3)	76.68±28.09		
TTR	A-ESES (1)	0.59±0.07	0.560	None
	non-ESES (2)	0.56±0.07		
	Healthy (3)	0.57±0.09		
Nouns	A-ESES (1)	8.17±1.17	0.275	None
	non-ESES (2)	9.57±2.64		
	Healthy (3)	10.13±3.26		
Verbs	A-ESES (1)	13.67±4.08	0.193	None
	non-ESES (2)	16.26±4.87		
	Healthy (3)	14.42±3.74		
Adjectives	A-ESES (1)	2.17±0.75	0.418	None
	non-ESES (2)	2.91±1.68		
	Healthy (3)	2.90±1.33		
Adverbs	A-ESES (1)	0.50±0.55	0.190	None
	non-ESES (2)	1.22±1.04		
	Healthy (3)	1.74±2.13		
Conjunctions	A-ESES (1)	4.83±3.25	0.627	None
	non-ESES (2)	6.91±4.88		
	Healthy (3)	6.39±3.68		
Number of complex sentences	A-ESES (1)	3.67±2.66	0.001	1–3 2–3 1–2
	non-ESES (2)	5.22±3.63		
	Healthy (3)	6.58±2.36		
Maze	A-ESES (1)	13.17±14.62	0.001	1–3 2–3
	non-ESES (2)	9.30±7.68		
	Healthy (3)	2.29±1.83		

IST: internal state terms; MLU: mean length of utterance; TNRT: Turkish non-word repetition test; TTR: type token ratio.

to achieve grammatical complexity in speech production. Complex syntax is critical for the development of storytelling skills that are logically sequenced and structured in a consistent and coherent way (14). The complexity of a narrative is determined by the integration of the main sentence components into the subordinate clauses and the number of these clauses. Cognitive stimulation, external world information and abstract thinking are considered as factors affecting the development of complex syntax. In healthy children, as they transition from adolescence to adulthood, more and more nominalizations are used and the rate of production of subordinate and dependent clauses increases. This increase in the insertion of dependent sentences into independent sentences is considered a result of the maturation of the language. In this context, while complex sentence production points to a high level of syntactic development, the abundance of connected and simple sentence productions can be interpreted as proof of syntactic immaturity. The correlation between age and complex syntax is indexed to general linguistic development (14).

The increase in the number of clauses connected to a main clause while generating a complex syntax requires the ability to keep all the components of a sentence in mind during the production effort, and increases the cognitive processing load. Therefore, working memory capacity plays a fundamental role in determining the management of the operation of complex syntactic units (15). Working memory capacity and complex syntax production have a predictive effect on school success. (16). Subordinate structures used in narration are created with adverbial, adjective, relative and noun clauses. Some subordinate structures also have pragmatic contributions to the content of a narrative. For example, adverbial clauses are used for sequencing, time, cause-effect and comparison purposes. The relationship between the use of subordinate and 'Theory of Mind' performance has been discussed in various studies (17). Therefore, complex syntax generation during narration can be considered a global executive function, which requires morphosyntactic and pragmatic skills and includes affective cognitive dimensions (18).

Turkish is an agglutinative language with a rich morphology in terms of derivational and inflectional suffixes. In agglutinative languages, dependent morphemes have the capacity to change the class to which the word is added. In Turkish, dependent morphemes are added to independent morphemes in a certain and hierarchical order, and the rules of addition are extremely strict (19). In order to obtain morphosyntactically complex sentences with subordinate clauses in Turkish, various suffixes must be added to the verb root, nominalizing the verb. While forming complex sentences, Turkish infinitives include adjective-verbs and gerunds that contain verb roots and do not receive tense suffixes and pronouns. Instead, it is necessary to add different suffixes to the verb root to produce relative, adverbial and noun clauses. After these suffixes are added, changes (phonological harmony) are made in certain phonemes, taking into account the vowel and consonant harmony. A sentence can contain multiple judgments, so it requires the use of a larger number of verbals. These computational operations that necessarily occur when creating a complex sentence in Turkish increase the working memory load (20).

Non-word repetition tests, which aim to measure phonological working memory performance, are one of the tools used to determine specific language impairments in childhood and adolescence (21). Performance in these tests, which consist of non-words that resemble a language and those that do not resemble a language are related to the level of phonetic and phonological development of the child, the capacity of preserving phonotactic representations and phonological traces in the phonological working memory, sustaining attention, and lexical knowledge (22). Although there is no difference by means of TNRT performance between the A-ESES and non-ESES groups, the low complex syntax production of the A-ESES group seems to support the language-specific involvement in this subgroup. Structural and functional differences were also observed in areas related to linguistic processing in imaging studies of children with SFEC. It has been suggested that the language functions of children with RE are localized to the bilateral or right hemisphere instead of the left hemisphere, and this difference develops in an effort to compensate for cognitive linguistic difficulties (23). Although the language and intelligence test scores of the patients with RE with a high frequency of ESES are low, this finding is not related to clinical variables such as age, disease onset age, duration of illness, duration of education and total number of seizures. In cases of RE accompanied by ESES, brain activity in intrinsically connected networks such as central executive network and salience network differed from RE without ESES (24). Syntactic comprehension and production in healthy individuals is the function of a large linguistic network including the domains such as inferior and medial frontal gyrus in the left hemisphere, superior parietal lobule, left anterior temporal pole, right basal ganglia, left angular gyrus, and bilateral precuneus (25). However, imaging studies have shown increased activation of many regions in the right hemisphere during phonological perception, derivational suffix use, speech production, and processing of abstract words (26). When all findings are assessed together, it appears that a large part of the left and right hemisphere, and specific subcortical structures are involved in linguistic processing. The precise language-related brain regions affected by ESES need to be further investigated with advanced methods. Likewise, whether ESES directly causes linguistic/cognitive dysfunction or both ESES and intellectual impairment are merely different manifestations of a shared epilepsy-induced brain dysfunction needs to be further scrutinized.

Although AEDs and polytherapy have often been accused of negatively affecting linguistic-cognitive functions (27,28), there are only a limited number of studies examining the impact of pharmacological agents on linguistic functions, in detail. Valproate has been shown to induce adverse effects particularly on language and cognition (29). However, in our cohort, there were no differences between patients taking valproate and carbamazepine, which means that valproate at the dosages used in SFEC patients did not have an exceptionally high adverse effect on language. Treatment with multiple AEDs rather than any individual anti-epileptic may be more closely associated with language/cognition impairment (30). A notable feature of the A-ESES group was that it included more patients using polytherapy, suggesting that disruption in the production of complex sentences might have been due to the use of multiple AEDs rather than ESES. In our previous study, we showed that there was no relationship between the number and type of seizures, types of treatment, treatment resistance and the language impairment in SFEC (10). Similarly, in this study, we showed that the effect of ESES on complex sentence production did not depend on the number of AEDs and once again demonstrated that clinical and treatment characteristics of epilepsy do not play an important role in language dysfunction in SFEC.

An important limitation of our study is the small sample size due to the rarity of ESES in the SFEC population. In this respect, our study is preliminary. Studies with more participants should be planned to understand the effects of polypharmacy on language in SFEC patients with and without ESES. Another technical limitation is that the verbs in complex sentences are not counted individually. Since a complex sentence may contain more than one verb, this should be addressed in more detail in future studies.

Conclusion

We were able to determine, through the use of narrative tools of descriptive analysis, that complex grammar production could be adversely influenced when SFEC is accompanied with ESES. Thus, a notable result of our study is that objective measurement tools of language are not sufficient alone to diagnose language impairment in epileptic children. Although profound intellectual impairment is not necessarily a common associate of ESES, failure in school is frequently observed in patients with ESES, as recognized in our cohort. Therefore, this electrophysiological phenomenon may be the cause or harbinger of relatively subtle changes in the functioning of the brain, which lead to reduced capacity of working memory, mild linguistic/cognitive impairment and subsequent school failure in epileptic children.

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