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A different look on the importance of lateralization and localization of figure 4 symptoms in epilepsy

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Abstract

Background : Clinical seizure semiology provides valuable information in the evaluation of focal-onset bilateral tonic–clonic seizures. In the evaluation of these patients, long-term video-EEG monitoring (VEM) and neuroimaging studies are of great significance in determining lateralization together with clinical semiology. In this study, we examined the features of the figure 4 sign that we detected in patients with refractory epilepsy whom we followed up in the VEM unit.

Methods: In the study, 175 patients followed in the VEM unit were examined. Twenty-two patients for whom the figure 4 sign was detected were included in the study. Patients with the side indicated by the figure 4 sign comply with ictal EEG compatible were named as 1st group (G1), and those not were named as 2nd group (G2). Demographic characteristics, seizure type, number of seizures per month, duration of epilepsy, number of seizures during VEM, duration of figure 4 sign, medical history, and cranial MRI characteristics were compared between the two groups.

Results: When G1 and G2 were compared, it was observed that temporal lobe seizures were statistically significantly higher in G1. When the figure 4 sign durations were examined, this period was 16.3 ± 8.2 s in frontal lobe seizures and 20.8 ± 7.4 s in temporal lobe seizures. When the duration of the figure 4 sign was examined by gender, it was found that the duration was longer in males, which was statistically significant.

Conclusion: In conclusion, it is essential to evaluate ictal EEG findings together with brain imaging while performing semiological localization and lateralization in epileptic patients.

Keywords: Asymmetric limb posturing, Figure 4 sign, Epilepsy, Semiology, Video-EEG monitoring

Background

Clinical seizure semiology provides valuable information in the evaluation of focal-onset bilateral tonic–clonic seizures. In the assessment of these patients for epilepsy surgery, long-term video-EEG monitoring (VEM) and neuroimaging studies are of great significance in determining lateralization together with clinical semiology. However, reliable lateralizing semiological signs have great importance for the correct identification of the symptomatic zone [1].

Various studies have been conducted on the lateralization and localization value of symptoms such as unilateral tonic or dystonic posture, hand automatisms, genital automatisms, figure 4 sign, versive or non-versive head rotation, unilateral mouth deviation, ictal spitting in patients with focal epilepsy. In temporal lobe seizures, the combination of versive head rotation, unilateral dystonic limb posture, asymmetric tonic limb posture, and unilateral hand automatisms and dystonic posture have been reported as semiological features with high lateralization significance [2].

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In extratemporal lobe seizures, there are more semiological features with lateralization value in frontal lobe seizures. One of them is the figure 4 sign. During the transformation of focal-onset seizures into bilateral tonic–clonic seizures, the tonic extension movement of one upper extremity and the approach of the other upper extremity to the flexion posture in a way that wants to catch the extended arm is known as the figure 4 sign or asymmetric tonic limb posture [3]. According to this finding, which was first described by Bleasel and colleagues, the contralateral of the arm in the extension posture shows the hemisphere where the seizure begins [4].

Various studies examined the semiological findings with high lateralization value in temporal and extratemporal lobe seizures. However, few studies have examined the figure 4 sign. Therefore, we wanted to contribute to science by conducting clinical and electroencephalographic examinations of patients for whom the figure 4 sign was observed in the video-EEG monitoring unit in our clinic.

Methods

The data of 175 patients between the ages of 18 and 55 hospitalized at the Ufuk University Faculty of Medicine VEM Unit between 2016 and 2020 with a pre-diagnosis of resistant epilepsy were retrospectively analyzed. The patients underwent continuous VEM recording using 32-channel digital video-EEG systems (Nicolet v32, Natus Neurology Incorporated, Middleton, WI, USA). Twenty-two patients for whom the figure 4 sign was observed were included in the study. The duration of the figure 4 sign was noted. One hundred and sixteen seizures of these 22 patients were followed up by two researchers experienced in epilepsy and EEG for possible additional lateralizing semiological findings. While recording lateralizing semiological findings, attention was paid to keeping the patient's face, body, and all extremities in the field of vision. The semiological findings of the patients that were not at an angle that the camera could see clearly were not included in the evaluation. (For example, in the patient with the last clonic jerk in the right arm, attention was paid to ensure that the right arm was in the full field of view on the camera. If part of the extremity was not visible, this finding was not considered to be present.) The patients' sociodemographic information, seizure type, number of monthly seizures, epilepsy duration, number of seizures observed during VEM hospitalization, medical history and family history characteristics, neurological examination findings from patient files, and brain imaging findings were examined and recorded from the hospital imaging system or patient file. The seizure videos recorded during the hospitalization of the patients in the VEM unit were watched, and the features of the figure 4 sign (which arm is in extension), and other accompanying semiological features, if any, were also determined. Then, ictal and interictal EEG findings were examined. The patients with the same starting side in the ictal EEG as the side pointed by figure-4 were named as the 1st group, and the patients with a different starting side in the ictal EEG with the side pointed by the figure-4 were named as the 2nd group. Demographic characteristics, seizure type, number of seizures per month, duration of epilepsy, number of seizures during VEM, duration of figure 4 sign, medical history, and cranial MRI characteristics were compared between the two groups. The study was approved by the local ethics committee and was accordant with the ethical standards of the Declaration of Helsinki.

Statistical Package for Social Sciences (SPSS) for Windows, version 22.0 (IBM Corporation, Armonk, NY, USA) program performed the statistical analysis in our study. Pearson's Chi-square and Fisher exact tests were used in nominal cross tables, test of Kolmogorov–Smirnov in the distribution quantitative data, and Levene's test in homogeneity test. Student's T was performed to compare binary-scale parametric data, and Mann–Whitney U test was used for nonparametric data. One-way ANOVA test compared scaled parametric data of three or more groups, and Bonferroni test was performed for parameters found to be significant. $p < 0.05$ was considered statistically significant.

Results

Of the 22 patients included in the study, 14 were male, and 8 were female. Of these 22 patients with figure 4 sign, 10 were temporal lobe epilepsy (7 male, 3 female), 6 were frontal lobe epilepsy (3 male, 3 female), and 6 were other epilepsy types (1 parietal, three frontotemporal, two hemispheric). As known, the contralateral of the arm in extension in the figure 4 sign shows the initial localization of the seizure. When evaluated based on this information, 12 patients (Group 1-G1) showed a correlation between the side indicated by figure 4 and the baseline in the ictal EEG in our study, while there were ten patients (Group 2-G2) who did not show correlation. When G1 and G2 were compared, it was observed that temporal lobe seizures were statistically significantly higher in G1 (p: 0.047) (Table 1).

In G2, it was observed that the number of focal-onset seizures, whose seizure onset region could not be differentiated, was higher. When G1 and G2 were compared in terms of gender, medical history, and brain MRI features, no statistically significant difference was found (Table 2).

However, the number of febrile convulsion histories was higher in G1. Although no significant difference was found between the two groups in terms of MRI features,

Table 1 Comparison of the epileptic region of G1 and G2

	Epileptic zone			Total	*p* value
	Frontal	Temporal	Others		
G1	3	8	1	12	
G2	3	2	5	10	**0.047**
Total	6	10	6	22	

*G1: Group 1, G2: Group 2

Table 2 Comparison of the of gender, medical history, dominant hand and brain MRI features of G1 and G2

	Group 1 (*n*: 12)	Group 2 (*n*: 10)	*p* value
Medical history			
Normal	2	4	0.385
Febrile convulsion	6	2	
Difficult birth	2	3	
Head injury	2	1	
Brain MRI			
Normal	2	5	0.343
Mesial temporal sclerosis	4	1	
Encephalomalacia	3	2	
Other	3	2	
Dominant hand			
Right	11	9	0.892
Left	1	1	
Gender			
Female	4	4	0.746
Male	8	6	

it was observed that the number of mesial temporal sclerosis was higher in G1. When G1 and G2 patients were evaluated in terms of whether they had epilepsy surgery or not, there was no statistically significant difference, but three patients were operated on in G1 and zero in G2. When G1 and G2 were compared in terms of age, the number of monthly seizures, duration of epilepsy, and the number of seizures in VEM, no significant difference was found between the two groups (Table 3).

When the figure 4 sign durations were examined, this period was 16.3 ± 8.2 s in frontal lobe seizures and 20.8 ± 7.4 s in temporal lobe seizures, and there was no statistically significant difference (*p*: 0.41). No significant difference was found between G1 and G2 when the duration of the figure 4 sign was compared. When the duration of the figure 4 sign was examined by gender, it was found that the duration was longer in males, and this was statistically significant (*p*: 0.008) (Table 4).

When G1 and G2 were evaluated in terms of additional semiological features, we observed that in 5 patients in G1, versive head deviation contributed to lateralization. 4 of these patients had TLE and 1 had frontal lobe epilepsy. In the patient with frontal lobe epilepsy, it was observed that additional vocalization accompanied the figure 4 sign and versive head deviation. While the figure 4 sign was observed in the 2nd seizure of one of the patients with versive head deviation was observed in seizures. In this patient, the figure 4 sign and the forced head deviation were lateralized to the same side. While figure 4 sign and versive head deviation were observed in the first three seizures in one of the patients with TLE, genital automatism was observed in the 4th seizure of the patient. All these semiological findings in this patient

Table 3 Comparison of the age, number of monthly seizures, duration of epilepsy, and the number of seizures in VEM of G1 and G2

	Number of patients (%)		*p* value
	Group 1 (12 Patients %54)	Group 2 (10 Patients %46)	
Age, year, mean ± SD, range	32.75 ± 9.56 (19–55)	35.80 ± 13.35 (21–55)	0.54†
Number of monthly seizures, mean ± SD, range	7.67 ± 8.27 (1–30)	12.8 ± 12.43 (1–30)	0.26†
Duration of epilepsy, year, mean ± SD, range	22.08 ± 9.7 (1–34)	25 ± 11.89 (9–43)	0.53†
Number of seizures in VEM, median ± SD, range	3.92 ± 2.15 3 (2–10)	6.9 ± 9.37 2.5 (1–30)	0.381‡

**SD* standard deviation †Student's *T* test ‡Mann–Whitney *U* test

Table 4 Comparison of figure 4 sign duration by gender

	Female (*N*: 8)	Male (*N*: 14)	*p* value
Figure 4 sign duration (second) mean ± SD, range	14.0 ± 7.3 (6–27)	23.71 ± 7.6 (10–40)	**0.008**

pointed to the right hemisphere. While the figure 4 sign indicated the right hemisphere in all four patients, the last clonic jerk finding observed in the same seizure supported that the epileptogenic focus was on the right.

Discussion

Video-EEG monitoring is the most vital tool used to detect epileptogenic zones. In addition to allowing the examination of the ictal EEGs of the patients, it also helps to determine the lateralizing and localizing features by providing the advantage of examining the seizure semiologies in detail. Although it is known that the figure 4 sign also has a lateralization significance, there are few studies regarding this subject. A study conducted by examining 149 secondary generalized tonic–clonic seizures of 80 patients showed that the epileptogenic focus was contralateral in 96.7% of the cases [100% in extratemporal lobe epilepsy (ETLE), 94.8% in temporal lobe epilepsy (TLE)] with a figure 4 sign [3]. In the same study, the rate of performing correct lateralization with this finding alone was found to be 58.4%. Bleasel et al., who defined the figure 4 sign for the first time, found the rate of showing a contralateral relationship with the seizure focus as 90.9% in TLE and 87.5% in ETLE. Besides, they claimed in their study that although the figure 4 sign is less common than the versive head deviation, the rate of correct lateralization is higher [4]. In another study conducted, it was reported that the figure 4 sign has a high lateralizing significance of 90% in the contralateral hemisphere. This study also stated that the figure 4 sign occurred at the beginning of the tonic phase of the secondary generalized tonic–clonic seizure. However, the authors emphasized that in some seizures, the extension may occur first in one arm and then in the other arm and that the figure 4 sign can be seen on different sides consecutively. This may lead to confusion in detecting the epileptogenic zone. In the article, it is recommended to consider the figure 4 sign that first appears during the seizure. Besides, it is recommended that patients with generalized seizures should be carefully examined for the figure 4 sign, in case TLE and primary generalized epilepsies rarely coexist [1].

Considering the duration of figure 4 in TLE and ETLE patients, it was observed that the duration was longer in ETLE patients, although there was no statistically significant difference in the study conducted by Kotagal and colleagues [1]. In our study, when the duration of the figure 4 sign was examined according to frontal, temporal, and other lobe seizures, no statistically significant difference was found. However, when the duration was examined by gender in our study, it was found that the figure 4 sign lasted longer in the male gender, and this was statistically significant.

It is known that the figure 4 sign typically occurs in supplementary motor area (SMA) seizures and can also be created by electrical stimulation of SMA. In ictal SPECT studies conducted, it was shown that there is hyperperfusion in the primary and supplementary motor areas and basal ganglia in frontal lobe seizures [5–7]. However, we know that frontal lobe seizures spread very rapidly, and sometimes the scalp VEM cannot provide enough information for clear epileptogenic focus detection. In this case, invasive VEM and SPECT may be more guiding.

In a study published in 2016, ictal motor signs observed in 236 patients with focal-onset secondary generalized tonic–clonic seizures were examined, and a positive predictive value was calculated for each motor sign. Unilateral tonic posture, versive head deviation, M2e posture, unilateral clonic seizure, asymmetric end clonic jerk, Todd's paralysis were determined as reliable motor signs with a positive predictive value of more than 80% and strong lateralizing significance. Since figure 4 sign (PPD: 74%) and hand dystonia (PPD: 67%) have a positive predictive value below 80%, they were not included among the reliable motor signs with strong lateralizing value [8].

As in figure 4, the versive head deviation, unilateral tonic posture, Todd's paresis, focal clonic jerks in the upper extremity also indicate the contralateral focus [2, 8, 9]. In particular, the figure 4 sign can occur with or after the versive head and eye deviation, and it is usually on the same side. The version occurring 10 s before motor generalization indicates a contralateral hemisphere more than 90%. Combining two or more of the classical motor signs almost completely lateralizes the epileptic zone [8]. In our study, in 5 patients for whom figure 4 sign was observed, a versive head deviation was also observed and contributed to the detection of lateralization. In our study, these patients who had both figure 4 signs and versive head deviation were temporal lobe epilepsy, and two of them underwent surgery for mesial temporal sclerosis after VEM hospitalization. In our study, while a figure 4 sign was observed in some seizures of the patients, it was observed that there was a versive head deviation in some seizures. This finding reveals that the more seizures we see in the VEM unit, the more accurate it will be to determine the epileptogenic focus. It may be more instructive to evaluate the patient not according to a single seizure but according to the semiological characteristics of all seizures observed in VEM and to perform lateralization accordingly. A study published in 2020 reported that patients in VEM had their first seizure on an average of the 5th day [10]. In another study, it was emphasized that patients with resistant epilepsy should stay in the VEM unit for at least 72 h [11]. However, these studies did not address the issue of how many seizures of patients should

be recorded during VEM. We think that studies on this subject are also needed.

The M2e posture were defined as a tonic movement or lifting one arm in 1957 by Ajmone Marsan [12]. This posture starts with the flexion of the elbow and continues with the abduction and external rotation of the shoulder. The hand can be in a punch position or open. It is emphasized that the other arm should be free during this posture but should participate in the tonic activity that will develop later. Also, it was reported that versive head deviation might be seen before, simultaneously, or after this posture. The M2e posture occurs contralateral to the epileptogenic focus. In the study conducted by Ajmone Marsan and Marasly and colleagues in 2016, it is claimed that there is a strong lateralization significance indicating the contralateral hemisphere [8–12]. In another study conducted, it was reported that the figure 4 posture might occur following the M2e posture [1]. However, we did not evaluate the M2e posture in our study.

Studies conducted have shown that the asymmetric clonic jerk (last clonic jerk) has a specificity that lateralizes the epileptogenic region with the ipsilateral hemisphere at a rate of 83% [13, 14]. The last clonic jerk was also observed in our four patients in whom the figure 4 sign was observed, and both of them lateralized the same side for the epileptogenic focus. In a study examining the seizures of patients who remained seizure-free after focal surgical resection limited to the temporal, frontal, parietal, and occipital lobes, the positive predictive value of the lateralization finding of the last clonic jerk, which is ipsilateral, was found to be 86% [15].

Current studies show that lateralizing and localizing clinical semiological seizure features are of great significance in epileptogenic focus detection when evaluated together with ictal EEG and brain imaging methods. We think that the figure 4 sign is one of these critical clinical semiological features, and we think that more detailed investigations and studies with large populations are needed on this subject.

Our study has some limitations. These are the retrospective nature of the study, the small number of patients, the inclusion of patients whose epileptogenic focus is not identified, and the absence of invasive video-EEG.

Conclusions

In conclusion, the figure 4 sign is a significant ictal finding that can be used in the lateralization of seizures. However, monitoring together with a few ictal semiological findings increases the lateralization significance. What is essential is to make sure that a sufficient number of seizure features are examined while performing semiological localization and lateralization in epileptic patients and to evaluate the findings of ictal EEG together with brain imaging.

Abbreviations

VEM: Video-EEG monitoring; G1: 1st group; G2: 2nd group; SPSS: Statistical package for social sciences; TLE: Temporal lobe epilepsy; ETLE: Extratemporal lobe epilepsy; SMA: Supplementary motor area.

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Authors' contributions

Concept: GM and AL. Study design: GM, KI, AL. Data collection: GM and KI. Statistical analysis: GM. Literature overview: GM and KI. Discussion: GM and AL. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to current Ufuk University regulations, but are available from the corresponding author on reasonable request and after institutional approval.

Declarations

Ethical approval and consent to participate

This study was performed according to the Declaration of Helsinki and with the approval of our hospital's Ethics Committee. (Ufuk University Ethics Committee /15.04.2021/2021-04-04).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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