Vol 5 | Issue 2 | Pages 197-201

Journal of Pediatric Neurology and Neuroscience
ISSN: 2642-4797

Original Article

DOI: 10.36959/595/438

Focal Electrographic Hints in Epileptic Spasms

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Abstract

Objective: Epileptic spasms (ES) is an age specific seizure disorder which is more frequent in infancy. Frequent untreated epileptic events have negative effect on development in ES patients so early diagnosis and appropriate treatments are key factors in management to avoid neurodevelopmental delay in survivors.

Methods: we reviewed retrospectively all documents of twenty patients who were diagnosed as ES in Pediatric Epilepsy Monitoring Unit in a 3-years duration (2014 -2017). All previous medical documents were evaluated in details. Definition of ES was mentioned based on the latest International League against Epilepsy (ILAE) determination. All records were captured by EEG-Monitoring apparatus (NIHON KOHDEN, Neurofax, EEG-1200 Japan, 2014), using standard 10-20and different appropriate montages if needed. All records were reviewed by two qualified clinical neurophysiologists.

Results: Twenty children who suffered from ES were enrolled in the study. In 70% of cases Focal hints were detected. Focal interictal activity which was identified in 10 patients (50%) was the most frequent finding. Focal ictal transients in approximately half of the patients (9 patients: 45%) was detected as the second more prevalent feature. No correlation between focality and neuroimaging, semiologic features and age at onset was revealed.

Conclusion: Our study revealed that focal findings are more frequent than mentioned previously. The findings could be implemented in better management of ES patients in terms of diagnosis and early appropriate treatment.

Significance: Early focality detection has a great diagnostic value to imply advanced seizure control methods (epilepsy surgery).

Keywords

Epileptic spasm, Surface EEG, Focal hints

Introduction

Epilepsy is one of the most prevalent neurologic disorders [1] as more than 50 million people were affected around the world [1,2].

Epileptic spasm (ES), one of the most common and catastrophic epilepsy syndromes predominantly in infancy, is classified in focal, generalized and unknown onset groups [3].

The term of infantile spasms (IS) was suggested for the first time by International League Against Epilepsy (ILAE) workshop commission, 1991. ES is a widely accepted terminology instead of infantile spasms, to presenting a more

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Accepted: January 19, 2022

Published online: January 21, 2022

Citation: Mohammadi M, Badv RS, Yarali B, et al. (2022) Focal Electrographic Hints in Epileptic Spasms. J Pediatr Neurol Neurosci 5(2):197-201

comprehensive meaning [4,5]. Incidence of ES was reported as a range of 1.6-4.5 in 10,000 live births based on the region where the study performed [6-8].

Clinically, ES presents as a brief and sudden contraction which is followed by less severe tonic phase more prolonged than myoclonic jerks but shorter than tonic seizures. They can involve axial muscles such as neck and trunk as well as both lower and upper limbs. ES could present in flexor type, extensor or mixed type as well as symmetric versus asymmetric ones [9].

Several presumed causes are assumed as the underlying etiology in epileptic spasm such as metabolic, genetics, structural abnormalities as well as acquired events such as traumatic brain injury. However, in a great number of patients, no definite cause is found notwithstanding the routine workup [10,11]. On the other hand, a newer theory compatible with inflammatory basis is proposed based on proinflamatory cytokines and immune modulators found in cases otherwise no other causes found [12]. Indeed, there is some evidence in favor of the same cellular mechanism in both epileptic spasm and focal seizure [13].

ES is presumed as a devastating epileptic syndrome due to vigorous seizure progression, and development regression leading to poor neurodevelopmental outcome. It is widely accepted that early detection and prompt effective treatment play a crucial role in neurodevelopmental outcome [9].

It's widely accepted that the best method for accurate evaluation in diagnosis and even evaluation of treatment efficacy is video-EEG monitoring. It's well known that disappearance of abnormal EEG activity could lead to better clinical prognosis [3,14]. Video EEG monitoring is helpful to make sure that the event is epileptic otherwise frequent not-epileptic ones might easily be misdiagnosed as epileptic events [15]. EEG pattern could be used as a guild line for choosing both the therapeutic method and prediction of drug response [9].

Both medical and surgical methods play a principle role in the management of seizures. Beyond corticosteroids/ Adrenocorticotropic hormone (ACTH) and vigabatrin, ketogenic diet (KD) could be considered as a medical treatment option in highly selected groups to treat the spasm [16]. Curative surgery could lead to seizure freedom in 60-80% of cases. In cases that curative method could not be apply, a palliative approach might make a better quality of life due to attenuate the seizure frequency [17]. Surgery should be considered as an early therapeutic method in drug resistant epileptic spasm [15].

Historically it was accepted that infantile spasm was a generalized seizure and that focal electrical seizure discharges were only a coincidence that was supported by some surveys [17]. After several study, some evidence supported that epileptic spasm could be focal originally [2]. Seizure semiology makes a low field for both localization and Lateralization in ES. Indeed MRI could be used as a primary guidance although is not capable of detecting the exact epileptic zone as it is often beyond the lesion detected on MRI [15].

Here we reported the clinical and imaging findings of 20 epileptic spasm patients as well as surface video-EEG monitoring to detect any focal hints. The study focused on the point that early evaluation of focality in this devastating syndrome could lead to appropriate candidate selection for both curative and palliative epilepsy surgery.

Material and Methods

Patients and documents

All medical documents of ES patients referred to Pediatric Epilepsy Monitoring Unit in Children Medical Center in a 3-year duration (from May 2014 to May 2017) were reviewed respectively. The diagnosis of ES was made based on clinical observation or video clip during Video-EEG monitoring.

Neonates were excluded from the study. All previous medical documents such as history of perinatal events, previous medication, semiology of seizures (other seizure types besides ES), age at onset, current age during the study and brain MRI, were revised thoroughly.

Definition of ES was mentioned based on the latest International League against Epilepsy (ILAE) determination. We classified seizures based on features reported by parents and video monitoring as flexor, extensor and mixed type defined as both flexor and extensor type.

The spasms mentioned as symmetric if both sides of the body were involved at the same time in the beginning of the event. Asymmetric ES consisted of spasms involving only one side of the body or non-coincident bilateral involvement. Some important prenatal events such as need to resuscitation, meconium aspiration and respiratory distress leading to hospitalization have been noticed.

Video-EEG recording

All records were captured by EEG-Monitoring (NIHON KOHDEN, Neurofax, EEG-1200, Japan, 2014) using standard 10-20 system to electrode replacements method, but all epochs were reviewed by some more appropriate montages in order to achieve any focality such as pearled leads and paired group referential montages whenever needed. For instance, if there was any abnormal focality, in order to avoid phase cancelation phenomenon, the epoch's re- montaged in referential montage and reviewed again. In ictal event in addition to bipolar montage, referential ones were studied as well, especially Pz in sleep patients and CZ in awake children. We used 1 Hz filter as low frequency filter (LFF) and 70 Hz as high frequency filter (HFF). Extra-leads such as surface electromyography and electrocardiographic ones were placed. Notch filters and other filters were used whenever it was necessary.

All records were reviewed by at least two qualified clinical neurophysiologists. None of them knew nothing about history and clinical courses except the age and gender to avoid any possible bias in interpretation. They reviewed the records separately. If there was any disagreement in reports, they negotiated to make a general agreement. The case was excluded if no agreement was reached.

Several patterns were mentioned as focal. Glossary used to Explain focality in EEG records were described as below:

Asymmetry was defined as unequal amplitude, phase, frequency or morphology of EEG activity in channels over homologous areas of the two hemispheres in referential montages [18].

Asynchrony was mentioned when the non-coherent wanes occur of EEG activities over regions on the same or opposite hemisphere [18].

Focal interictal Epileptiform waves were described as any Epileptiform waves that occurred in interictal phase. Epileptiform pattern was defined according to the latest Glossary [18].

Focal ictal activity referred to any focal activity taking place in ictal phase.

Focal activity referred to any Epileptiform activity limited to a small area of the brain in one hemisphere [18].

Any focal polymorphic delta activity was considered as focality. Polymorphic activates imply any irregular EEG waves having multiple forms, which may also vary in frequency and amplitude. Delta waves defined as waves with duration of 250-2000 millisecond [18].

Data collection and statistical analysis

All data such as demographic, clinical, radiological and neurophysiologic, was collected and revised according to the study goals. All previous medical documents were reviewed and whenever it was necessary, patients and their family were recalled to make an appointment in order to achieve more additional data. All data (such as demographic, clinical, Paraclinical and neuroimaging information) was registered in SPSS (version 20) software and analyzed with appropriate statistical methods by a demographic specialist. Statistical tests such as Chi-Square 2, using number and percentage in order to determine qualitative variables as well as median and inter quartale percentile for description of quantitative variables, were performance to get final information.

Results

Twenty patients monitored in Long Term Monitoring Unit in a tertiary children hospital in Tehran, Iran. Eleven girls (55%) and nine boys (45%) were enrolled in the study who fulfilled criteria mentioned in methodology.

Most of the patients experienced the seizure in the age of 6-12 months of age (Table 1).

Median age at study was 15.5 months (Interquartile Range (IQR) 25 Percentile was 11.5 and 75 Percentile was 29.25 months).

All patients were monitored by video EEG monitoring in Epilepsy Monitoring Unit (EMU) where trained nurses were caring them entirely with the median 33 hours monitoring duration (Maximum 48 hours and minimum 24 hours).

In order to determine seizure semiology (based on caregivers comments / video reviewing), nine children (45%) presented only ES as seizure phenotype. Seven children (35%) were defined as ES in combination with focal seizure. Two patients (10%) had ES with generalized seizure. In one patient (5%) seizure could not to be classified.

Table 1: Distribution of age of onset in patients

Age at first seizure (month)	0-1	01-Jun	06-Dec	≥ 12
Percentage	10	25	50	15

Table 2: Neuroimaging findings.

Etiology	*IUI	**Abn.Mig	***TSC	****HIC	Unknown
Percentage	5	5	5	30	55

*IUI: Intra Uterine Infection; ** Abn.Mig: Abnormal migration anomalies; ***TSC: Tuberous Sclerosis Complex; ****HIC: Hypoxic Ischemic Changes,

Table 3: Prevalence of focality finding.

Focality Findings	Focal inter ictal activities	Focal ictal activity	*PDA	Asymmetry	Asynchrony
Percentage	50	45	15	15	10

*PDA: Poly morphic delta activity

The majority of cases (85%) suffered from generalized developmental delay (GDD). All patients have been evaluated by Magnetic Resonance Imaging (MRI). While in more than half of the cases no etiology found, the most common detected cause was hypoxic Ischemic changes (Table 2).

In more than two thirds of cases (70%) focality was detectable on surfaced EEG. Detailed data is summarized in Table 3.

No correlation between MRI findings and EEG focality. Asymmetry detected in EEG evaluation of two cases with normal brain MRI.

We found no correlation between EEG focality and presumed underlying etiology as well as semiology of ES (Flexor-extensor or mixed type ones).

Discussion

ES considered as a devastating epilepsy predominantly in infancy. ES supposed to be a generalized seizure at first, though more recent data supports a focal onset for ES [19,20].

Present survey, as the first one designed to focality in ES, evaluated 20 patients referred to a tertiary pediatric EEG monitoring center during a 3 year period (2014-2017). The results show that up to 70% of cases have focal hints when evaluated with surface EEG. Focal Inter-ictal discharges were the most common findings.

EEG is not only the method of diagnosis, but also a valuable predictor for response to treatment. Koichihara et.al evaluated 22 epileptic spasm patients during a 10 year period (2007-2017) whose EEG shows no hypsarryhtmia pattern. The results showed that early appropriate treatment leads to an acceptable seizure control. On the other hand, Adrenocorticotropic hormone (ACTH) was ineffective in patients with epileptic spasm without hypsarryhtmia [9].

Caraballo, et.al showed that half of 12 ES patients evaluated during 8 years had focal seizure clinically. The

most EEG Interictal patterns were focal hypsarrhythmia and background abnormality. On the other hand, high-amplitude slow waves recorded in half of the patients was the most common ictal finding [21].

Nariai and colleges studied 34 children with West syndrome during 2005 to 2014 by video-EEG monitoring and time frequency analysis. The results showed that gamma and beta waves detected in scalp EEG, could be considered as a helpful character for focality [22].

More than two decades ago, Donat, et al. evaluated asymmetric hypsarrhythmia in 24 infantile spasm patients (1987-1990). Unilateral hypsarrhythmia was detected in 37.5 % of patients. Lateralized hypsarrhythmia and symmetric ones in 54% and 8% respectively [23].

Haga et.al studied 37 patients with tonic spasms during 1978 to 1992. Focal spikes and multifocal spikes were the most common EEG findings [24].

Drury et.al evaluated 26 children with infantile spasm during 4 years. Asymmetric hypsarrhythmia was detected in 23 % of patients [25].

22 epileptic spasm children were evaluated by Honda et al. in a 7-year period (2006-2013). The results showed that positive slow waves originated predominantly from cortico-subcortico-cortical during motor components of spasms, indicate a high diagnostic value [6].

Whereas we report more than two-thirds (70%) focality in our study apply surface EEG, Focality could be detected as high as 90% if intracranial EEG would apply [26].

On the other hand, applying more advanced EEG such as high frequency oscillations (HFO), to detect ripple waves (80-200 Htz), showed that these waves as well as gamma loops and sensorimotor cortex could play a role in detecting the epileptogenic zone [27]. Limura, et al. during a 4 year period of time (2009-2013) evaluated 24 drug resistant children whose seizure diagnosed as epilepsy with multilobar onset by using invasive intra cranial video EEG monitoring (IVEEG). The results showed that ES patients had both more widespread and severe epileptogenesis in comparison with the patients with no ES. The study presented that using High-Frequency Oscillations (HFOs) is a useful method in the ES patients to detect ripple/fast ripples due to its high sampling rate capacity [27,28].

In cases that the epileptogenic zone (EZ) remains unclear, more invasive methods such as subdural grid electrodes or stereo electroencephaligram (SEEG) could make a higher spatial resolution than scalp EEG [27-29]. For example, De la Vaissière, et al. showed that in 10 of 11 children with drug resistant epileptic spasm, focal seizure origin were detected when they have been evaluated by intra cranial EEG [26].

MRI plays a fundamental role in finding the etiology. We evaluated all patients by MRI. Almost half of the cases studied presented with normal brain imaging (55%), though hypoxic changes were the most frequent radiologic findings in abnormal neuroimaging. Similar study found lesion in MRI in half of the cases [28]. On the other hand, Caraballo, et al. revealed that all evaluated patients had structural abnormalities in MRI [21].

MRI is not able to detect the lesion in all cases, so more advanced investigation such as positron emission tomography (PET) scan and Magnetoencephalography (MEG) need to be done [15,17,22,28].

Sakaguchi, et al. showed that using serial longitudinal MRI and even more sensitive methods such as Positron Emission Tomography (PET) scan until two years old, could result in detection of some subtle focal cortical dysplasia [30].

Less than half of our patients presented with an etiology based on using MRI. By considering the high consanguinity rate among families based on our community's cultural background, several metabolic and genetic disorders could be presumed as etiology that are detectable by appropriate metabolic screening and genetic tests. Although based on similar study, it is accepted that in about one fifth of cases, no etiology was found. Notably subtle focal cortical dysplasia and genetic disorders are presumed the main etiology in this group [18].

In this study we did no correlation among focality with etiology, imaging findings, seizure type and developmental status. Drury revealed relationship between EEG asymmetry and focal MRI findings [25]. Indeed Honda presented that there was no correlation between brain structural lesions and slow waves distribution in EEG [6].

We detected asymmetry in EEG of two cases with normal brain MRI. Several studies focused on superiority of EEG finding to detect focality against both neurologic examination and MRI [22,25].

Our study should be considered as primary step of a comprehensive approach. The ultimate goal is early detection of any probable focality in order to use advanced seizure control methods such as epilepsy surgery to prevent subsequent developmental regression. Some authors believe that not only drug resistant epileptic spasm [17], but also all focal onset ES should be evaluated for potential surgery benefit [15]. Data showed that by using a precise patient selection, the result of surgery could be compatible with other medical methods in control of drug resistant focal seizures [15,29,31]. An early surgery could lead to a better seizure control post surgically [31]. Indeed epilepsy surgery not only could lead to seizure control, but also make progression in neurodevelopmental course [13]. Though determination of seizure onset zone might be excruciating, indeed different locations could be followed by various presentation and outcome [15].

The study faced several limitations. All patients evaluated with MRI, as imaging method with a limited diagnostic yield. On the other hand, surface EEG used in our study is incapable to detect all focality hints. Applying more advanced methods, such as PET scan, MEG and intra cranial monitoring, will lead to a higher resolution field to detection of focality in ES patients.

Conclusion

Focal component in ES is much more than supposed previously. This kind of devastating epilepsy syndrome should be considered as a susceptible choice for epilepsy surgery leading to better neurodevelopmental outcome if any focal epileptic zone could be detected in early evaluation. This study is a herald to magnify the importance of focal hints in epileptic spasm diagnosis and therapeutic methods.

Declaration of Competing Interest

The authors declare no competing interests.

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DOI: 10.36959/595/438

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