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Electro-clinical relationship and source analysis of absence seizures in childhood

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Abstract

Purpose: *This study was to deepen into the electro-clinical relationship and source analysis of absence seizures in childhood.* **Methods:** *Thirty-three subjects were studied with clinical and electrophysiological diagnosis of absence seizures without antiepileptic medication, video-electroencephalogram was applied. We obtained clinical behavior and electrophysiological variables during seizures and General Linear Model was applied, with p < 0.05. Source analysis was carried out with VARETA method.* **Results:** *174 seizures were evaluated. 75.75% showed interictal epileptiform discharges (IED) and 12.12% showed posterior delta activity. There was an unequal behavior in relation with total electro-clinical seizures and presence or no of IED (p = 0.02), namely between subjects without IED in EEG and multifocal EEG (p = 0.008). Quantity of seizures recorded during HPV had a different behavior between subjects without IED in EEG and multifocal EEG (p = 0.03) and between focal and multifocal EEG (p = 0.04). Source analysis (VARETA) evidence the onset frontal of seizures in 57.47%, mesial and dorsolateral regions in 43% and 57%, respectively.* **Conclusion:** *These data suggest that absence seizures are not "generalized" if we considered global cortical activation but rather involve localized discharges from specific cortical regions, mainly frontal lobe.*

Keywords: *Absence seizures. VARETA. Source analysis.*

Relación electro-clínica y análisis de fuentes de las crisis de ausencia en la infancia

Resumen

Objetivo: *Profundizar en las relaciones electro- clínica y el análisis de fuentes de las crisis de ausencia en la infancia.* **Métodos***: Se estudiaron 33 sujestos con el diagnóstico clínico y electrofisiológico de crisis de ausencia sin medicación antiepiléptica, se realizó Video-EEG. Se recogieron los comportamientos clínicos y variables electrofisiológicas durante las crisis y se aplicó un Modelo General Lineal, con p < 0.05. El análisis de las fuentes se realizó con el método VARETA.* **Resultados:** *Se evaluaron 174 crisis El 75,75% mostró descargas epileptiformes intericitales (DEI) y el 12,12% mostró actividad delta posterior. Existió un comportamiento desigual en relación con el total de crisis electroclínicas y la presencia o no de DEI (p = 0.02) y entre los sujetos sin DEI y DEI multifocales (p = 0.008). El número de crisis registradas durante la HPV tuvo un comportamiento diferente entre sujetos sin DEI y EEG con DEI multifocales (p = 0.03) y entre EEG focal y*

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multifocal (p = 0.04). El análisis de las fuentes evidenció el inicio frontal de las crisis en el 57,47%, con la participación de las regiones mesial y dorsolateral en el 43% y 57% respectivamente. **Conclusiones***: Los datos sugieren que las crisis de ausencia no son ¨generalizadas¨ si se considera la activación cortical global, sino que involucran descargas localizadas en regiones corticales específicas, principalmente del lóbulo frontal.*

Palabras clave: *Crisis de ausencia. VARETA. Análisis de fuentes.*

Introduction

Childhood absence epilepsy (AE) represents the prototype of idiopathic generalized epilepsies (IGEs). AE is a specific type of brief, generalized nonconvulsive epileptic seizure disorder. The seizures are characterized by a transitory alteration in consciousness associated with electroencephalograms (EEGs) indicating bilateral 3-4 Hz spike-wave discharges (SWDs) of variable duration[1-3].

Typical SWD in absence seizures is dependent on long range corticothalamic and corticocortical network interactions[1,4,5]. Today, however, the neural networks involved in the generation and propagation of these seizures remain under debate. Despite advances in knowledge about the etiology of IGE and evidence of the involvement of thalamus-cortical networks at the onset of generalized tip-wave discharges, there is no consensus about a common cortical source for generalized spike-wave[6-11].

Quantitative electroencephalography provides the opportunity to study measurements of brain electrical activity using non-invasive means, such as mathematical algorithms, for the solution of the inverse problem in electroencephalography, which consists in estimating the location of the generators of the electrical activity of the brain from voltage measurements on the scalp. Modern techniques for locating sources of brain activity allow mapping brain sources in physiological and physiopathology processes in a non-invasive way[12-15].

The purpose of this study was to deepen the electrophysiological and clinical characteristics of the absence seizures in childhood.

Methods

Subjects

The study were included those patients with the clinical diagnosis of childhood absence crisis and normal neurological examination. The electro-clinical seizures were confirmed through the evaluation by video-electroencephalogram (V-EEG) performed at the time of diagnosis. Patients who had a history of other types of seizures or were under antiepileptic treatment were excluded from the study. Demographic variables and related to AE were collected.

EEG-video

The records were acquired using a digital video-electroencephalograph of 32 channels, Medicid 5 (Neuronic SA). The electrodes of AgCl surface were placed according to the international system of placement of electrodes 10-20 and the ears circuited as reference. The bandwidth was 0.5-30 Hz, the digitization of the electroencephalographic signal was carried out with a sampling period of 5 ms, and the gain of the amplifiers was 10,000. The impedance of the electrodes considered acceptable was <5 000 Ω. V-EEG evaluations were performed awake for a minimum duration of 30 minutes, with opening activation manoeuvres, and hyperventilation (HPV) for 3 min, recovery and intermittent light stimulation between 1 and 33 Hz.

Sources analysis

Variable Resolution Electric and Magnetic Tomography (VARETA) is a type of Distributed Inverse Solution (IS)[16]. This mathematical algorithm poses a smooth solution discrete distributed to the inverse problem. The sources of currents are restricted to the estimates of probability of existence of gray matter derived from the probabilistic cerebral atlas (PCA) developed at the Neurological Institute of Montreal[17]. Three-dimensional tomographic images generated with a color code show the IS on the trans axial, coronal, and sagittal cuts of the PCA. In each case, the site of maximum energy was taken as the main IS, considering the large number of measurements and their correlation.

The method of locating distributed sources VARETA was used in the time domain to confirm the ictal start zone, defined by spectral analysis (amplitude maps). For the analysis of the ictal current generators, the point of maximum energy of the tip component of the

spike-wave complexes contained in the first second of each of the electro-clinical seizures was measured.

Statistical analysis

To know if there were different behaviors for the electro-clinical variables: time of evolution of the disease, total electro-clinical seizures, duration of the seizures, topography of the interictal epileptiform discharges (IED), presence of the IED, focal and multifocal IED, a general linear model was applied, with a 95% confidence in the hypothesis tests ($p < 0.05$). The frequency distribution of the variables as well as their average and standard deviation is described. IS percent are described.

Ethical considerations

For the inclusion of the children in this investigation, the informed consent of the parents was requested, the individual data were not divulged, and the established ethical norms were fulfilled. The investigation was approved by the Ethics Committee of the investigations of the Pediatric Hospital "Juan Manuel Márquez" fulfilling with the ethical norms of the declaration of Helsinki.

Table 1. Distribution of the absence seizures

Maneuvers	n	%
Closed eyes	39	22.41
Open eyes	8	4.60
HPV	90	51.72
Recovery	30	17.24
Intermittent light stimulation	7	4.02

Table 2. Clinics features of the absence seizures

	n	%
Arrest or Detention of the activity	120	68.96
Opening eyes	75	43.10
Oral Automatism	47	27.01
Others automatism	26	14.94
Clonic component	22	12.64
Atonic component	11	6.32
Between 4 and 20 s	118	67.81
Less than 4 s	40	22.99
More than 20 s	16	9.19

Results

We studied 33 patients (16 of the female sex). The age range of the patients was between 5.62 and 10.92, (7.63 ± 1.79 SD) (SD, standard deviation), the time of evolution of the disease varied between 10 and 365 days (112 ± 95 SD). The electro-clinical seizures were recorded in 100% of the subjects. A total of 174 seizures (5.27 ± 3.4 DS) were recorded and majority percent occurred at HPV (Table 1).

The average duration of the seizures was 10.57 s ± 6.79 SD. Other clinics features of the AE showed in Table 2.

The totality of the patients showed a normal background activity with the presence of IEDs in a 75.75% (25/33) and the presence of posterior delta activity in a 12.12% (4/33). Focal IED were present in 72% (18/25) and multifocal IED in 28% (7/25) of subjects.

The statistical analysis by a Linear General Model revealed that there was no different behavior in relation to the time of evolution of the disease, the duration of the seizures and the localization of the IED $p = 0.55$ and $p = 0.26$, respectively.

However, there is an unequal behavior in the total of electro-clinical seizures and the presence or not of IED ($p = 0.02$), particularly among subjects without IED and IED with multifocal presentation ($p = 0.008$). The number of seizures recorded during HPV behaves in a different way between subjects with normal interictal EEG and with multifocal IED $p = 0.03$ and between the EEG with focal and multifocal IED $p = 0.04$.

The topographic analysis in the time domain using the VARETA method was applied to ictal discharges to the 174 electro-clinical seizures, it showed that the ictal onset area was in the frontal lobes in 57.47% (100/174), mesial and dorsolateral regions in 43% and 57%, respectively (Fig. 1).

At the same, the frontal structures most involved in the ISs were the supplementary motor area, middle and superior frontal gyrus and the cingulum. Generators of the ictal epileptiform activity were also found in parietal 25.86% (45/174), temporal 9.77% (17/174), and occipital 6.89% (12/174) regions.

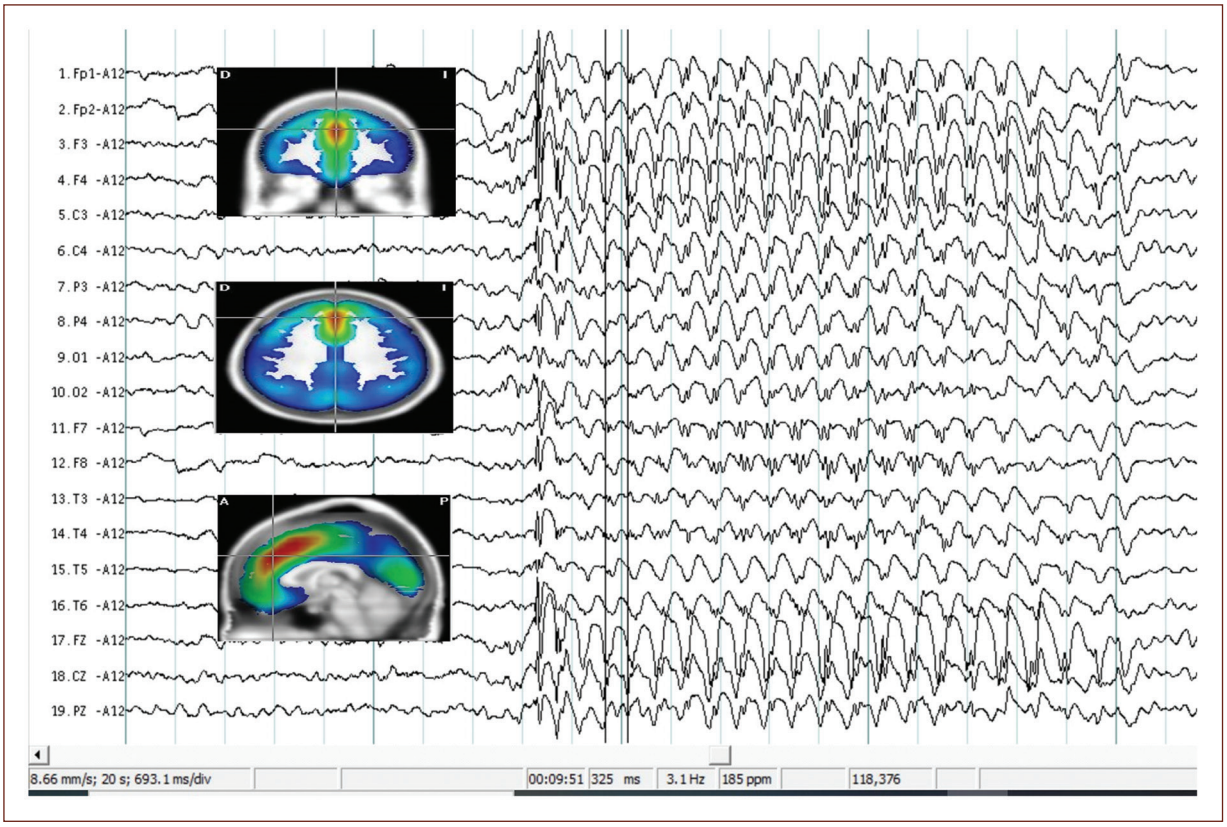

Figure 1. EEG with generalized spike-wave discharge at 3.1 Hz in patient with absence seizure. Inverse solution in the supplementary motor area by applying the VARETA method.

Discussion

There is little research that addresses the study of the electro-clinical characteristics of absence seizures despite representing approximately a quarter of epilepsy in childhood[18,19].

In this research, the average seizures per capita registered was 5.5, and the highest percentage of the seizures was obtained during HPV 51.72% very similar to the values of 5.8 and 47% reported by Saldier[20]. The same author reported the average duration (9.4 s), duration <4 s (26%) and more than 20 s (8%) similar values were found in this study.

One result of this investigation was that exist a different behave in relation to the total of seizures, in those patients whose had or no IED, especially those presenting with independent presentation of IED in various regions of the cortex brain. These results are expected if we consider that the interictal epileptiform activity constitutes a good marker of epileptogenicity and the extension of the epileptogenic focus.

Approximately, 76% of the patients assessed showed IED. The high percentage of patients with IED in their EEG could be related to the high frequency of absence seizures that characterizes this epileptic syndrome[21]. It is also reported that there is an increase in the incidence of IED in those patients who have presented seizures between 2 and 7 days before the EEG and describes a strong association between a high frequency of clinical seizures and a greater likelihood of detecting IED[22,23].

In the pathophysiology of IGEs, there are two pillars they are: pathological thalamus-cortical interaction and the so-called light diffuse epileptogenic state of the cortex[11,24-26]. The existence of areas of the cerebral cortex with icthyogenic properties have been demonstrated by numerous investigations carried out with neuroimaging that reveal significant morphological and functional disturbances restricted to various regions of the cerebral cortex in patients with IGE, more notable toward the frontal regions. By definition, there should be no structural anomalies in patients with IGE. However, the report of diffuse cortical abnormalities and focal cortical microdysgenesis in subjects with IGEreaffirms the possible focal cortical origin of this epilepsy[27-33].

The results of this study indicate the selective involvement of cortical networks including lateral dorsum and mesial frontal regions in the generation of ictal discharges, which coincides with that reported by others investigator[6,7,9,34]. From the pathophysiologic point of view, the cortical areas where the generators of the ictal discharges are found suggest having ichthyogenic properties possibly as a result of an increase in synchronized neural activity[6].

A study using magnetoencephalography to determine the cortical and subcortical contribution to the formation of ictal SWDs showed the location of the generators in the frontal cortex and thalamus in more than 70% of the seizures[9]. The quantitative analysis of the generalized interictal discharges in patients with IGE also reveals the frontal lobe as the main generator, highlighting in this lobe structures such as the middle frontal gyrus and the anterior cingulum cortex[10]. The results of both works coincide with the findings of this research.

More recently, a paper with Magnetoencephalography data from 14 patients with AE were recorded during and between seizures at a sampling rate of 6000 Hz and analyzed in seven frequency bands. Neuromagnetic sources were volumetrically scanned with accumulated source imaging. Effective connectivity networks of the entire brain, including the cortico-thalamo-cortical network. It showed that the low-frequency (1-80 Hz) activities showed significant frontal cortical and parieto-occipito-temporal junction source localization around seizures. The high-frequency (80-250 Hz) oscillations showed predominant activities consistently localized in deep brain areas and medial frontal cortex[34].

Conclusions

The results of this research suggest that in the generation of childhood absence seizures there is no homogeneous activation of the cerebral cortex. The generation of these seizures mainly involves cortical networks circumscribed mostly to the frontal regions, which present abundant connections with structures as the thalamus and the ascending reticular activator systems.

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Conflicts of interest

The authors declare that they have no conflict of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animal for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

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