SYNDROMIC CLASSIFICATION OF PATIENTS WITH TYPICAL ABSENCE SEIZURES

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ABSTRACT - The aim of this study is to compare ILAE classification (1989) and Panayiotopoulos’ criteria (1997) for absence epilepsies. We studied 455 typical absences (ILAE, 1981) by video-EEG in 43 patients with normal neurological and neuroradiological examinations and interictal EEG with spike-wave complexes higher than 2.5Hz. Syndromic diagnosis was possible in 60.5% and 67.4% of the patients using ILAE classification and Panayiotopoulos’ proposal, respectively. According to ILAE criteria 19 patients had childhood absence epilepsy (CAE), five juvenile absence epilepsy (JAE), one juvenile myoclonic epilepsy (JME) and one epilepsy with specific modes of seizure precipitation. According to Panayiotopoulos’ proposal, 10 had CAE, 14 JAE, one JME, three myoclonic absence epilepsy and one eyelid myoclonia with absences. We conclude that Panayiotopoulos’ criteria and ILAE classification for absence epilepsies, which did not allow for the classification of 32.6% and 39.5% of cases, respectively, were still insufficient to classify all patients under specific diagnosis.

KEY WORDS: absence epilepsy, generalized epilepsy, idiopathic epilepsy, epilepsy syndromes, classification.

There are several controversies regarding typical absences classification. The International League Against Epilepsy (ILAE) classification (1989) recognizes the following syndromes with typical absences: childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), juvenile myoclonic epilepsy, epilepsy with specific modes of seizure precipitation and myoclonic absence epilepsy. Panayiotopoulos (1994, 1997) discussed the electroclinical differences of typical absences in these as well as in other syndromes recently described such as eyelid myoclonia with absences, perioral myoclonia with absences, phantom absences with generalized tonic-clonic seizures (GTCS) and absence epilepsy with single myoclonic jerks.

All these syndromes have different prognosis and outcomes. Children with CAE have good outcome and antiepileptic drugs (AED) can be discontinued after some years of treatment. On the other hand, most patients with a defined diagnosis of juvenile myoclonic epilepsy and JAE must take AED throughout their lives. The new described syndromes, such as eyelid myoclonia with absences and perioral myoclonia with absences, also carry a worse prognosis. For this reason it would be very important to rigoro-
usly define the syndromic classification for every particular patient as an individual.

The aim of this paper is to compare the ILAE classification (1989) and Panayiotopoulos' criteria (1997) for absence epilepsies in 43 patients with typical absences in order to analyze both systems of classification.

**METHOD**

We studied 455 seizures recorded in 43 patients with typical absences (mean 10.5 per patient) by video-EEG. All patients signed an informed consent to participate in the study. Typical absences were defined based on ILAE classification (1989): "sudden onset, with interruption of ongoing activities, a blank stare, possibly a brief upward rotation of the eyes lasting from a few seconds to half a minute". All patients had normal neurological and neuroimaging examinations and EEG interictal bursts of spike-wave complexes (SWC) higher than 2.5 Hz. For the video-EEG recording, we utilized a Telefactor 32 channel system in 41 patients and a Nihon-Kohden 18 channel-EEG machine in two.

The video-EEG monitoring consisted of a minimum of three hours of recording, in the morning after sleep deprivation and without any change in the current medication. Forty patients had muscular electrodes in the deltoid muscles. Intermittent photostimulation was performed in all patients and hyperventilation in 42. These patients were then submitted to several periods of hyperventilation with the eyes open, when they were asked to count aloud the last two numbers of respiratory incursions, as suggested by Panayiotopoulos et al.

The analysis of semiological characteristics included alteration of consciousness graded as severe, when the patient stopped hyperventilation and/or the counting and there was an alteration of the reactivity and the memory; and as subtle, when either one of these tasks was not abolished or when the seizure lasted less than 1.5 seconds. The reactivity was measured by asking the patient to obey simple commands (such as to stick out the tongue) and the verbal memory by asking to remember some words during and after the seizures.

The EEG study consisted of the analysis of the background activity, interictal discharges and ictal abnormalities such as the frequency of the SWC. The following frequencies were analyzed: initial (first second), intermediate (two-four seconds), final (last three seconds) and total, which consisted of the average of all the former. Two neurophysiologists analyzed these data, one of them blind to clinical findings.

The patients were followed in the outpatient unit for a period ranging from two years to four years and three months (mean 40 months).

The criteria of the ILAE classification (1989) and the Panayiotopoulos proposed classification (1997) were strictly utilized to classify these patients and are listed in Tables 1 and 2, respectively. In the ILAE classification two points were not considered sufficiently clear: school age and seizure frequency. Since school age was not precisely defined, in this study we considered it as four to 10 years of age. Regarding the frequency of the seizures, they were considered as very often if the patient presented more than 10 seizures per day.

**RESULTS**

Age of typical absences onset ranged from five to 16 years. The patients' age at the time of examination ranged from one year and five months to 53 years. A syndromic diagnosis was possible according to ILAE criteria and Panayiotopoulos proposed classification in 60.5% and 67.4% of the patients, respectively. Graphic 1 shows the number of patients classified by these two criteria.

Eleven patients (25.6%) did not present electroclinical characteristics that could permit the inclusion either in ILAE system of Classification or in Panayiotopoulos proposal. Three subgroups were identified: early onset of the seizures (n=4); fast activity (10-20Hz) associated to SWC (n=4); inadequacy of clinical and electrographical pattern that would fit a specifically described syndrome (n=3).

**ILAE criteria**

According to ILAE criteria 19 patients were classified as CAE, five as JAE, one as juvenile myoclonic epilepsy and one, as having absences precipitated by photostimulation, as epilepsy with specific modes of seizure precipitation. In 17 patients (39.5%) the syndromic classification was not possible. The following clinical findings did not permit the inclusion in syndromes described in the ILAE classification: very early onset of absence and GTC seizures (n=5); ictal fast electrophorical activity (10-20 Hz) associated to SWC (n=4); incongruence between EEG and clinical criteria, such as age of onset, seizure frequency and electrographical pattern (n=8). Graphic 2 shows the syndromic classification regarding ILAE’s criteria.

**Panayiotopoulos’ criteria**

According to Panayiotopoulos' proposal we were able to classify the patients in the following groups: CAE (n=10), JAE (n=14), juvenile myoclonic epilepsy (n=1), myoclonic absence epilepsy (n=3) and eyelid myoclonia with absences (n=1). In 14 patients specific syndromes could not be identified due to the following features: very early onset of absences and GTCS (n=4); short duration of absence seizures (less than four seconds) (n=4); ictal fast electrophorical activity (10-20 Hz) associated to SWC (n=4); and fi-
nally, two patients with clinical characteristics of perioral myoclonia with absences had EEG patterns which differed from those described by Panayiotopoulos, such as long duration of seizures (20 seconds) and regular SWC.

Graphic 3 shows the syndromic classification regarding Panayiotopoulos’ criteria.

Comparison between ILAE/Panayiotopoulos’ criteria
There was congruence in the syndromic diagnosis according to ILAE and Panayiotopoulos’ criteria in 14 patients (32.6%). The results of the comparison between the two criteria can be verified in Graphic 4.

In cases with different diagnosis the greater discrepancy was found in the groups of CAE and JAE. In the ILAE classification a greater (n=19) number of cases could be placed under the diagnosis of CAE than in Panayiotopoulos’ proposal (n=10). On the contrary, in this group, a greater number of patients received the diagnosis of JAE (n=19) when compared to the ILAE classification (n=5).

The following diagram shows the classification according to Panayiotopoulos’ proposal of 19 patients classified as CAE when ILAE’s classification was used.

In the patients who were classified as CAE in ILAE classification and as JAE in Panayiotopoulos’ proposal we observed a mean age of onset of seizures older (mean 8.6 years) than in the patients classified as CAE according to this author (5.2 years).

One patient was diagnosed as having epilepsy with specific modes of seizure precipitation according to ILAE and eyelid myoclonia with absences in Panayiotopoulos’ proposal.

Six patients classified according to Panayiotopoulos’ criteria could not be classified by that of ILAE. Three of these patients were classified as myoclonic absence epilepsy according to this author’s criteria and were not classified according to ILAE, because of the presence of polyspikes that were not described
in this category. Another patient classified as CAE according to Panayiotopoulos’ proposal was not classified by ILAE because of the very early absence onset (2.5 years).

Two patients classified as JAE by Panayiotopoulos’ criteria were not classified by ILAE, one because of ictal frequency lower than 3 Hz, and another because of irregular SWC and polyspikes.

Two patients classified as CAE and one as JAE according to ILAE could not be classified by Panayiotopoulos’ criteria because of the short duration of seizures (less than four seconds) and did not meet all the criteria for the diagnosis of phantom absences with GTCS.

**DISCUSSION**

In this series, the syndromic classification was performed in 67.4% and 60.5% of the cases according to Panayiotopoulos’ criteria (1997) for absence epilepsy and ILAE’s classification (1989), respectively. Eleven patients (25.6%) presented electroclinical characteristics that could not permit the inclusion in syndromes described in those two systems of classification, such as early onset of the seizures, fast activity (10-20Hz) associated to SWC and finally discrepancy in clinical and electrographical findings that would fit a specifically described syndrome.
Table 2. Syndromes with typical absences described in Panayiotopoulos proposal for absence epilepsies (1997)².

**Childhood Absence Epilepsy (CAE)**
- Frequent (many per day), brief (around ten seconds, more than four seconds) typical absences with abrupt and severe impairment of consciousness
- Age of onset between two and eight years, with a peak at five years
- Remission occurs before the age of 12 years
- Generalized, spike or double-spike and slow wave regular complexes at 3 Hz (2.7-4 Hz) in EEG

**Clinical Exclusion Criteria**
- Absences with marked eyelid or perioral myoclonus, single or rhythmic limb and trunk myoclonic jerks
- Absence with mild or not clinically detectable impairment of consciousness
- Other types of epileptic seizures in the early stages of the disease (infrequent GTCS in adult life may occur in no more than 3% of the patients)
- Stimulus-sensitive absences (photosensitive, pattern-sensitive, fixation-off sensitive, etc.)

**EEG Exclusion Criteria**
- Discharge fragmentation (within one second) and multiple spikes
- Irregular, arrhythmic spike and multiple spike and slow wave discharges with marked variations of the intradischarge frequency or of the spike and multiple spike and slow wave relations
- Predominantly brief discharges of less than four seconds
- Posterior rhythmic slow activity is accepted and probably favors diagnosis

**Juvenile Absence Epilepsy**
- Typical absences manifested by abrupt and severe impairment of consciousness (less than CAE) which occur less frequently (one to ten per day) than in CAE
- Age of onset of absences is at seven to 16 years, with a peak at 10-12 years
- Random and infrequent myoclonic jerks as well as infrequent GTCS in the majority of patients
- Lifelong disorder, although the absences tend to become less severe and less frequent
- Regular complexes of generalized spike or multiple spike and slow waves at 3 Hz and discharge fragmentation in EEG may be present

**Clinical Exclusion Criteria**
- Absences with marked eyelid or perioral myoclonus, single or rhythmic limb and trunk myoclonic jerks
- Absence with exclusively mild or clinically undetectable impairment of consciousness

**EEG Exclusion Criteria**
- Irregular, arrhythmic spike and multiple spike and slow wave discharges with marked variations of the intradischarge frequency or of the spike and multiple spike and slow wave relations in EEG
- Predominantly brief discharges (less than four seconds)

**Myoclonic Absence Epilepsy**  (based on Tassinari et al., 1995)⁶
- Absence seizures with impairment of consciousness that vary from mild to severe and rhythmic myoclonic jerks mainly of the shoulders, arms, and legs with a concomitant tonic contraction lasting 10 to 60 seconds
- Frequent absences (pyknoleptic character)
- Age of onset varies from 11 months to 12 years (mean seven years)
- Other seizure types (mainly GTCS) occur in 2/3 of the patients
- Mental retardation is present in 45% before onset and is developed in 25% during the course of the disease
- Generalized rhythmic 3 Hz spike or multiple spike and slow wave discharges in EEG

**Eyelid Myoclonia with Absences**  (based on Jeavons, 1977)⁷
- Frequent seizures of eyelid myoclonia associated with brief absences with upward deviation of the eyes
- Mean age of onset six years
- Resistance to treatment with sodium valproate, persisting in adult life, during which infrequent GTCS are almost inevitable
- Photosensitivity
- Characteristic brief generalized discharges of polyspikes and slow waves at 3 to 6 Hz occurring on closing of the eyes inhibited by total darkness in EEG
The age of onset of all seizure types did not permit the classification in 4 patients. ILAE criteria considers school age that varies according to time and place of study and we have arbitrarily chosen the ages of 4 to 10 years and Panayiotopoulos' proposal has also set the limit at 2 years. Hirsch et al. (1994) have considered that age of onset is not an important factor in classification and prognosis of TA. However the coexistence of GTCS and precipitating factors as photosensitivity would imply in a worse prognosis for the latter mentioned.

We observed 4 patients that had absence seizures with SWC associated to ictal fast electrographical activity (10-20Hz). They were all adult male patients that had had absences and GTCS since adolescence. According to Gastaut & Broughton (1974), atypical absence seizures could present besides the pattern of SWC with frequencies lower than 2.5Hz, fast activity or recruiting epileptic rhythm, and this pattern was associated with slow background activity also cognitive disturbance, which was not observed in our patients.

Gastaut & Broughton (1974) described the composition of the rhythm in absence seizures as a mixture of slow waves at 3 Hz superimposed to one or two sharp waves lasting around 100 msec which correspond to the frequency of 10Hz, considered the recruiting epileptic rhythm. For them there would be overlap of several frequencies, predominating 3 to 10Hz and their harmonics.

Michelucci et al. (1996) described 2 patients with modification of SWC to polyspikes and fast activity (10-20Hz) several years later. Gastaut et al. (1986) described deterioration of EEG pattern with appearance of recruiting epileptic rhythm in 4 of 22 patients with typical absence seizures followed up more than 20 years.

Three patients could not be classified in both criteria because of inadequacy of clinical and electrographical findings that would fit a specific described syndrome. Two of them had different syndromic diagnosis according to clinical and EEG criteria using both systems of classification.

Another patient with clinical characteristics of PMA had EEG patterns different from those described by Panayiotopoulos such as long duration of seizures (20 sec) and regular SWC. Clemens (1977) described the case of a girl with a probable clinical picture of EMA and EEG showing regular SWC at 3Hz of prolonged duration. We believe that a greater number of patients is necessary as well as a longer follow up period to perform a more appropriate syndromic classification in these patients.

Panayiotopoulos’ criteria (1997) for absence epilepsies may include more patients under specific diagnosis than the ILAE’s classification (1989). The greater discrepancy between these two classifications was observed in the cases of CAE and JAE, since Panayiotopoulos has suggested more homogeneous and restrictive criteria for the diagnosis of CAE. The presence of infrequent GTCS as well as the lack of remission before 12 years were exclusion criteria for this syndrome in his proposal leading to the diagnosis of the juvenile form, independent of either the
pykno- or spanioleptic character of the seizures. Probably these factors would constitute prognostic implications such as lower seizure remission, which may determine a lifelong disorder.

In patients in whom Panayiotopoulos’ classification changed the diagnosis from the childhood to the juvenile form because of the occurrence of GTCS or the lack of remission after 12 years, the age of onset was higher than in patients without these factors (8.6 and 5.2 years, respectively). It probably reflects greater similarity to the juvenile form. Obeid (1994) studied 15 patients with JAE and observed frequent pyknolepsy and mean age of absences at 11.4 years. In his report these absences always preceded GTCS.

The age of onset of all seizure types did not permit the classification in five patients according to ILAE criteria and in two according to Panayiotopoulos’ proposal. His proposal has excluded seven cases with associated GTCS to be diagnosed as CAE. According to some authors, the frequency of the absence seizures is fundamental for the correct diagnosis. Pyknolepsy would be characteristic of CAE and spaniolepsy of JAE. For Panayiotopoulos, pyknolepsy would not be patognomonic of CAE and could occur in JAE, although less frequently. In the present study when we utilized his criteria we observed pyknolepsy in all patients with CAE and in 64.2% of those with JAE.

Three patients were classified as myoclonic absence epilepsy according to Panayiotopoulos’ criteria. Polygraphic studies with muscular activity recording is fundamental in these cases since they can have an EEG pattern similar to CAE but with a worse prognosis according to Tassinari et al. (1995). The clinical findings were suggestive of CAE according to ILAE classification, but not the EEG, which revealed polyspike-waves not described there.

One patient classified as having epilepsy with specific modes of seizure precipitation in ILAE criteria was diagnosed as presenting eyelid myoclonia with absences according to Panayiotopoulos’ proposal. After the initial description by Jeavons in 1977, several other publications also have described other cases. The prognosis of this syndrome is restricted and most of the patients analyzed in the literature are refractory to treatment. Our patient is seizure free after valproate administration. We consider the denomination of eyelid myoclonia with absences more appropriate in selecting patients to establish a better delimited clinical and prognostic evaluation and to select patients for genetic studies.

Two patients with clinical characteristics of perioral myoclonia with absences had EEG patterns which differed from those described by Panayiotopoulos. The short duration of the seizure (less than four seconds) was a factor that did not permit the classification according to his criteria in four patients. The syndrome of phantom absences with GTCS was described with defined criteria by Panayiotopoulos in 1995 in 12 adult patients with brief absences documented by video-EEG associated with the lack of perception of the episodes, GTCS in adult life and absence status epilepticus in 50% of them. Neither our patients nor their relatives had noticed the episodes until the age of 10 and they all had had GTCS during adolescence. This syndrome may present a larger clinical spectrum including younger patients that could have perception of some of these brief absences.

In this study, Panayiotopoulos’ proposal permitted to group under the diagnosis of the juvenile form, a greater number of patients than the ILAE classification, which implies that these patients would probably have a lifelong disorder. Therefore, a syndromic classification is necessary in patients with typical absences in order to obtain therapeutic and prognostic implications in groups of higher uniformity, as well as to select patients for genetic evaluation. Long term studies are necessary to define the real prognostic factors in this type of epilepsy in spite of the already known factors considered as inclusion criteria for the characterization of the several typical absences syndromes. Nevertheless, Panayiotopoulos’ criteria (1997) and ILAE classification (1989) for absence epilepsies, which could not allow the inclusion of 32.6% and 39.5% of cases, respectively, were still considered insufficient to classify all patients under specific diagnosis.

The new proposal of classification of ILAE for epileptic syndromes describes, besides childhood absence epilepsy and epilepsy with myoclonic absences, a group of idiopathic generalized epilepsies with variable phenotypes which includes JAE, juvenile myoclonic epilepsy and epilepsy with GTCS. This proposal is still under discussion and it will be continuously revised. Nevertheless, this approach understands that a syndromic diagnosis may not always be possible and more detailed classification systems might be necessary for specific epidemiological and genetic studies.

We consider that some of these cases in which the described classification could not be performed may constitute the concept of continuum suggested by Pazzaglia et al. in 1969. For these authors, there
would be electroclinical variations of spike-wave patterns since the benign diffuse epilepsy, such as pyknolepsy, to malignant diffuse epilepsy as the Lennox-Gastaut syndrome. Gloor et al. 1982 have considered that epilepsy would be a multifactorial condition, in which acquired factors could exacerbate the genetically determined neuronal excitability. Wolf & Inoue 1984, confirming the concept of continuum, considered that the therapeutic response in patients with absence seizures is not uniform and is related to the electroclinical presentation. Berkovic et al. 1987 reinforced the concept of biological continuum between primary and secondary generalized epilepsy, with different proportions of genetic and acquired factors in intermediate cases. We believe that the different syndromes are probable genetically distinct subgroups. According to individual seizure susceptibility and exposition to acquired factors, they could manifest as a continuum although they still remain grouped in relatively specific entities of higher occurrence. These would permit categorization into syndromes and isolated cases, which would not fit into nosological classifications.

REFERENCES