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Absence Epilepsy. Continnum presentation of clinical syndromes and epigenetics?
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Highlights

- Several nosological entities present absence seizures according to different proposals of epileptic syndromes classification.
- Although other antiepileptic drugs are effective, ESM is the choice for treatment of childhood absence epilepsy.
- Albeit absence seizures in children have been previously considered benign, there is risk of academic failure and attentional deficits that persist despite seizure freedom.
- In adults prognosis is influenced by rare clinical presentations such as perioral and eyelid myoclonic components that poses worse outcome.
- Overall prognosis depend on age of onset, presence of other seizure types and response to initial treatment.
Abstract

Purpose: Although absence seizures do predominate in childhood they may occur at all ages and clinical presentation varies widely. Albeit considered a benign seizure type, chronic evolution with therapeutic refractoriness is possible in some patients with absences. The aim of this paper is to summarize the main syndromic presentation of absence seizures and its outcome regarding treatment and prognosis.

Methods: We performed a review of literature with emphasis in historic and classical manuscripts about absence epilepsy.

Results: Absence was described in the beginning of last century as a seizure type with good evolution, but it is still difficult to preview a strict prognosis for an individual patient. Some positive early predictors were reported such as response to initial treatment and seizure onset in childhood. Genetic aspects are not yet well understood although some families have been reported with rare mutations in ion channel coding genes.

Conclusion: Absence seizures are present in different epilepsy syndromes and nosological classification is not always possible. Outcome depends on clinical variables such as age of onset, presence of other seizure types and initial response to treatment.

Key-words: absence seizure; generalized epilepsy; treatment; prognosis; classification; nosology.
I- Historical aspects

In this important 25th anniversary issue of Seizure – European Journal of Epilepsy it is of significance to remember one of the first clinical description of a seizure type, the absence, which was topic of publication in this periodical for 592 times. Absences and the related epileptic syndromes are still an area of controversy because of possible clinical presentation overlap that may poses difficulties in classification, prognosis and treatment. Absence seizures incidence varies from 0.7-4.6/100,000 in general population and 6-8/100,000 in children up to 15 years-old [1,2]. It is very meaningful to perform syndromic characterization in order to define therapeutic and prognostic implications in these cases.

In the beginning of last century there was the first descriptions of absence seizures in German medical literature and in 1916 Sauer presented the term pyknolepsy, which is originated from Greek, πικνός (picnós), and means very frequent or grouped, to describe absence seizures with multiple daily recurrences [3-5]. In 1924 Adie described pyknolepsy, an epilepsy type with good remission in children, characterized by, “abrupt onset, between 4 and 12 years of age, with epileptic seizures of short duration, very frequent, which recurred almost daily, for weeks, months or years” [6].

In the first reports of EEG recording by Hans Berger in 1933, there was an example of rhythmic spike-wave discharges, and two years later, Gibbs, Davis and Lennox described their main characteristics, such as rhythmicity at 3Hz, at times accompanied by concomitant rhythmic clonic movements of the eyelids [7,8]. Gibbs, Lennox and Gibbs, in 1936, reported that ictal spike-wave complexes (SWC) were faster in the beginning of seizures and had predominance in anterior regions [9]. Finally, these authors differentiated this pattern from another, which they called “slow spike-wave complex” at 2Hz. In this slower pattern, a diverse clinical presentation was associated that they called “petit mal variant” in which seizures affected awareness less prominently than in 3Hz SWC seizure. Afterwards this clinical entity was entitled as the Lennox-Gastaut syndrome.
II- Nosology

The International League Against Epilepsy (ILAE) in its publications about seizure classification since the first proposal leaded by Gastaut in 1970 considered absences within generalized seizure types which affected both cerebral hemispheres clinical and electrografically, and differentiated them from “atypical absences” [10]. The ILAE Commission of 1981 described typical absence seizure as “of sudden onset, interruption of ongoing activities, staring, possible upwards version of eyes with few seconds duration, associated to symmetrical 2-4Hz, mainly 3Hz, SWC, normal background activity [11]. At that time absences were subdivided according to its different clinical presentation based on the video-EEG study of Penry et al. from 1975 into: 1) with impairment of consciousness only; 2) with association of other clinical components such as clonic, atonic, tonic, autonomic, and with automatisms [12]. Atypical absence seizures would have less abrupt onset and termination associated to slow irregular SWC, fast activity and slow background activity.

Other proposals of classification of seizures and syndromes of ILAE and its members were also published along the years. The glossary published by Blume in 2001 endorsed by ILAE in 2010 described absences seizures as dyscognitive seizures [13,14].

Regarding the syndromic classification there were the first classical papers of ILAE from the 1980th in which epilepsies with typical absence seizures were considered as “primary” or "idiopathic” that were observed in people without neurological deficits and etiological factor and were divided into childhood absence epilepsy (CAE), juvenile absence epilepsy (JAE), and myoclonic absence epilepsy. It also considered other epileptic syndrome types that could present with absences, such as juvenile myoclonic epilepsy (JME) as well as others in which occurrence of absences was possible such as epilepsy with specific modes of seizure precipitation and generalized tonic-clonic seizures (GTCS) upon awakening [15].

Myoclonic absence epilepsy, described by Tassinari in 1969, was classified in criptogenic (with probable but unknown etiology) or symptomatic (known etiology) epilepsy syndromes. In this, absences are accompanied by
bilateral massive myoclonic jerks in cephalic region and upper limbs, at times associated to tonic muscle contraction and in EEG, bilateral 3Hz SWC, similar to CAE. The prognosis is less favorable in this myoclonic syndrome with more refractoriness to treatment and possibility of intellectual disability [16].

In 1977, Jeavons described absences with eyelid myoclonia immediately after eye closure and upwards eye deviation with onset in childhood and rare GTCS in adolescence. Ictal EEG reveals brief discharges (one to three seconds) of 3-6Hz spike-wave or polyspike-wave, mainly after eye closure, or during intermittent photic stimulation [17].

In ILAE’s proposal of classification for epileptic syndromes from 2010, besides CAE and epilepsy with myoclonic absences, a group of idiopathic generalized epilepsies with variable phenotypes was set that includes JAE, JME and epilepsy with GTCS [14]. Absence syndromes were classified into childhood and juvenile types and absences with eyelid myoclonia were included. This proposal is still under discussion and it has been continuously revised. Several nosological entities present absence seizures according to this and other classifications.

Although a syndromic diagnosis may not always be possible and more detailed classification systems might be necessary for specific epidemiological and genetic studies, it is considered by some authors that certain cases in which the described classification cannot be performed may constitute the concept of continuum suggested by Pazzaglia et al. in 1969 [18,19]. For these authors, there would be electroclinical variations of spike-wave patterns since a benign diffuse epilepsy, such as pyknolepsy, to malignant diffuse epilepsy as Lennox-Gastaut syndrome.

Gloor et al. have considered that epilepsy would be a multifactorial condition, in which acquired factors could exacerbate the genetically determined neuronal excitability [20]. Berkovic et al. reinforced the concept of biological continuum between primary and secondary generalized epilepsy, with different proportions of genetic and acquired factors in intermediate cases [21]. Different syndromes may probably have distinct genetic trait subgroups. According to
individual seizure susceptibility and exposition to acquired factors, as well other epigenetic modulation, they could manifest as a *continuum* although they remain grouped in relatively specific entities of higher occurrence. These would permit categorization into syndromes and isolated cases, which would not fit into nosologic classifications. 

III- Clinical Presentation

The main clinical characteristics of epileptic syndromes with absence seizures regarding ILAE classification are described in Table 1. Although there are other proposal of nosological grouping, this description is frequently used for its practical application.

Panayiotopoulos proposed strict criteria for CAE and JAE that are shown in Table 2. This author discussed the electroclinical differences of typical absences in these as well as in other syndromes in adults such as eyelid myoclonia with absences, perioral myoclonia with absences, phantom absences with 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 JME and JAE must take AED throughout their lives. Other 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 rigorously define the syndromic classification for every particular patient as an individual.

Prognosis is also associated with syndromic classification that is usually age dependent. Wirrel et al. observed that terminal remission was more likely if initial AED was successful and those who persisted with absences were more prone to evolve to JME. Trinka et al. described 163 patients with absences with onset at mean age of 10.9 years and followed for mean period of 25.8 years, and only 58% were in remission. These authors considered that CAE and JAE are closely related syndromes with large overlap of age of onset. Classification according to predominant pattern of absences (not pyknoleptic) at onset combined with later
development of myoclonic or GTCS was useful in predicting less favorable long term seizure remission [25].

Shinnar et al. discussed early predictors of GTCS in CAE, such as failure of treatment response at week 16-20, older age at onset and shortest burst duration on baseline EEG, which may superpose the characteristics seen in patients with JAE [26]. Loiseau et al. considered that an accurate diagnosis is mandatory for establishing, when possible, a prognosis and management in a given patient [27]. Remission rates of patients with CAE may be influenced by the classification criteria used for selection. Stricter diagnostic criteria allow the definition of a homogeneous group of patients with excellent prognosis [28].

IV- Treatment

The syndromic approach is important for treatment evaluation. Wolf & Inoue considered that therapeutic response in patients with absence seizures is not uniform and is related to electroclinical presentation [29].

One important randomized controlled trial (RTC) performed by Glauser et al. in 2010 considered for initial therapy ESM to be superior to VPA and LTG in a cohort of 446 children with CAE. After 16 weeks of treatment seizure free rate was not very high (53% ESM, 58% VPA, 29% LTG) as in 12 months follow-up, when only 37% had controlled the absences (45% ESM, 44% VPA, 21% LTG) [30, 31]. Children with CAE had also risk of academic failure and high rates of attentional deficits that persisted despite seizure control [32,33]. This study concluded that ESM was more efficacious than LTG and similar but with fewer cognitive side effects compared to VPA. These authors pointed to ESM as drug of choice for CAE, even with concerns for high risk of GTCS, as it is not considered effective against these. Nevertheless, the same group in a long-term evaluation of this cohort observed that risk of GTCS was much lower especially if the child responds to ESM initial therapy. The most important finding of this prospective study was the low incidence of GTCS in CAE [26].
Berg et al. discussed the potential disease modifying effect of ESM in CAE. When studying 68 children followed for 10 years a higher rate of remission was observed with ESM compared to VPA independent of atypical EEG patterns or other factors present in treatment selection [34].

V - Genetic Aspects

Lennox in 1951 observed that 66% of monozigotic twins showed concordance for the EEG pattern of 3Hz SWC [35]. Metrakos & Metrakos, in 1961, studied families of 211 patients and proposed autossomic dominant mechanism of inheritance of 3Hz SWC with maximum penetrance age dependent not related to seizure occurrence [36]. Janz et al. (1994) observed in 31 families with more than one affected member that there was concordance for the presence or not of the pyknoleptic pattern, suggesting that there was different genetic subsyndromes [37]. Multifactorial heritance was discussed by Doose et al. when describing 252 patients with absences with 3Hz SWC [38].

Proposed genes include T-calcium channel gene CACNA1H, likely a susceptible gene in Chinese Han population and a contributory gene in Caucasians [39]. Although the mechanism underlying altered thalamic T-type currents remains unknown, future work can elucidate the role of both P/Q-type and T-type calcium channels in corticothalamic circuit dysfunction and absence epilepsy. Besides that, both human and experimental evidence strongly supports the view of brain region-specific changes in phasic and tonic GABA_A inhibition in typical absence seizures [40].

VI - Conclusions

Different absence syndromes are probable linked to genetically distinct trait subgroups. According to individual seizure susceptibility and exposition to acquired factors, they could manifest as a continuum, despite they remain grouped in relatively specific entities of higher occurrence. This fact would permit categorization into syndromes and isolated cases, which would not fit into
nosological classifications. Whenever possible syndromic approach is fundamental in order to better evaluate and advise patients with absence seizures.

Conflict of interest statement
The author has no conflict of interest to disclose.
References


35. Lennox W. The heredity of epilepsy as told by relatives and twins. JAMA 1951;146:529-36.


Tables
Table 1. Syndromes with typical absences described in the Proposal for Revised Classification of Epilepsies and Epileptic Syndromes of the Commission on Classification and Terminology of the International League Against Epilepsy (1989) [15].

<table>
<thead>
<tr>
<th>Childhood Absence Epilepsy (Pyknolepsy)</th>
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<tbody>
<tr>
<td>Children of school age (peak manifestation 6-7 years)</td>
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<tr>
<td>Very frequent (several to many/day) absences; EEG with bilateral, synchronous, symmetrical spike-waves, usually at 3Hz</td>
</tr>
<tr>
<td>Development of GTCS often occurs during adolescence</td>
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<tr>
<th>Juvenile Absence Epilepsy</th>
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<tbody>
<tr>
<td>Absences are the same as in pyknolepsy though retropulsive movements are less common</td>
</tr>
<tr>
<td>Clinical manifestation occurs around puberty</td>
</tr>
<tr>
<td>Seizure frequency lower than in pyknolepsy, less frequently than every day</td>
</tr>
<tr>
<td>Frequent association with GTCS which precede absence seizures more often than in pyknolepsy</td>
</tr>
<tr>
<td>Not infrequently, presence of myoclonic seizures</td>
</tr>
<tr>
<td>Spike waves are often &gt;3Hz</td>
</tr>
<tr>
<td>Excellent response to therapy</td>
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<thead>
<tr>
<th>Juvenile Myoclonic Epilepsy (“Impulsive Petit Mal”)</th>
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<tbody>
<tr>
<td>Appears around puberty</td>
</tr>
<tr>
<td>Seizures with bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in arms with no noticeable consciousness disturbance</td>
</tr>
<tr>
<td>Often, there are GTCS and less often, infrequent absences</td>
</tr>
<tr>
<td>Rapid, generalized, often irregular spike-waves and polyspike-waves in interictal and ictal EEG</td>
</tr>
<tr>
<td>Frequently patients are photosensitive</td>
</tr>
<tr>
<td>Good response to appropriate drugs</td>
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<tr>
<th>Epilepsy with Specific Modes of Seizure Precipitation</th>
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<tr>
<td>Environmental or internal factors consistently precede seizures</td>
</tr>
<tr>
<td>Consistent relationship can be recognized between occurrence of one or more definable nonictal events and subsequent occurrence of a specific stereotyped seizure</td>
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<tr>
<th>Epilepsy with Myoclonic Absences</th>
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<tr>
<td>Absences accompanied by severe bilateral rhythmical clonic jerks, often associated with tonic contraction</td>
</tr>
<tr>
<td>Bilateral, synchronous and symmetrical discharges of rhythmical spike-waves at 3Hz in EEG, similar to childhood absence</td>
</tr>
<tr>
<td>Seizures occur many times a day</td>
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<tr>
<td>Rare association with other seizure types</td>
</tr>
<tr>
<td>Age of onset is around 7 years</td>
</tr>
<tr>
<td>Prognosis is less favorable than in pyknolepsy owing to refractoriness, mental deterioration and possible evolution to other epilepsy types</td>
</tr>
</tbody>
</table>
Table 2. Syndromes with typical absences described in Panayiotopoulos’ proposal for absence epilepsies [16,17,22,23].

<table>
<thead>
<tr>
<th></th>
<th>Childhood Absence Epilepsy</th>
<th>Juvenile Absence Epilepsy</th>
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<tbody>
<tr>
<td><strong>Clinical Criteria</strong></td>
<td></td>
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</table>
| **Inclusion**        | - Frequent (many per day), brief (around 10 seconds, more than 4 seconds) typical absences with abrupt and severe consciousness impairment  
                       - Age of onset between 2-8 years (peak 5 years)  
                       - Remission occurs before age of 12 years | - 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 (peak at 10-12 years)  
                       - Random and infrequent myoclonic jerks as well as infrequent GTCS in majority of patients  
                       - Lifelong disorder, absences tend to become less severe and frequent |
| **Exclusion**        | - Absences with marked eyelid or perioral myoclonus, single or rhythmic limb and trunk myoclonic jerks  
                       - Absence with mild or not clinically detectable consciousness impairment  
                       - Other types of epileptic seizures in early stages (infrequent GTCS in adult life may occur in no more than 3% of patients)  
                       - Stimulus-sensitive absences (photic, pattern, fixation-off sensitive, etc.) | - 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 Criteria**     |                            |                           |
| **Inclusion**        | - Generalized, spike or double-spike and slow wave regular complexes at 3Hz (2.7-4Hz) | - Regular complexes of generalized spike or multiple spike and slow waves at 3Hz and discharge fragmentation may be present |
| **Exclusion**        | - 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 | - Irregular, arrhythmic spike and multiple spike and slow wave discharges with marked variations of intradischarge frequency or of spike and multiple spike and slow wave relations  
                       - Predominantly brief discharges (less than 4 seconds) |

Cont.
Myoclonic Absence Epilepsy
(based on Tassinari et al., 1995)

**Clinical Criteria**
- Absence seizures with consciousness impairment that vary from mild to severe and rhythmic myoclonic jerks mainly of shoulders, arms, legs with concomitant tonic contraction (10-60 seconds)
- Frequent absences (pyknoleptic character)
- Age of onset varies from 11 months to 12 years (mean 7 years)
- Other seizure types (mainly GTCS) occur in 2/3 of patients
- Intellectual disability is present in 45% before onset and may develop in 25% during the course of disease

**EEG Criteria**
- Generalized rhythmic 3Hz spike or multiple spike-slow wave discharges

Myoclonic Absence Epilepsy
(based on Jeavons, 1977)

**Clinical Criteria**
- Frequent seizures of eyelid myoclonia associated with brief absences and upward eye deviation
- Mean age of onset 6 years
- Resistance to treatment with VPA, persisting in adult life, during which infrequent GTCS are common

**EEG Criteria**
- Photosensitivity
- Characteristic brief generalized discharges of polyspikes and slow waves at 3-6Hz occurring on eye closing inhibited by total darkness

Perioral Myoclonia with Absences

**Clinical Criteria**
- Brief absences (mean 3.7 seconds) with rhythmic contractions of perioral muscles with variable frequency and severity of consciousness impairment
- Age of onset from 2-13 years
- Infrequent GTCS in all patients; frequent absence status
- Persistence into adult life

**EEG Criteria**
- Generalized discharges of multiple spikes and slow waves at 3-4Hz, with frequent irregularities and discharge fragmentation in ictal EEG

Syndrome of Phantom Absences and Generalized Tonic-Clonic Seizures

**Clinical Criteria**
- Brief absences (3-4 seconds) of which patients are unaware with mild impairment of cognition (detected by video-EEG)
- Age of onset difficult to determine, usually starting after the adolescence
- Infrequent GTCS; absence status in half of patients

**EEG Criteria**
- Brief 3-4Hz spike or multiple spike in ictal EEG