Therapeutic Options for Childhood Absence Epilepsy

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Childhood absence epilepsy (CAE) is a common pediatric generalized epileptic syndrome. Although it is traditionally considered as a benign self-limited condition, the apparent benign nature of this syndrome has been revaluated in recent years. Old and new therapeutic options in particular for resistant forms of CAE are discussed in this entry.

Keywords: childhood absence epilepsy ; absences ; epilepsy treatment

1. Introduction

Childhood absence epilepsy (CAE) is a common pediatric generalized epileptic syndrome that affects between 10% to 17% of all school-aged children diagnosed with new onset epilepsy [1]. It is defined by the presence of multiple daily typical absence seizures that are characterized by a sudden interruption of on-going activities, possibly an upwards rotation of the eyes and a blank stare with impaired consciousness [2]. These episodes of altered awareness can be activated by hyperventilation or photic stimulation and are characterized by generalized symmetrical and synchronous spike-wave discharges at 3 Hz or more on electroencephalogram (EEG) [2], usually lasting between 9 and 10 s [3].

The first descriptions of CAE date back to the last century in German medical literature and in 1916 Sauer presented the term pyknolepsy, from the Greek word piknoz (πικνός), meaning “very frequent or grouped”, to describe absence seizures with daily recurrences [4]. The typical age of onset is between 6 to 7 years but it can also be observed between 4 to 10 years of age in patients with a normal psychomotor development and without a particular personal or family history for neurologic diseases [5].

Recent studies have also shown a possible association of absence seizures and other epileptic syndromes such as idiopathic occipital epilepsy, Gastaut idiopathic occipital epilepsy [6], West syndrome, myoclonic epilepsy of infancy and benign epilepsy with centro-temporal spikes [2][7][8][9].

Most of the molecular-genetic studies on CAE have failed to precisely identify its genetic pathways that could be particularly useful for precision therapy [10]. However, the newest science frontiers are constantly trying to describe the genetic variants associated with this epilepsy, in order to improve disease risk predictability. In particular, most of the genes associated with CAE are ion channel genes (calcium channel, GABA receptor, acetylcholine receptor etc.); in detail, genetic investigations in patients with CAE have demonstrated the role of the calcium channel genes CACNA1H, CACNA1G and CACNG3 along with GABA A and B receptor genes [11][12]. Moreover, absence seizures result principally from disruptions in thalamocortical pathways involving T-type calcium channels and antiepileptic drugs effective against absence seizures among other mechanisms, exert their effect principally at these channels [13]. In fact, recent studies have focused their attention on pretreatment connectivity in children diagnosed with CAE, with the objective of providing clearer insights into antiepileptic drug response variability for these patients [14].

Although CAE is traditionally considered a benign self-limited epilepsy syndrome, data from the multicenter Childhood Absence Epilepsy Study Group have led to the review of this notion [15][16]. During the past years, the apparent benign nature of the syndrome has in fact undergone many contradictions on a few basis, mainly the possibility of treatment failure (5–10% of patients) and the evidence of considerable psychosocial difficulties that can be found up to adulthood [17] [18].

In particular, attention deficits are observed in about 1/3 of the patients and there is an increased risk of cognitive disorders [17]. In light of this new knowledge, as already performed for children with other forms of epilepsy [19], it is fundamental for patients with new onset absence epilepsy to undergo neuropsychological assessments and treatment. The reason for an early cognitive dysfunction in CAE remains unclear but cognitive side effects should be taken into consideration in the choice of antiepileptic treatment with a specific assessment during follow up [5].

CAE diagnosis is often straightforward and highly suspected in school-aged children who present with brief multiple daily episodes of staring without memory of the event or ability of caretakers to interrupt the episodes [20]. Episodes can be classically activated by hyperventilation; doctors can evoke this kind of seizure and furthermore, parents can evoke a staring spell even during telemedicine consultations that have become more and more necessary during the past year [20].

Diagnosis is then confirmed by a routine electroencephalography (EEG) before beginning treatment and to diagnose CAE, only typical absences have to be registered. The presence of other types of seizures (tonic-clonic generalized seizures, atypical absences etc.) rules out a diagnosis of CAE. On EEG the typical findings are a bilaterally symmetrical and synchronous discharge of 3-Hz spike wave complexes with an abrupt start and ending [1]; the background EEG track has a normal and well organized rhythm. If the clinical symptoms and the electrical pattern are typical, there is no differential diagnosis from CAE. However, if there is a poor response to classical CAE treatment or in the suspicion of precocious absence epilepsy (before 3–4 years of age), the initial diagnosis must always be revaluated. In fact, especially in younger children, 10% of poor responders have been found to have a deficit in the type GLUT-1 glucose transporter [21]. This diagnosis can be confirmed through a lumber puncture with glycorrhachia measurement and contemporary measurement of venous glycemia, along with genetic studies of the SLC2A1 gene [5].

Traditional prophylactic anticonvulsant therapy of CAE is based on three antiepileptic drugs: ethosuximide (ETX), valproic acid (VPA) and lamotrigine (LTG) [22] and in particular, the 2010 childhood absence epilepsy study provided class I evidence for the use of ETX as the optimal initial treatment of CAE [15][23]. In the case of first line treatment failure, after having reconsidered and confirmed the initial diagnostic suspect, after two monotherapies it is usual to start a bi-therapy (for example the association of VPA and LTG) carefully watching out for adverse effects [5]. In the case of absence seizures that are refractory to traditional treatment, other antiepileptic drugs may be introduced such as levetiracetam, topiramate and zonisamide [24][25][26].

2. Childhood Absence Epilepsy Therapeutic Options

2.1. First Line Treatment

In the last 10 years, various studies have been carried out to compare the different molecules proposed for CAE treatment. However, there are very few randomized trials in literature to guide treatment strategies for CAE. Glauser et al. in 2010 [15] performed a double blind randomized controlled trial comparing the use of ethosuximide, valproate and lamotrigine. A total of 453 children aged between 4 and 10 years with a new diagnosis of CAE were enrolled and were randomly assigned to treatment with ETX, VPA or LTG. The principal outcome that was studied was the freedom from seizures after 16 weeks of treatment and the absence of major adverse effects. The results of this study showed that the freedom from seizures rates of ETX and VPA were similar (53% and 58% respectively, $p = 0.35$) and higher than those of LTG compared to the other two drugs (29%, $p < 0.001$). However, post treatment attention disfunction was more frequent in patients treated with VPA rather than ETX (49% versus 33% respectively, $p = 0.03$) and patients treated with VPA also presented problems related to weight gain in the following months, causing discontinuation of therapy. ETX was therefore considered the drug of choice as initial therapy for CAE [27]. This was also confirmed by Berg et al. in 2014 [28] who demonstrated a higher complete remission rate over 5 years in patients treated with ETX rather than VPA. A recent Cochrane review [29] confirmed these data adding that concerning efficacy and tolerability, ETX represents the optimal initial empirical monotherapy for CAE patients but in the case of coexistence of absences and generalized tonic-clonic seizures, VPA is the drug of choice as ETX has no effect on tonic-clonic seizures. LTG on the other hand, can be preferred if VPA is not considered the drug of choice for a specific patient. To summarize, ethosuximide, lamotrigine and valproate are the principal antiepileptic drugs used to treat children and adolescents with childhood absence epilepsy [30].

2.1.1. Ethosuximide

Ethosuximide (2-ethyl-2-methyl-succinamide) is the drug of choice for classical CAE with simple absence seizures as it does not suppress focal onset or generalized tonic-clonic seizures [23]. Its mechanism of action is not well defined but seems to be based on the blockade of transient, low-threshold calcium currents produced by the thalamus, that cause the synchronous activation of spike wave discharges causing absence seizures [31]. The recommended dosage for CAE is an initial dose of 10–15 mg/kg/day, maintained at 20–30 mg/kg/day divided in two doses (maximum dose 40 mg/kg/day) [23]. Various oral formulations exist (syrup, capsules) and when used in association with other anticonvulsant therapies, it is important to take into consideration its susceptibility to the effects of enzyme inducing and inhibiting antiepileptic drugs [32]. This can happen for example when associating ETX and VPA. The principle side effects of ETX include gastrointestinal disturbances (abdominal discomfort, nausea, vomiting, diarrhea), headache, drowsiness and much rarer side effects such as behavioral and psychiatric disturbances, blood dyscrasias and allergic reactions [23].

2.1.2. Valproic Acid

One of the greatest concerns for pediatric neurologists is to differentiate classic isolated CAE from other forms presenting also with generalized tonic–clonic seizures. This is one of the prevailing reasons to start child treatment with either VPA or LTG as first line treatment, instead of ETX [33]. Valproic acid (N-dipropylacetic acid), is a broad spectrum antiepileptic drug with pre and post-synaptic effects that depend on a very broad spectrum of actions [34], including the regulation of ionic currents and the facilitation of inhibiting GABAergic over glutamatergic transmission. The initial dosage for all oral formulations is 10–15 mg/kg/day, maintained at 20–40 mg/kg/day divided in two doses (maximum dose 60 mg/kg/day) [23]. Contrary to ETX, one of the main problems and causes of discontinuation with VPA therapy are the numerous potential side effects, some of which are dose-related whereas others are idiosynchrasic. In particular, even Glauser et al. in their 2010 trial [15] showed that valproic acid negatively affected patients attention to a greater degree than the other tested drugs. This confirmed that persisting attention problems and neuropsychological dysfunction are an important feature of this syndrome that must be precociously identified when choosing an appropriate antiepileptic treatment [35]. Among the most frequently reported side effects of VPA are increased appetite and weight gain along with the rarer but well known possible occurrence of pancreatitis and hepatic failure [36]. Other potential metabolic side effects include hyperammoniemia, hypothyroidism, hair loss polycistic ovary syndrome and teratogenicity [34]; thrombocytopenia and depletion of coagulation factors can be another dose-dependent side effect of VPA that must be remembered in the case of surgery [23].

2.1.3. Lamotrigine

Lamotrigine acts through blockage of voltage-dependent sodium channels; it also stabilizes presynaptic membranes and inhibits the release of excitatory neurotransmitters, especially glutammate and aspartate [37]. As we have previously underlined, the 2010 double blinded randomized CAE trial [15] has somehow downgraded the use of LTG as first line monotherapy for CAE as the seizure freedom rate after 12 months was lower in patients treated with LTG compared with those treated with ETX or VPA. Moreover, discontinuation for lack of efficacy was more frequently observed in the group treated with LTG. In fact, LTG had previously been considered among first line treatment for CAE and the seizure freedom rates concerning this drug had been reported between 50% and 80% [22][38][39]. However, LTG can be considered as a second monotherapy in the case of ETX failure and VPA is not the appropriate drug for certain patients. For patients not taking other antiepileptic drugs the initial dosage for all oral formulations is 0.6 mg/kg/day, maintained at 5–12 mg/kg/day (maximum dose 300 mg/day) [23]. The initial dosage is very low, and titration must be achieved very slowly over many weeks to avoid Stevens–Johnson Syndrome, a rare but life-threatening adverse effect of this drug. On the other hand, LTG is generally well tolerated and there is a lower risk for cognitive adverse effects compared to VPA although diplopia, dizziness and ataxia have been reported [40].

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