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Updates on epilepsy

Care of pharmaco-resistant absence seizures in childhood



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ABSTRACT

In childhood absence epilepsy, pharmaco-resistance occurs in 20–30% of patients. In that situation, glucose transporter type 1 deficiency has to be ruled out, especially if absences started before the age of four years and if neurological signs are present. If ethosuximide, valproate and lamotrigine have failed in monotherapy or in association, there are currently no valuable therapeutic options. The same rules apply for epilepsy with myoclonic absences. Importantly, arguments supporting that making the patient seizure-free will improve eventual associated cognitive deficits such as attention deficit are very weak. Therefore, limiting the cognitive side effects of the anti-epileptic drugs has always to be a priority when faced with typical refractory absences in childhood. In epilepsy with eyelid myoclonia, the majority of patients are pharmaco-resistant. However, absence seizures, if present, tend to be very brief, and seizures are limited in many patients to eyelid myoclonia that eventually do not affect their quality of life and are well attenuated by wearing blue lenses. Atypical absences occurring in the course a developmental and/or epileptic encephalopathy are often pharmaco-resistant. In that situation, characterizing the type of epilepsy syndrome and searching for a specific genetic or structural etiology are needed to offer the best therapeutic options to the patient.

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1. Introduction

Absence seizures are sudden brief lapses of consciousness associated with lack of voluntary movements and distinctive electrographic generalized spike-wave discharges at 2.5–4 Hz [1]. These epileptic seizures are classified in the operational classification by the International League Against Epilepsy among generalized onset seizures [2]. In this classification,

four types of absences are recognized: typical absences, atypical absences, myoclonic absences and absences with eyelid myoclonia [2]. Typical absences are seizures that occur in idiopathic generalized epilepsies (IGE), mainly childhood absence epilepsy (CAE) and juvenile absence epilepsy (JAE) [3]. Myoclonic absences and absences with eyelid myoclonia are seizures that are very specific of two particular epilepsy syndromes classified among the genetic generalized epilepsies: epilepsy with myoclonic absences (EMA) and epilepsy

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with eyelid myoclonia (EEM), previously called Jeavons syndrome [4]. Finally, atypical absences may be encountered in various epilepsy syndromes that belong to the spectrum of developmental and/or epileptic encephalopathies (DEE): epilepsy with myoclonic-atonic seizures (EMaTs), previously called Doose syndrome, Lennox-Gastaut syndrome (LGS), DEE with spike-and-wave activation in sleep (DEE-SWAS) and Dravet syndrome (DS) [4]. However, it should be noted that patients may have atypical absences in the context of DEE that do not fit with criteria of a specific epileptic syndrome; we'll use the terminology "unclassified DEE" for such cases.

The aim of this paper is to review the therapeutic options that should be proposed for these various types of absence seizures in childhood. For this purpose, the different epilepsy syndromes in which absences may occur will be discussed separately.

2. Absence seizures in the context of IGE

The main source of data comes from the "CAE trial". This trial included 453 naive patients who were randomized into three groups according to treatment assignment with ethosuximide (ETX), valproate (VPA) or lamotrigine (LTG) [5]. Ages at inclusion ranged from three to 12 years. The > 4 to < 8 year-old subgroup accounted for more than half of the patients. Therefore, most patients had CAE but some of them had JAE considering the debatable but traditional age threshold of 9–10 years at seizure onset to separate CAE from JAE. This trial showed that, at one year, about half of the patients assigned to either ETX or VPA were seizure-free [6]. This contrasted with the LTG subgroup where only 25% of the patients were seizure-free, the difference being highly significant. Moreover, attentional difficulties, as evaluated by Conners' Continuous Performance Test, concerned about a third of the children and were more frequent in the subgroup assigned to VPA. Using the same cohort, authors were unable to find clinical signs of absences (ocular or motor phenomenon) associated with drug responsiveness [7]. However, they found an association with some genetic polymorphic variants and response to drugs, in particular association between response to ETX and polymorphism for T-type Ca^{2+} channels, and association between response to LTG and polymorphism for P-glycoproteins. In a second study, 208 patients of the initial cohort who had not responded to a first drug after one year were randomized to one of the two other drugs [8]. This study confirmed the greater efficacy of ETX and VPA over LTG, 55–60% of the patients being seizure-free after a second monotherapy with either ETX or VPA against 40% with LTG. It can be concluded from these two studies that pharmacoresistance, i.e. failure of two first-line monotherapies, concern 20–25% of patients with CAE (and probably also with JAE) when ETX and VPA are used whatever the order of introduction of these two drugs.

Interesting data also emerged from the study of Berg et al. who followed 59 children with CAE for at least five years [9]. Patients were treated with either ETX or VPA as initial monotherapy and 56–59% were seizure-free after a first monotherapy, confirming data of the "CAE trial". However, authors found complete remission at five years in only 64% of the patients. They also found that complete remission was

achieved statistically more frequently when ETX was introduced as first drug, suggesting a disease-modifying effect of ETX.

From all these data, there is now consensus to propose ETX as first-line monotherapy in CAE. If ETX is not efficient or not well tolerated, it should be replaced by VPA. If VPA is not well tolerated, it should be replaced by LTG. Pharmacoresistance, i.e. failure of two monotherapies using this strategy, will occur in about 20–30% of patients. In that situation, a drug combination should be considered. If VPA was well tolerated, LTG should be added to take advantage of the synergic pharmacodynamic interaction between these two drugs. If LTG add-on was inefficient or not well tolerated, an association of VPA and ETX should be tried [10]. If these two bitherapies were inefficient but well tolerated, a tri-therapy associating ETX, VPA and LTG could be tried.

The next question is what to do if ETX, VPA and LTG have failed in monotherapy or in combination. This question is very difficult to answer. A first recommendation is to search for a pathogenic genetic variant. This is a general recommendation for all patients having pharmacoresistant absence seizures. In case of typical absences, glucose transporter type 1 (GLUT-1) deficiency needs to be particularly considered. Indeed, GLUT-1 deficiency accounts for about 10% of CAE cases starting before the age of four years [11]. Features other than young age at epilepsy onset and pharmacoresistance that could suggest GLUT-1 deficiency are developmental delay and microcephaly. As GLUT-1 deficiency requires specific care with a ketogenic diet (KD), this diagnosis needs to be ruled out in the presence of pharmacoresistant absences. Diagnosis may be puzzling and relies on a cerebrospinal fluid glucose level less than 40 mg/dl, the identification of a heterozygous pathogenic variant in SLC2A1 gene, and a decrease of GLUT-1 expression on the erythrocyte surface using the METAglyt1 test, none of these three procedures showing 100% sensitivity [12,13].

If GLUT-1 deficiency is ruled out, various options are proposed but all of them rely on small and uncontrolled series. Among the other anti-epileptic drugs (AED), clobazam is regularly cited but this recommendation is not supported by any published series. Topiramate (TPM) was reported in an open trial of five children, two of them being drug-naive [14]. One of them, a drug-naive patient, became seizure-free. This led to a trial of TPM in drug-naive patients with CAE which was stopped after the inclusion of 12 patients considering the absence of efficacy [15]. Effect of zonisamide (ZNS) was reported in only one paper [16]. This was a retrospective review of the files of 48 patients aged under 18 years with typical or atypical absences, including five drug-naive patients. Authors report that 23 of them became seizure-free, but, from this paper, it is impossible to know how many patients had pharmacoresistant CAE or JAE. Levetiracetam (LEV) was reported as leading to epilepsy remission in half of the cases in an open study that included 21 drug-naive children with CAE [17]. This led to a randomized placebo-controlled trial that included patients with CAE and JAE and showed a significant effect of LEV: 23.7% of patients became seizure-free after two weeks in the LEV arm against 4.8% in the placebo arm [18]. So, these data suggest that LEV is less efficient than the three traditional first-line drugs. One paper reported three patients with CAE who became either seizure-

free (two patients) or substantially improved (one patient) after sulthiame (SLT) add-on and failure of many previous AED trials [19]. These data are encouraging but so far no other trials with SLT have been published. Finally, peramppanel (PER) was studied in an open add-on trial that included 20 children with CAE whose first monotherapy had failed [20]. Fifteen of them became seizure-free. The first drug was then removed and nine of them stayed in remission on PER monotherapy. This suggests that PER could be a valuable candidate to be studied in pharmaco-resistant CAE.

Among the non-medicament approaches, KD could be of interest even in the absence of GLUT-1 deficiency. This is suggested by a paper that reviewed files of 21 patients with pharmaco-resistant CAE treated at John Hopkins Hospital, including 13 patients who had followed an Atkins-modified diet, and showed that 10 of them achieved > 90% seizure reduction and four became seizure-free [21]. Finally, the effect of vagus nerve stimulation (VNS) was reported in a paper that reviewed files of nine patients (7 CAE and 2 JAE) who were very pharmaco-resistant, with a mean of five AEDs tried [22]. Under VNS, five patients showed > 50% seizure reduction and one patient became seizure-free. Curiously, this patient had not received ETX during his previous drug trials.

From this review of the literature, it is quite clear that CAE should no longer be considered as a benign easy-to-treat epilepsy syndrome. Pharmaco-resistance is not very different from pharmaco-resistance that is encountered in epilepsies in general, and there is no good option when ETX, VPA and LTG have failed in monotherapy or in combination. Moreover, cognitive deficits are frequent, in particular attention deficit (for a review, see [23]), and are usually not improved with AED, even if the treatment is effective to control seizures. Studies suggest that some drugs, in particular VPA, could even aggravate the attention deficit. Therefore, limiting the cognitive side effects of AED is a priority in patients with refractory typical absences in childhood.

This review also underscores that the development of new therapeutic approaches is mandatory. In recent years, new drugs that specifically act on the pathophysiological mechanisms involved in absence seizures were proposed and tested on animal models. It is now largely accepted that absence seizures are driven by enhanced GABAergic inhibition of the thalamocortical neurons that derives from the reticular thalamic neurons and from extra-thalamic sources (substantia pars reticulata in particular) [1]. One important target is the T-type Ca^{2+} channels that mediate the bursts of action potentials of the GABAergic reticular thalamic neurons [1]. Selective blockers of these T-channels are of great interest, and results of phase II trials in adults using two different compounds (CX-8998 and PRAX-944) are awaiting. Other therapeutic strategies could be to develop blockers of the thalamic GABA-A receptors, or agonists of the 5-HT_{2C} receptors and the metabotropic glutamate receptors type 1 and 5 [1].

3. Epilepsy with myoclonic absences (EMA)

EMA is classified as an epilepsy syndrome different from CAE and is believed to be more pharmaco-resistant than CAE,

control of seizures being achieved in about 40% of the patients [4]. However, this distinction between EMA and CAE is debatable. Indeed, the age at onset is the same, the EEG hallmarks are also identical, and the genetic investigations remain inconclusive in most of the patients with both syndromes. The only difference between these two syndromes is the severity of the myoclonic component associated with the 3-Hz spike-and-wave discharge, which is very marked in EMA and can be present but “discrete” in CAE. Moreover, some patients may be diagnosed as EMA at the onset of their epilepsy and then evolve to classical CAE in the course of their disease, and vice-versa (personal unpublished observations). This further suggests that EMA could be included among CAE. To the best of our knowledge, there are no published series on the AED response in EMA in the last two decades. So therapeutic recommendations are similar to CAE.

4. Epilepsy with eyelid myoclonia (EEM)

Contrary to EMA, the signs and symptoms of the seizures as well as the EEG hallmarks are very different in EEM and CAE. A comprehensive narrative review of EEM was recently published [24]. It is important to note that absences are not always present in EEM. Indeed, eyelid myoclonia, which is required for the diagnosis, may or may not be associated with brief absences. So, response to AED in papers is not assessed on absences but on eyelid myoclonia or associated generalized tonic-clonic seizures. Pharmaco-resistance is seen in 64–80% of the patients. However, if seizures are limited to eyelid myoclonia, they eventually do not affect the quality of life of the patients. Pathogenic genetic variants are found in up to 30% of the patients presenting with associated intellectual disability or any other neurodevelopmental/psychiatric disorder [25]. The genetics of this syndrome is complex and heterogenous, variants most commonly identified being CHD2, SYNGAP1, NEXMIF, RORB and GABRA1 [25]. The finding of such pathogenic genetic variant probably increases the risk of pharmaco-resistance [24].

There is only one open-label multicenter pilot trial in EEM [26]. This trial investigated the effect of LEV in 35 patients, eight of them being naive patients. Twenty-eight patients (80%) were responders and six of them were seizure-free. Retrospective studies and case reports support the use of VPA, LTG, ETX, ZNS, lacosamide and benzodiazepines. It should be stressed that these patients show photosensitivity, which is an essential feature for diagnosis. Therefore, the use of blue lenses to limit photosensitivity appears as important as the use of AED [24].

5. Atypical absences

Atypical absences are usually seen in DEE in association with other types of seizures that are often easier to recognize by the parents than absence seizures. Therefore, the response rate to AED will be assessed on either the most recognizable seizure type (for instance, drop attacks in LGS), or the total number of seizures. It is thus extremely difficult to extract the response rate of atypical absences to AED in the various trials (open-label or placebo-controlled) that were published in the literature in these different DEE. For a child with atypical

absences, it is thus mandatory to perform an extensive individual electro-clinical study in order to characterize the type of epilepsy syndrome and then to propose complementary investigations (in particular oriented genetic investigations) and individualized therapeutic strategies accordingly.

Some particular genetic conditions associated with DEE deserve special comments regarding atypical absences. The first one is the *SLC2A1* gene. As previously discussed, pathogenic variants may be associated with a phenotype of early onset CAE. But a phenotype of DEE may also be encountered, in particular EMAtS or LGS, stressing the need to search for GLUT-1 deficiency in the presence of pharmacoresistant atypical absences [13]. The second gene is *SLC6A1*. This gene encodes the glutamate transporter GAT-1. The loss of function of this transporter was demonstrated in animal models of absence seizures [1]. In humans, pathogenic variants are associated with atypical absences, intellectual disability and, in most patients, other types of seizures, in particular myoclonic-atonic seizures [27]. The electro-clinical diagnosis of these patients is thus usually EMAtS, but some patients present with atypical absences as the only type of seizures and should therefore be considered as unclassified DEE. Pharmacoresistance is found in about one-third of the patients. A KD could be of particular interest in pharmacoresistant patients [28]. Finally, the systematic gene panel or whole exome sequencing in patients with pharmacoresistant atypical absences in the context of DEE shows that many patients harboring pathogenic genetic variant have unclassified DEE. This situation was well illustrated when analyzing the phenotype/genotype correlation of epilepsy associated with pathogenic variants of the gene *KCNB1*: authors found atypical absences in about 25% of the patients and most of them had unclassified DEE [29].

6. Conclusions

Pharmacoresistant absences are frequent in childhood. In this situation, a comprehensive electro-clinical work-up should be performed in order to characterize the type of epilepsy syndrome and, eventually completed by other investigations, to search for a specific etiology. When three drugs that are suitable regarding the epilepsy syndrome have been tried in monotherapy or in combination, the chances of making the child seizure-free are weak. Therefore, it is important to put in the balance the adverse cognitive effects of the AED and their benefit on the seizures, and to consider alternative approaches such as KD.

Disclosure of interest

The authors declare that they have no competing interest.

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