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Pharmacological treatment of attention-deficit/hyperactivity disorder **in children and adolescents with epilepsy**

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Abstract:

Attention-deficit/hyperactivity disorder (ADHD) is the most frequent comorbidities in children with epilepsy with an increased risk of other psychiatric comorbidities and academic underachievement. In children with epilepsy, the attentive form is the most common clinical presentation in pediatric epilepsies. A systemic review and a consensus from the ILAE have been recently published on diagnosis, screening and management of ADHD in children with epilepsy. We give an overview of the **pharmacological** treatment of ADHD in children with epilepsy based on the lecture given at the International League Against Epilepsy (ILAE(French Chapter meeting, October 2018, Lyon. Although only class II and class III studies are available, methylphenidate is the most appropriate pharmacological option for the treatment of ADHD in children with epilepsy with a limited risk of seizure worsening. The medical treatment should be used in combination of the global management including optimal antiepileptic drug treatment avoiding polytherapy, management of psychiatric comorbidities and support at school.

Keywords: attention; epilepsy; methylphenidate

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is the most frequent comorbidities in children with epilepsy [1, 2]. The prevalence of ADHD is higher in epilepsy patients than in the general population [3]. ADHD is observed in about one third of the children and adolescent with epilepsy. ADHD can be seen very early in the course of epilepsy. Epilepsy has been also reported more frequently in ADHD patients that in the general population. This suggests a bidirectional relationship between ADHD and epilepsy as it has been also described for other psychiatric comorbidities [3].

The ADHD in epilepsy patients clinically differs from the most common clinical pictures of ADHD. The epilepsy patients have mostly an inattentive form of ADHD as compared to the hyperactive/impulsive form [4]. This might lead to an absence of diagnosis in some epilepsy patients with an increased risk for academic underachievement and other psychiatric comorbidities like anxiety or depression [5].

The ADHD needs to be adequately treated. The purpose of this paper, based on the lecture that was given at the 2018 epilepsy meeting of the French Chapter of the International League Against Epilepsy (ILAE), is to describe the medical management of ADHD in epilepsy patients. A systematic review and a consensus from the pediatric commission of the ILAE has just been published on screening, diagnosis, and management of ADHD in children with epilepsy [6]. This ILAE consensus should be considered as the reference document [6].

General rules of ADHD management

Pharmacological treatment is the mainstream treatment for ADHD in routine practice as well as in guidelines. Several drugs are available for ADHD [6]. We describe them briefly in the next section. We will then focus in this paper on the evidence for the use of these drugs in case of ADHD in epilepsy patients.

Moreover, a careful evaluation of the antiepileptic drug should be conducted since polytherapy seems to be more likely that monotherapy associated with a behavioral problem [7]. There is a lack of studies to decipher the exact role of antiepileptic drugs as compared to the underlying etiology. There is also a need for studies to better evaluate the role of each molecule. To date, there is strong evidence only for

valproate that can exacerbate attention in children with childhood absence epilepsy [8, 9].

Non-pharmacological treatments are usually described either as a complementary approach or as an alternative to medication. Most of these non-pharmacological treatments consist in behavior parent training and social skills training.

One of the major goal of ADHD treatment in epilepsy patient is to prevent academic underachievement in addition to improving quality of life. The school environment is challenging for a child with ADHD. In epilepsy patients, the large predominance of the inattentive form leads to have a plan to manage distractibility. Through the French education system, it is possible to have some recommendation written for the teachers by the physician from the school system. Most of the time, advice is requested from a specialist. Some general rules are generally recommended to decrease distractibility due to the attention deficit (box 1).

A child psychiatrist or psychologist should be involved at diagnosis if the healthcare professional seeing the patient does not have an expertise in ADHD diagnosis [6]. Attention deficit as seen in ADHD of epilepsy patients can also be seen in anxiety, depression and other psychiatric comorbidities. In addition, the child psychiatrist can provide the child and the family with general counseling to manage the symptoms [5].

Drugs for ADHD

Methylphenidate is a synthetic central nervous system stimulant drug. Methylphenidate has been approved for the treatment of ADHD. Methylphenidate is available in France in different formulations and different dosages. Immediate release as well as extended release formulations are available in France. A network meta-analysis based on the analyze of 190 randomized clinical trials strongly supported the use of psychostimulants as the most efficacious treatment available for ADHD considering pharmacological and non-pharmacological options [10]. As stated below, they is less evidence for the efficacy of methylphenidate in case of ADHD in epilepsy patients.

Atomoxetine is a norepinephrine (noradrenaline) reuptake inhibitor which is approved in the US for the treatment of ADHD. Atomoxetine is not considered as a central

nervous system (CNS) stimulant. This drug is not available in France. It may sometimes be authorized by the French medicine agency under an exception access program. Meta-analysis also suggests that atomoxetine has an acceptable efficacy and safety for ADHD, but the effect seems to be weaker than with psychostimulants [10]. A limited number of studies have evaluated its efficacy and safety for the treatment of ADHD in epilepsy patients.

Clonidine is an alpha-agonist acting though the CNS. It is used to treat high blood pressure. It is currently unclear how clonidine acts to improve attention and modulate impulsivity. It is thought that it is by interacting with some specific brain area. Clonidine is not approved for ADHD. A meta-analysis found a moderate effect for the reduction of ADHD symptoms, particularly hyperactivity [11]. This drug cannot be recommended in case of ADHD in epilepsy patients since no study has been conducted.

Evidence for efficacy of medical treatment of ADHD in epilepsy patients

The recent systematic review of the ILAE pediatric commission reported level B evidence for the use of methylphenidate in children with epilepsy and ADHD while atomoxetine and amphetamines were classified as level U [6]. This has been based on the available evidence with no class I study, seven class II studies and eight class III studies. Most of the studies focused on pediatric populations using methylphenidate. Three studies have been conducted in adult epilepsy patients [12-14]. The overall improvement in ADHD symptoms of children with both AHDH and epilepsy is 65-83%.

Among the class II studies, there is one prospective double-blind placebo-controlled study and six observational prospective studies.

Adams et al. reported 30 adult patients (aged 20-60 years) involved in a prospective double-blind placebo-controlled treated with methylphenidate who displayed an improvement on Conner's continuous performance test [14]. Using a blind cross over design, Feldman et al. reported an improvement of ADHD symptoms in 70% of patients with both ADHD and epilepsy [15]. The largest observational study was conducted in France. In this multicenter study, 167 children were included: 46% had active epilepsy and 26% were on $\geq$2 AEDs. Sixty-one have been treated with methylphenidate. A validated scale used for the assessment of ADHD showed a

significant improvement in AHDH symptoms in 75% of the treated group while only 42% of the untreated group showed any improvement [16].

There are two class III and one class IV studies on the use of atomoxetine for ADHD in epilepsy patients consisting in two prospective observational studies and one retrospective observational study. The largest study reported the use of atomoxetine in 27 patients (4-18 years of age). The main outcome was maintenance of treatment in 37% of the patients without clear report of ADHD improvement [17].

Do psychostimulants have a worsening effect on seizures?

There is a fear of seizure exacerbation with the use of psychostimulants because the Summary of Product Characteristics includes a warning for a change in seizure susceptibility [18]. It is also mentioned that use in epilepsy patients should be cautious.

Exacerbation has been reported with methylphenidate in well-conducted openstudies. In the absence of a placebo-controlled study, it is not yet possible to determine if there is any causality with the use of methylphenidate. Exacerbation seems to occur in 0-18% of the studied groups. But these exacerbations remained mild and led to a discontinuation of methylphenidate in only 5% [6].

A similar phenomenon has been suggested for 7-9% but the limited available data could not allow any clear conclusion for this molecule.

Conclusion

Even though there is no need to further demonstrate that ADHD is common in pediatric epilepsy, there is unfortunately a lack of high quality studies on the impact of AED on attention and on the efficacy of ADHD treatment including methylphenidate [6]. As stated by the recent consensus paper of the psychiatric comorbidities of the ILAE pediatric commission [6], polytherapy is more likely to result in behavioral problems than monotherapy. Studies support the efficacy of methylphenidate in children with epilepsy and comorbid ADHD but the data for the efficacy of atomoxetine in children with epilepsy and ADHD are very limited [6]. Data also support that methylphenidate is tolerated in children with epilepsy (both controlled and refractory).

Disclosure of interest

The author has not declared any links of interest in relation to this article

Box 1: Advice to decrease distractibility due to attention deficit.

- Seat the patient away from windows and doors
- Do not seat close to noisy or hyperactive child
- Divide big assignments into smaller ones
- Provide written instruction that are easy to read and remind where the information can be found
- Allow frequent breaks

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