



# A 6-year-old with childhood absence epilepsy and motor hyperactivity

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## ABSTRACT

A case study of a child with childhood absence epilepsy and hyperactivity introduces the discussion around the psychiatric diagnosis, differential considerations, and pharmacologic treatment options for ADHD/hyperactivity in children with epilepsy. Most of the time, ADHD in children with epilepsy is an inattentive form.

The assessment emphasizes the need to differentiate ADHD symptoms from other psychiatric comorbidities. This is also crucial to evaluate when symptoms emerged, their impact on daily life, and if it could be a potential medication side effect. Speaking about hyperactivity signs, differential diagnoses include anxiety disorders, autism spectrum disorders, learning disabilities, and thyroid disorders. Valproate use is associated with an exacerbation of attentional issues in childhood absence epilepsy, but there are also studies suggesting its possible role in hyperactivity symptoms.

Regarding pharmacologic treatment, limited studies exist on ADHD management in children with epilepsy. Methylphenidate shows effectiveness without significant risk of epilepsy worsening. Atomoxetine and clonidine, usually use in ADHD, lack sufficient data for efficacy and safety in children with epilepsy and ADHD. Pharmacologic treatment should be a part of a global management plan that involves psychoeducation, environmental adaptations, and collaborative efforts between healthcare providers, caregivers, and schools.

## 1. Illustrative case study

Pierre is a 7-year-old boy who was referred for evaluation. His parents report a history of recurrent episodes of altered consciousness, characterized by brief, frequent disruptions in awareness. These episodes occurred multiple times a day, usually lasting around 10 s. There are no other paroxysmal events. The patient has normal cognitive development. After an electroencephalographic recording, Pierre was diagnosed with Childhood Absence Epilepsy (CAE) [1]. Ethosuximide was initiated but did not fully control the absence seizures. Then valproate was initiated. The absence quickly disappeared and the EEG recording with hyperventilation did not record any seizure. He is now stable on valproate monotherapy.

Despite the complete seizure freedom, Pierre's parents are exhausted. Pierre has symptoms of hyperactivity. Pierre has difficulty sitting still. He is constantly fidgeting. When he plays a game, he has difficulty waiting his turn and usually jumps on his seat. Pierre has trouble focusing on any task for more than a short period at home as well as at school. Pierre's teacher said that any small noise during any desk work

would lead to interrupting him on the task. Pierre might also be from time-to-time interrupt conversations. Their pediatrician now refers them after the complaints of the school teacher.

## 2. Brief discussion of the psychiatric diagnosis, based on

### 2.1. Clinical symptoms

The patient has CAE associated with some hyperactivity signs. It is then crucial to identify when they started, how long they've been around, and how they affect daily life. It is also important to clarify if signs of hyperactivity were observed before the epilepsy onset, and whether ethosuximide or valproate influenced the emergence of these symptoms or worsened already existing symptoms.

A full assessment of the diagnosis criteria of ADHD should also be conducted. This will include an evaluation for hyperactivity signs but also inattention and impulsivity signs (Table 1). To diagnose ADHD, it is essential to 1) employ validated ADHD rating scales derived from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV and -5),

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obtained from both parents and teachers (Table 1); 2) gather rating scale data through a comprehensive interview with the parents; and 3) ensure the exclusion of alternative causes for the symptoms. In particular, it should be kept in mind that anxiety or depression which are also common epilepsy comorbidities might affect attention function.

## 2.2. Differential diagnosis

Usually, ADHD in epilepsy patients clinically differs from the most common clinical pictures of ADHD without epilepsy. Epilepsy patients have mostly an inattentive form of ADHD as compared to the hyperactive/impulsive form in non-epilepsy patients [2].

Before considering an ADHD diagnosis some differentials should be ruled out:

- Anxiety disorders: Children with anxiety may display restlessness and hyperactivity, especially when feeling anxious or overwhelmed
- Autism spectrum disorders: Hyperactivity can be present in some children with ASD, especially in the context of repetitive behaviors or difficulties with social interactions.
- Learning disabilities: in some neurodevelopmental disorders, hyperactive behavior is more frequently observed.
- Thyroid Disorders: Hyperthyroidism can cause increased activity levels in children.
- Antiseizure medication side effects. This is discussed in the next section of this article

## 2.3. Consideration for a possible iatrogenic process

There are two studies reviewing ethosuximide, lamotrigine, and valproate related to the same population group with CAE and provide strong evidence that valproate is associated with exacerbation of attentional issues in this population [3,4]. Valproic acid was associated with worse behavioral outcomes (significantly higher total problems, externalizing, attention problems, and attention-deficit/hyperactivity problems) than ethosuximide or lamotrigine [5].

There are also other studies looking at the effect of antiseizure medications (ASM) on attention. These studies have various limitations,

in particular lack of controlled, double-blind randomized studies and the lack of specific evaluation of attention and also other symptoms of ADHD.

The ILAE Pediatric Commission in the 2018 systematic review reported strong evidence (level A) to support that valproate can exacerbate attentional issues in children with CAE. It is also mentioned that polypharmacy is more likely to result in behavioral problems than monotherapy (level C) [6].

The hyperactivity symptoms have not been used as an endpoint in any controlled studies. A retrospective study examined the behavioral side effects of ASM in new-onset epilepsy. They found that younger children seem to be more prone to ASM-related behavioral side effects [7]. These are likely to be higher if youths with epilepsy have baseline hyperactivity/impulsivity. Valproic acid demonstrated a higher behavioral side compared to all other ASM, except levetiracetam. Levetiracetam and carbamazepine also exhibited significantly more pronounced behavioral side effects than ethosuximide [7].

## 2.4. Available rating scales to screen ADHD in children with epilepsy

There are no studies evaluating when to screen children with epilepsy for ADHD. Based on a systematic review, the ILAE pediatric commission suggested that children with epilepsy should be screened at epilepsy diagnosis and repeated annually. The paper also suggests a reevaluation after any change in antiseizure medication [6].

Rating scales permit screening to assess ADHD symptoms but no formal recommendations state using one tool over the other (see details in the systematic review of the ILAE pediatric commission [6]).

There is limited literature on the use of validated ADHD tools specifically for children with epilepsy. Here is a summary of what is available:

- Strengths and Difficulties Questionnaire (SDQ): It was used in several studies and showed varying sensitivity and specificity in identifying ADHD. The SDQ generally had better sensitivity than specificity, indicating its potential as a screening tool. However, it sometimes missed the inattentive presentation of ADHD. The SDQ's limitations in specificity can be addressed through further diagnostic

**Table 1**

DSM 5 Criteria for Attention-Deficit/Hyperactivity Disorders.

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- 1. Inattention: Six or more symptoms of inattention for children up to age 16 years, or five or more for adolescents age 17 years and older and adults; symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level:**
- Often fails to give close attention to details (careless mistakes in schoolwork or with other activities).
  - Often has trouble holding attention.
  - Often does not seem to listen when spoken to directly.
  - Often does not follow through on instructions and fails to finish schoolwork or any task.
  - Often has trouble organizing tasks.
  - Often avoids or dislikes tasks that require mental effort over a long period.
  - Often loses things necessary (e.g. school materials, books, tools...).
  - Is often easily distracted
  - Is often forgetful in daily activities.
- 2. Hyperactivity and Impulsivity: Six or more symptoms of hyperactivity-impulsivity for children up to age 16 years, or five or more for adolescents age 17 years and older and adults; symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for the person's developmental level:**
- Often fidgets with or taps hands or feet, or squirms in seat.
  - Often leaves seat in situations when remaining seated is expected.
  - Often runs about or climbs in situations where it is not appropriate.
  - Often unable to play quietly.
  - Is often "on the go" acting as if "driven by a motor".
  - Often talks excessively.
  - Often blurts out an answer before a question has been completed.
  - Often have trouble waiting their turn.
  - Often interrupts or intrudes on others
- In addition, the following conditions must be met:**
- Several inattentive or hyperactive-impulsive symptoms were present before age 12 years.
  - Several symptoms are present in two or more settings, (such as at home, school, or work; with friends or relatives; or in other activities).
  - There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning.
  - The symptoms are not better explained by another mental disorder (such as a mood disorder, anxiety disorder, dissociative disorder, or personality disorder). The symptoms do not happen only during schizophrenia or another psychotic disorder.
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evaluations by clinicians. The SDQ is a 25-item screen for behavioral problems in 5 scales (emotional, conduct, hyperactivity, peer problems, Total). This is publicly available in over 80 languages.

- Achenbach System of Empirically Based Assessment: Studies using the parent version (CBCL) showed varied sensitivity and specificity in detecting ADHD. There was low agreement between information from parents and teachers, with the teacher version often showing normal results for patients diagnosed with ADHD through psychiatric evaluation. The CBCL is a 120-question screening for a variety of social and emotional concerns. The CBCL screening test typically takes around 15 to 20 min to complete. It is available in many languages.
- ADHD-Rating Scale IV: This scale revealed discrepancies between parent and teacher ratings, with higher scores reported by parents. Sensitivity was higher in parent reports, while specificity was higher in teacher responses. The ADHD-rating scale is 18 items but the 5th edition incorporates the mild changes for older adolescents (e.g., restlessness rather than traditional hyperactivity) and assesses areas of impairment. This is easy to perform and widely available.

### 3. Pharmacologic treatment considerations

There are limited studies with adequate methodology on the treatment of ADHD in children with epilepsy. There is no clear data on the potential benefits of ASM on ADHD symptoms. These effects have not received as much attention as other psychogenic effects like the impact of ASM on mood [8]. While there are reports of lamotrigine showing positive effects on hyperactivity, it's worth noting that this same molecule has also been associated with hyperactivity as a side effect [8]. Then most of the treatments are based also the usual treatment of ADHD. Methylphenidate, a psychostimulant, stands as the standard treatment. Its mechanism of action involves blocking the reuptake of dopamine and norepinephrine, thus enhancing the action of these neurotransmitters in the central nervous system [9]. Its common side effects include eating disorders, weight loss, sleep disturbances, and irritability [9]. Methylphenidate is available in various formulations and dosages including immediate and extended-release options. There are very rare relevant drug-drug interactions in children with epilepsy. Methylphenidate can inhibit the metabolism of phenytoin increasing phenytoin plasma concentration. Methylphenidate also inhibits warfarin, tricyclic antidepressants, or SSRIs [10].

Seizure exacerbation with the use of psychostimulants is frequently feared because the Summary of Product Characteristics includes a warning for a change in seizure susceptibility [11]. It is also mentioned that the use in epilepsy patients should be cautious. Seizure worsening has been reported in some open studies. In the absence of evidence-based data, it is not possible to determine if there is any causality of the use of methylphenidate. The occurrence of this possible worsening might be 0–18 %. However, these exacerbations remain mild and lead to a discontinuation of the methylphenidate in only 5 % of [6].

In practice, we prefer to initiate methylphenidate with an extended-release formulation to have a once-daily administration in the morning. The treatment is usually initiated at 0.3–0.5 mg/kg/d. After 2–4 weeks, the efficacy should be assessed with particular attention to the time when the effect disappears. The presence of adverse events is also evaluated. Special monitoring should be focused at initiation on the emergence of tics, any behavioral change, or some difficulties sleeping. The decrease in appetite is not uncommon but is usually manageable. If the effect is limited or doesn't last the full school time in the absence of any side effect, the dose could be titrated up by step of 0.1–0.3mg/kg/d to 1 mg/kg/d.

Few other ADHD treatments exist. Atomoxetine, a norepinephrine reuptake inhibitor is approved for ADHD and is considered distinct from CNS stimulants [12]. Meta-analyses suggest it has acceptable efficacy and safety, though generally not as potent as psychostimulants. However, there are limited data on its efficacy and safety in ADHD patients

with epilepsy. Atomoxetine is usually started at 0.5 mg/kg with a progressive titration based on the efficacy and the side effects (most frequently various gastrointestinal side effects). The treatment is given once daily. The maximal dose is usually 1.2–1.5 mg/kg/d. Clonidine, an alpha-agonist acting in the CNS primarily used for high blood pressure, has an unclear mechanism for improving attention and controlling impulsivity, possibly through interaction with specific brain regions. While not approved for ADHD, a meta-analysis suggests moderate efficacy in reducing ADHD symptoms, especially hyperactivity [13]. However, its use is not recommended for ADHD in epilepsy patients due to the lack of conducted studies.

### 4. Global management of ADHD in children with epilepsy

ADHD in children with epilepsy, similarly to ADHD, requires global management beyond pharmacological interventions. It involves psychoeducation for both the individual and the caregivers as well as environmental adaptations in educational and home settings (Table 2). Guidance at school is crucial because ADHD is a major risk factor for academic underachievement. A written plan should be provided to the school (such as an individualized education plan). Collaborative efforts between healthcare professionals, caregivers, and schools are important in management.

Referral to a child psychiatrist should be considered when the child's emotional well-being significantly impacts their daily life, academic performance, or social interactions. If the symptoms are not improved by the ADHD global management or if ADHD is associated with other psychiatric comorbidities, the patient should also be evaluated by a child psychiatrist.

### 5. Conclusion

While it's well-established that ADHD commonly occurs in pediatric epilepsy, there is a gap in high-quality studies investigating how ASM affects attention or induces hyperactivity or any other behavioral issue. Dedicated studies are needed in children with epilepsy on the effectiveness of treating ADHD, including, but not only, the use of methylphenidate. Although studies confirm the effectiveness of methylphenidate in treating ADHD alongside epilepsy in children, there is very limited data on the effectiveness of atomoxetine or clonidine in this specific population. The pharmacological treatment should be a part of a global management plan.

### Ethics

The submitted manuscript does not report any data from patient. There is no ethical concern.

### Declaration of interest statement

S. Auvin is Deputy Editor for *Epilepsia*. SA has served as a consultant or received honoraria for lectures from Angelini Pharma, Biocodex, Biomarin, Eisai, Encoded, Jazz Pharmaceuticals, Grintherapeutics, Neuraxpharm, Nutricia, Orion, Proveca, Stoke, Takeda, UCB Pharma, Xenon. He has been an investigator for clinical trials for Eisai, Marinus, UCB Pharma, Takeda, Xenon.

### CRediT authorship contribution statement

**Stéphane Auvin:** Writing – review & editing, Writing – original draft, Conceptualization.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

**Table 2**

Example of advice that could be communicated to promote academic performance. More examples are available on the CDC website which is dedicated to ADHD [14] (not ADHD in children with epilepsy).

**To help with inattention**

- Position the patient away from windows and doors.
- Avoid seating them close to noisy or hyperactive children.
- Break down larger assignments into smaller, manageable tasks.
- Offer written instructions that are easy to read and indicate where additional information can be found.
- Permit frequent breaks to support their needs.

**To help with hyperactivity**

- Acknowledge and accommodate their need for movement during seated activities.
- Encourage appropriate movement breaks to help them manage hyperactivity during learning sessions.
- Provide discreet tools like stress balls or small toys that allow for tactile stimulation to help manage hyperactivity while seated.
- Engage children with ADHD by assigning small tasks or errands, even if it's as simple as walking across the room for a task.
- Balance screen time with opportunities for physical movement.

the work reported in this paper.

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