

ADHD and Epilepsy

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Abstract

ADHD symptoms occur in about 30% of children with epilepsy. The causes include “classical ADHD”, other forms of brain dysfunction, some antiepileptic drugs and the epilepsy itself. Management of the ADHD will depend on the cause. Standard ADHD treatment, such as methylphenidate, dexamfetamine and atomoxetine, is effective in about 70% of cases and is very unlikely to exacerbate seizures.

Introduction

ADHD is one of the more common comorbidities in children with epilepsy. It is typically reported in about 30% of children with epilepsy compared to 3-6% of controls (1;2). Approximately 70,000 school-age children in the UK have epilepsy and about 20,000 of these will have both epilepsy and ADHD. However, probably only a fraction of these children are treated for the ADHD. Reluctance to treat may be related to diagnostic issues but is more likely to be related to concerns about possible seizure exacerbation.

Epidemiology

Hermann et al. (1) studied 75 children aged 8–18 years with new or recent onset idiopathic epilepsy and compared them with 62 controls. ADHD was found in 31% of the children with epilepsy and 6% of the controls. Hesdorffer et al. (3) carried out a population-based study in Icelandic children under 16 years of age. They found that ADHD was 2.5 times more common in children with recent-onset epilepsy than in the controls. Dunn et al. (4) reported results on 175 children (90 M, 85 F) who had a history of epilepsy of at least six months duration. Of the 175 children, a total of 66 (38%) had ADHD of one type or another. There was an equal male to female ratio in the children with epilepsy and ADHD. Sherman et al. (5) reported on a population of children with more severe epilepsy in a tertiary centre. Of 203 children, over 60% met screening criteria for ADHD.

Gonzalez-Heydrich et al. (6) found that 61% of 36 children with both epilepsy and ADHD, aged 6 to 17 years, had a comorbid disorder: 36% had anxiety disorders and 31% had oppositional defiant disorder.

Possible causes of overactivity in children with epilepsy

There are many possible causes of the features of attention deficit hyperactivity disorder in children with epilepsy, including the following.

1. “Classical” ADHD.
2. Other psychiatric disorders.
3. Associated/underlying brain damage or dysfunction.
4. Causes related specifically to the epilepsy including:
 - frequent epileptiform discharges: Rolandic discharges, frontal discharges or generalised spike-wave discharges.
 - Post-ictal elevated mood.
 - Inter-ictal manic psychosis.
5. Adverse effects of medication.

Other psychiatric disorders, not necessarily related to the epilepsy, may present with features of ADHD but careful assessment should distinguish them as being different. These disorders include conduct disorder, generalised anxiety disorder and elevated mood states such as hypomania or mania.

Associated underlying brain damage or dysfunction may include global developmental delay and specific frontal lobe damage or dysfunction. It is interesting to note that, although these children may not present with the classical history of ADHD, they may nevertheless, in at least some cases, respond to the standard medication prescribed for this condition.

Causes related specifically to the epilepsy

Frequent epileptiform discharges

Holtman et al. (7) examined the frequency of Rolandic spikes in the EEGs of 483 ADHD children, aged 2 to 16 years. These were compared to 3726 normal school-age children. Rolandic spikes were found in 27 (5.6%) of the ADHD children. The Rolandic spike frequency in children with ADHD was said to have been significantly higher than expected. ADHD in the children with Rolandic spikes presented earlier; these children had more hyperactive-impulsive symptoms. In a further study, the same group (8) studied 48 children 6.7 to 14.9 years, of whom 16 had ADHD and Rolandic spikes, 16 had ADHD without epileptiform discharges and 16 were healthy controls. Rolandic spikes were associated with increased impulsivity, deficient inhibition and decreased interference control.

Sinzig and Gontard (9) analysed EEGs of 8132 children and adolescents retrospectively. A new diagnosis of absence seizures was made in only 12 of these (0.44%) in the first centre and none in the second. They concluded that there was a minimal occurrence of absences in child and adolescent patients and that this was therefore not the main differential diagnosis that has to be considered in children with ADHD. However, they added that it was important to regard absence seizures as a rare differential diagnosis. From the current author's own experience, in specialist centres, children certainly present with ADHD symptoms because of very frequent absence seizures or epileptiform discharges.

Elevated mood states

Children and teenagers who present with post-ictal elevated mood or inter-ictal manic psychosis certainly have some features of ADHD. However, the history should distinguish clearly between the two conditions, in most cases. For example, in the case of post-ictal elevated mood changes, the history of recent seizures, typically a cluster, is characteristic and usually diagnostic. Above all, for both post-ictal and inter-ictal elevated moods the nature of the condition is intermittent, in contrast to the persistence of the ADHD symptoms, although inter-ictal elevated mood states may persist for long periods, for example several weeks.

Antiepileptic drugs

Antiepileptic drugs that can cause symptoms of ADHD in children include the benzodiazepines, phenobarbitone and vigabatrin. It is also important to consider adverse drug interactions. For example, if lamotrigine is added to carbamazepine in someone who is unable to express their experiences verbally and the patient develops diplopia and/or dizziness, they may present with distressed and overactive symptomatology. Treatment of these symptoms with ADHD medication would be inappropriate; this situation can readily be resolved by decreasing the carbamazepine dose. The history should distinguish this situation clearly.

Should children with both epilepsy and ADHD be treated for the ADHD?

In the past there has been considerable reluctance about treating ADHD in the presence of epilepsy because of concern of possible seizure exacerbations. Are these fears justified by the evidence? What

are the ADHD treatments of choice in children with both conditions?

The first step in the management of the child with epilepsy and ADHD must be to consider the possible causes already described. The management might need to be very different, depending on the cause. For example, if frequent absence seizures are causing the ADHD symptoms, additional or different antiepileptic medication may be appropriate. In contrast, if the child is overactive because of the adverse effects of antiepileptic medication such as the benzodiazepines, medication reductions or a change in antiepileptic medication rather than increasing antiepileptic medication will be appropriate.

The first-line treatment for children with ADHD, regardless of whether they have epilepsy or not, remains methylphenidate. The second-line treatment is atomoxetine. Third-line treatments include dexamfetamine, clonidine and, particularly in children with learning disability and autism spectrum disorder in addition to the epilepsy, low-dose risperidone; the risperidone might act through decreasing agitation/anxiety rather than treating core ADHD symptoms. Neither clonidine nor risperidone is licensed for treating ADHD in children but both may be of benefit. How safe are these drugs for treating ADHD in children with epilepsy? What is the risk of seizure exacerbation? Formularies such as the British National Formulary recommend "caution" when prescribing methylphenidate and dexamfetamine, suggesting that these drugs may exacerbate seizures. What does the published evidence reveal with regard to possible seizure exacerbations?

Gross-Tsur et al. (10) reported a study on 30 children with ADHD and epilepsy, aged 6.4 to 16.4 years. For the first two months they were treated with antiepileptic medication only. Methylphenidate was added in the next two months. None of the 25 children who had been seizure free had attacks with methylphenidate. Of five children with active seizures, three had an increase in seizures and the other two had no change or a reduction in seizures. There were no statistically significant changes in seizure control. If children with active epilepsy are treated with any additional medication, or indeed with no additional medication, the expected outcome would be that some might have fewer seizures, an approximately equal number would have more frequent seizures and some would have no change in seizure frequency. This is exactly the outcome that was reported in the study by Gross-Tsur et al. It would appear that no conclusions can be drawn from the study or, perhaps more accurately, it could be concluded that methylphenidate has no major effect on seizure control. The same authors also reported that there were no significant EEG changes with the methylphenidate and that, in terms of the ADHD symptoms, 70% derived benefit. They concluded that methylphenidate was effective in treating children with epilepsy and ADHD, and added that it was safe in children who were seizure free. They commented that "caution is warranted for those who are still having seizures while receiving AED therapy", although it would appear that they had no evidence whatsoever from the results of their own study to support this statement.

Hemmer et al. (11) presented results on 234 children with complicated ADHD of whom 36 (15.4%) had epileptiform abnormalities. 40% of the abnormal EEGs had Rolandic spikes. 60% of the abnormal EEGs had other focal abnormalities. 205 of the 234 (87.6%) were treated with stimulant medication. Seizures occurred only in the treated group; 1/175 patients with a normal EEG had seizures and 3/30 with epileptiform discharges i.e. 10 % (95% confidence interval 0%, 20.7%). Seizures occurred in two of the 12 children (16.7%) with Rolandic spikes. It is very difficult to draw any conclusions from these results other than that children with epileptiform abnormalities on the EEG are more likely to have seizures than those who do not, regardless of what treatment is given. The authors stated the following conclusions. "These data suggest that a normal EEG can be used to assign children with ADHD to a category of minimal risk of seizure. In contrast, an epileptiform EEG in neurologically normal children with ADHD predicts considerable risk for the eventual occurrence of seizure. The risk, however, is not necessarily attributable to stimulant use."

Gucuyener et al. (12) compared 57 patients with ADHD and active seizures and 62 patients with ADHD and EEG abnormalities before and after treatment with methylphenidate. They found that seizure frequency did not change from baseline. The EEG appeared to improve, leading them to state that methylphenidate had a beneficial effect on the EEG. They concluded that methylphenidate is safe and

effective in children with ADHD and concomitant active seizures or EEG abnormalities.

There have been several reviews on ADHD and epilepsy, (Parisi et al. (13), Hamoda et al. (14), Torres et al. (15), Baptista-Neto et al. (16) and Dunn and Kronenberger (17)), all of which have drawn broadly the same conclusions, namely that there is no evidence that methylphenidate causes seizure exacerbations when used to treat ADHD in people with epilepsy.

Both evidence and opinion suggest that previous concerns about methylphenidate causing seizure exacerbations in children with epilepsy and ADHD were probably not justified. Dexamfetamine has been considered to be even less likely to worsen seizure control and it has even been suggested that it might improve seizure control.

Safety of other drug treatments for ADHD

Wernicke et al. (18) reviewed two independent Eli Lilly databases: the Atomoxetine clinical trial base and the Atomoxetine post-marketing spontaneous adverse event database. The crude incidence rates of seizure adverse events were between 0.1 and 0.2%; there was no significant difference between atomoxetine and placebo. These authors concluded that, although children with ADHD are increasingly recognised as being at an elevated risk of seizures, treatment of the ADHD with atomoxetine does not appear to elevate this risk further.

Gonzalez-Heydrich et al. (19) studied the seizure risk in 21 young people with epilepsy and psychiatric disorders, mean age 12 years, who were treated with risperidone 2.4 ± 3.5 mg/day. They reported that the psychiatric symptoms improved in 71% and the seizures were no worse in any patient. It should be noted, however, that there have been anecdotal reports of seizure exacerbations with higher doses of risperidone.

Conclusions

1. ADHD is under-diagnosed and under-treated in children with epilepsy.
2. There is a broad differential diagnosis for the causes of ADHD symptoms in children with epilepsy, including some antiepileptic drugs and the epilepsy itself. The management of ADHD in the child with epilepsy will depend on the cause.
3. Approximately 70% of children with ADHD and epilepsy will benefit from standard treatment such as methylphenidate and there appears to be no firm evidence that the usual treatments are likely to exacerbate seizures.

GP Comment

What have I learned from this paper?

1. As a GP, I am very cautious about prescribing medication to children and adults with epilepsy, in case it might cause seizure exacerbations. However, it appears that there is no evidence to confirm that methylphenidate exacerbates seizures.
2. ADHD is a risk factor for seizures. Children with ADHD often have abnormal EEGs. If seizures occur, it might be the result of a pre-existing tendency but is unlikely to be the result of medication prescribed to treat the ADHD.
3. ADHD is common in children with epilepsy and there are many causes but it can often be treated successfully.

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