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Attention deficit and hyperactivity disorder in people with epilepsy

Diagnosis and implications to the treatment

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ABSTRACT

The association between attention deficit and hyperactivity disorder (ADHD) and epilepsy can cause significant impact on the social life of affected individuals and their families. Clinical studies suggest that 30-40% of people with epilepsy also have ADHD. There are no studies which demonstrate that short or long-term treatment with methylphenidate increases the risk of seizures. Some studies attempt to relate drug interactions between methylphenidate and antiepileptic drugs, but adverse effects of methylphenidate have not been shown clearly. This review presents some neurobiological and physiopathogenic aspects, common to ADHD and epilepsy, from recent research studies, related to pharmacology, neuroimaging and electroencephalography. Possible risk of occurrence of seizures associated with the use of methylphenidate are also discussed.

Key words: ADHD, epilepsy, methylphenidate, comorbidities, seizures, antiepileptic drugs.

Transtorno de déficit de atenção e hiperatividade em pessoas com epilepsia: diagnóstico e implicações para o tratamento

RESUMO

A associação entre transtorno de déficit de atenção / hiperatividade (TDAH) e epilepsia pode causar importante impacto na vida social dos indivíduos afetados e seus familiares. Estudos clínicos sugerem que 30-40% das pessoas com epilepsia também apresentam TDAH. Não existem publicações que evidenciem que o tratamento a curto ou longo prazo com metilfenidato aumente o risco de ocorrência de crises epilépticas, e alguns estudos procuram relacionar as interações medicamentosas entre o metilfenidato e as drogas antiepilépticas, porém não foram demonstrados os possíveis efeitos do metilfenidato de uma maneira clara. Apresenta-se a seguir, revisão sobre os aspectos neurobiológicos e fisiopatogênicos comuns ao TDAH e epilepsia, a partir de pesquisas recentes relacionadas a estudos de farmacologia, neuroimagem e eletroencefalografia, e discuti-se os possíveis riscos da ocorrência de crises epilépticas associadas ao uso de metilfenidato.

Palavras-chave: TDAH, epilepsia, metilfenidato, comorbidades, convulsão, drogas antiepilépticas.

The association between attention deficit hyperactivity disorder (ADHD) and epilepsy has been the focus of numerous studies published recently[1-4]. Epilepsy as well as ADHD can cause an important impact on the affected individuals' social,

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school and emotional life, and they are highly prevalent disorders in childhood and adolescence[2,3]. The interpretation of neuropsychiatric symptoms as a natural consequence of epileptic seizures or as a side effect of antiepileptic drugs (AEDs) can be responsible for an inadequate evaluation and neuropsychiatric treatment[5]. People with epilepsy present high incidence of associated behavioral disorders. The presence of comorbidities can worsen the prognostic, making the treatment with antiepileptic drugs difficult and many times overshadowing the diagnosis of epilepsy[5]. In childhood and adolescence the neuropsychiatric disorders more observed in association with epilepsy are ADHD, autism, depression and anxiety[4-6]. Clinical studies suggest that 30-40% of people with epilepsy also present ADHD[5,6].

In epilepsy specialized centers, a systematic evaluation of children for the diagnosis of ADHD is rarely performed[7]. Attention deficit in patients with epilepsy should be carefully evaluated. When there is attention deficit in a patient with epilepsy, initially, it should be considered as a secondary symptom to the diagnosis of epilepsy, but the diagnosis of ADHD also should be considered[6]. Inattention could be due to subclinical seizures, secondary drowsiness due to AEDs, cognitive and behavioral disorders, or due to association with ADHD[4,6,8].

Methylphenidate (MPH) is the first choice in drug therapy to ADHD and this can be demonstrated by evaluating the size effect of the various drug options, as it is the most appropriate parameter to compare the effectiveness of medications, when there are not enough clarifying studies to assess directly how effective a medication is when compared to another[8]. The size effect of MPH in the various studies ranged from 0.8 to 1.3, considerably higher than other available medications such as clonidine, bupropion and imipramine, which present size effect of 0.6 and atomoxetine which presents size effect of 0.7 [9].

Attention deficit / hyperactivity disorder

ADHD is a behavioral disorder that begins in childhood, and persists into adulthood in more than half of the cases. Its basic features are inattention, impulsiveness and hyperactivity[5].

The diagnosis based on criteria established by the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition - DSM-IV)[10], requires the presence of at least six of nine behavioral characteristics of inattention / hyperactivity/impulsivity, which must be present for at least six months, had begun before the age of seven and these symptoms should result in a maladaptive and inconsistent functioning when compared to the developmental level.

The prevalence varies from 2.2% to 17.8%, and it is likely that this variation is more related to methodological characteristics of the various studies than to geographical differences[11]. Publications of higher methodological rigor, from all regions of the world as well as national studies, indicate a prevalence of around 5% in school age children[12]. Studies in adults estimate the prevalence to range from 2 to 4.0% [13].

Neurobiology

Evidence obtained through pharmacological, neuroimaging, and brain damage studies suggests that the catecholamines, dopamine and norepinephrine, play a important role[14,15]. However, despite this greater involvement of catecholamines, it is likely that an imbalance occurs between the various neurotransmitter systems that interact among themselves, determining the different phenotypes observed[14,16]. In recent years, a relevant role has also been assigned to other less studied biochemical neurotransmitters such as serotonin, glutamine, histamine and acetylcholine[17].

Some areas and brain circuits associated with cognition and attention are considered candidates for the most likely site of dysfunction in ADHD patients[27]. The involvement of the circuits of the pre-frontal and subcortical / fronto-striatal connections has been the focus of several studies[18-20]. However, research with functional magnetic resonance and imaging studies by diffusion tensor have demonstrated the involvement of other areas and functional connections such as the dorsal anterior cingulate cortex, posterior cingulate cortex and mid-posterior parietal cortex, basal ganglia, particularly the caudate nucleus, several circuits involving the white matter, identified by tractography (studies examining the integrity and pathway of the tracts and circuits) and other regions such as, amygdala, hippocampus, thalamus and cerebellum [18-20].

Some research indicates that there is a delay in cortical maturation in patients with ADHD [18, 21, 22]. Shaw et al.[21] using computacional neuranatomic techniques identified the growth pathway of thousands of points of the cerebral cortex, and demonstrated that the age to reach the peak of cortical thickness in children with ADHD was up to 2.5 years later when compared to controls, especially in prefrontal regions important areas for the control of cognitive processes including attention and motor planning.

This pattern of delayed maturity appears to be related specifically to ADHD than to other neuropsychiatric disorders[22], as demonstrated in research with children with autism or schizophrenia, which indicates a maturacional deviance rather than delay[23].

Environmental factors may play an important role in the clinical aspects of ADHD, or prognosis, but there is not a cause/effect relantionship[24]. Children whose parents have mental disorders, social adversities and poor family dynamics, have a worse prognosis[6,24]. Some studies have

shown that intra-uterine exposure to nicotine, is a significant risk factor for the development of ADHD in children whose mothers were smokers[25].

Genetic studies of molecular character show the participation of several genes in ADHD[26]. Gizer et al.[26] published a meta-analytic review of quantitative genetic studies (i.e., twin and adoption studies)), to determine which candidate genes show consistent evidence of association with ADHD. They found significant association for several genes including the dopamine transporter gene (DAT1), the D4 dopamine receptor gene (DRD4), the D5 dopamine receptor gene (DRD5), the serotonin transporter gene (5HTT), the serotonin receptor gene (HTR1B) and the synaptosomal-associated protein 25 (SNAP-25), and suggest that future studies could explore potential moderators for these associations, such as diagnostic subtypes, gender, presence of comorbidities or exposure to environmental risk factors[26].

ADHD: treatment

Appropriate medical treatment is essential. The psychostimulant methylphenidate is the most used medication in Brazil for treating ADHD. The therapeutic dose range between 20 and 60 mg/day (0.3 mg/kg/day to 1 mg/kg/day)[27].

The response to MPH is effective in more than 70% of the patients, and this response may vary depending on the dosage used, presence of comorbidities and drug combinations[8,27,28]. MPH has a low incidence of side effects, which were considered mild in 3% and moderate in 10% of the cases[29]. The most frequent side effects are decreased appetite, headache, abdominal pain, irritability, difficulty in initiating sleep and less frequently, tachyarrhythmia or hypertension. Studies show that 2 to 10% of patients using MPH suspend the use of the medication due to side effects[29,30].

ADHD: neuropsychiatric comorbidities

Studies show high rates of neuropsychiatric comorbidities associated with ADHD[5,13,31,32]. A consensus of international experts, emphasized the message that "comorbidity is the norm rather than exception"[31]. Souza et al.[32] studied a group of children and adolescents, and found that more than 85% had comorbid disorders. Conduct disorders and oppositional defiant were the most common ones. Other studies also indicate the presence of anxiety disorders, depression, bipolar disorder and motor tics[33].

Epidemiological studies of people with epilepsy indicate a frequent association with ADHD, with rates ranging from 8 to 77% depending on the sample and the criteria used for ADHD diagnosis. Most studies show prevalence between 30-40%[5,13,34]. Dunn et al.[35], evaluating behavioral disturbances in 175 children and adolescents with epilepsy, diagnosed ADHD in 38.7% of the total sample, 24% with ADHD predominantly inattentive type,11% predominantly combined and 2.3% of the hyperactive-impulsive type.

Controversy persists whether the symptoms of inattention, hyperactivity and impulsivity observed in children with mental retardation are part of mental retardation clinical features or other comorbidity, or is it really ADHD associated with mental retardation[36-38]. The fact is, that children and adolescents with mental retardation are at greater risk of developing neuropsychiatric disorders[37,38], and that these children respond to the treatment of ADHD symptoms in the same way that children with normal intelligence. ADHD is present in 7 to 18% of them[37]. Other authors studied the validity of diagnosing ADHD in adults with high intelligence quotient (IQ), and concluded that these individuals have a similar pattern of functional and familial impairment, and psychiatric comorbidities to those found in adults with ADHD and average IQ[39].

Epilepsy and neuropsychiatric comorbidities

Several studies indicate the presence of psychiatric comorbidities ranging from 40% to 70% in people with epilepsy[7,40]. This can affect significantly the prognosis, the quality of life and the treatment. Epilepsy and the use of AEDs can also affect these associated conditions[41,42].

Hanssen-Bauer et al.[42] investigated the occurrence of psychiatric disorders in 74 children and adolescents referred to a tertiary epilepsy center in Norway and found 77% with possible or probable associated psychiatric disorders. Other populational studies related higher frequencies of behavioral diseases in people with uncomplicated epilepsy when compared with other chronic illnesses with non-neurological origin or to the general population[43].

In a population-based epidemiological study, in the United Kingdom, aiming at determining the prevalence and risk factors for developing emotional and behavioral disorders in children and adolescents with epilepsy, Turky et al.[40] identified the severity of epilepsy as a risk factor for emotional problems and depression, while cognitive impairment was related to behavioral problems, specifically conduct problems and ADHD. The severity of epilepsy was also identified by Sherman et al.[43] as a determining factor for the association of ADHD and epilepsy.

In Brazil, Thome-Souza et al.[44], studying factors for the type of psychiatric disorder in a group of 78 children and adolescents with epilepsy, found that 70% had some psychiatric disorder, being depression (36.4%) and ADHD (29.1%) the most common ones, and partial epilepsy was the type of epilepsy most significantly associated with psychiatric disorders. 3

Epilepsy and ADHD

Hermann et al.[45] have studied 76 children and adolescents with idiopathic epilepsy of recent onset when compared to a control group of 62 healthy children, and found that 31% of children with epilepsy had ADHD compared to only 6% in the control group, being inattentive type the most common. The symptoms of ADHD in most cases preceded the onset of the first seizure.

Davies et al.[7] observed the presence of ADHD symptoms in 12% of children with epilepsy in 2.1% of children with diabetes mellitus and 2.2% in controls, whereas McDermott et al.[46] found 28% of children with epilepsy, 12% of children with heart disease and 5% in controls.

When children with epilepsy of recent onset (less than one year) were studied and compared with a control group, a greater frequency of depression (22% versus 4%), anxiety (35.8% versus 22%) and ADHD was shown (26.4% versus 10%)[34]. In the same group of patients Jones et al.[34] found that a subgroup (45%) had some kind of disorder before the first seizure, suggesting an influence of pre-existing neurobiological factors, independent of seizure, epileptic syndrome or drug treatment.

Epilepsy and ADHD: possible common physiopathogenic mechanisms

Different hypothesis try to explain the association between ADHD and epilepsy: the two conditions share the same neuropsychological basis, could have the same genetic predisposition; influence of AEDs on attention and behavior could have a common physiopathology, as in frontal lobe epilepsy and also the presence of subclinic epileptiform activity[2,6,40,45,47]. It has also been discussed the possibility of the relationship epilepsy / ADHD be a "successive comorbidity", that is, the possibility that epilepsy lowers the threshold for the development of ADHD[43].

Quantitative resonance and volumetric studies

Hermann et al.[48] presented the first study in the literature, which tries to correlate structural brain changes in patients with ADHD and epilepsy. They have studied 76 children and adolescents with idiopathic epilepsy of recent onset and compared them to a control group of 62 healthy children. The analysis of quantitative magnetic resonance imaging showed that ADHD in epilepsy patients was associated with a significant increase in gray matter in regions of the frontal lobe and their brainstem was significantly smaller. As it was observed that in this group the symptoms of ADHD in most cases, preceded the onset of the first seizure, the authors hypothesized that this finding could be a static alteration, i.e, a non-progressive alteration. They also noticed that this finding was different from those found in other studies of cerebral volumetry in patients with ADHD, which showed changes in regions other than the front, such as the cerebellum, the corpus callosum and the caudato[18,19,49].

Bechtel et al.[49] studied a group of 14 boys with ADHD and epilepsy, comparing a group of eight boys with ADHD without epilepsy and a control group of 12 healthy boys, assessing the maps obtained by imaging techniques by diffusion tensor, by evaluating the fractional anisotropy, focusing the study on the cerebellum areas. They tried to identify a correlation between epilepsy, ADHD and the cerebellum, as some studies of brain volumetry have strongly suggested the involvement of the cerebellum in ADHD, and because there is no evidence of involvement of the cerebellum in epilepsy. Deficient cerebellar connections were found in both groups (ADHD with and without epilepsy), which suggest that patients with ADHD and epilepsy may have a similar cerebellar pathology to patients with ADHD without epilepsy.

In other studies Kanemura et al.[50] compared the growth of the frontal and prefrontal brain volume in children with benign childhood epilepsy with centro-temporal spikes (BCECTS) with cognitive and behavioral disorders with children with BCECTS without behavioral disorders. They showed that there was a volumetric difference between these two groups, and concluded that the BCECTS with presence of behavioral disorders had a greater volume change of the frontal lobe.

Electroencephalography (EEG) studies

Some studies have shown that the presence of electroencephalographic abnormalities are more frequent in patients with ADHD when compared to the population in general[51], and it also questions what is the risk of seizures in patients with ADHD who show epileptiform discharges in the EEG[52,53].

Richter et al.[51] have found epileptiform changes in 6.1% of 347 children and adolescents with ADHD without epilepsy, and Reséndiz-Aparicio et al.[54] in a retrospective study that analyzed 1000 EEG tracings in children and adolescents with psychiatric disorders (422 with ADHD). They have found epileptiform changes in 7.1%, while it is estimated that in the general population the prevalence is 3.5%[55].

Despite finding several electroencephalographic abnormalities in patients with ADHD, their pathogenic significance has not still been determined[51,53,56]. The most important and consistent EEG abnormality found in patients with ADHD is the increase of theta waves during resting conditions, most evident in frontal regions[51,56].

For some researchers, these EEG abnormalities indicate that there must be changes in neuronal circuits, which have no specific neurological manifestations such as epilepsy, but could be the cause of psychiatric symp-

Table. Studies on efficacy and safety of the MTF in patients with ADHD and epilepsy.

Reference	Study	Result
Feldman et al.[68], controlled, 1989	10 children with controlled seizures (seizure-free for 3 months); double-blind, placebo	• None increased seizure frequency;
Wroblewski et al.[64], retrospective, 1992	Use of MPH in 30 inattentive and epileptic patients, with active epilepsy pos-traumatic brain injury	• Without increasing seizures frequency in 26 patients
Finck, et al.[63], prospective, 1995	20 children with several types of epilepsy	• There was no increase in seizure frequency
Gross-Tsur et al.[58], prospective, 1997	25 children with controlled seizures; 5 with non-controlled seizures; 8 weeks of MPH	• Without seizures in the epileptic controlled group • 3/5 children with active epilepsy increased frequency of seizures after MPH
Semrud-Clikeman, Wical[66], prospective, controlled,1999	12 children with complex partial epilepsy	• Without increasing seizure frequency
Hemmer et al.[59], retrospective, 2001	30 children with ADHD , with epileptiform changes in the EEG and without epilepsy	• 4/30 developed seizures
Moore et al.[67], prospective, 2002	8 adults - (3 uncontrolled seizures)	• One increased the frequency of seizures
Gucuyener et al.[81], prospective, 2003	57 children with active epilepsy and 62 with abnormal EEG, without epilepsy	• 5 from 57 patients with epilepsy have increased seizure frequency
van der Feltz-Cornelis e Aldenkamp et al.[1], prospective, 2006	6 adults (3 epilepsy, 3 psychogenic crisis);	• Without worsening the seizures
Gonzalez-Heydrich et al.[69], (apud Baptista et al.[3]), double-blind, placebo, 2006	27 patients, MPH for 10 months; 1 month without seizures before	• 3 patients had seizures (being 1 with placebo)
Gonzalez-Heydrich et al.[70], (apud Torres et al.[4]), retrospective, 2004.	36 children with epilepsy, (19 with uncontrolled seizures) – MPH compared with dextroamphetamine	• 1/19 uncontrolled seizures using MPH increased the frequency of seizures

toms such as psychotic symptoms, hallucinations, dysphoria, irritability, and attention disorders[51,54].

Clarke et al.[53] examined the effects of psychostimulants (methylphenidate and dexamphetamine) on the EEG of a group of 50 boys with ADHD without epilepsy, compared with a control group before the use of a psychostimulant and six months after using it and they observed that the use of stimulants resulted in normalization of the electroencephalographic abnormalities.

ADHD, epilepsy and methylphenidate

The perceived effectiveness of the MPH in the treatment of ADHD suggests that this medication should be also used in children with associated epilepsy[5,6]. During a long period of time it was believed that the MPH could trigger seizures in vulnerable patients or reduce the epileptogenic threshold. The PDR (Physicians' Desk Reference)[57], the recommendation and guideline manual for prescribing commercially available drugs, widely used by American doctors, and reviewed annually, warns and recommends caution when using the MPH in people with epilepsy, and in the presence of seizure its prescription should be suspended, although there is no controlled study to demonstrate effectively this great vulnerability[1-4,58-62].

Risk of seizures in people who use psychotropic drugs

People with epilepsy often require other psychotropic drugs, especially antidepressants and antipsychotics, which increase the concern of doctors to prescribe these medications without knowing the actual epileptogenic potential of each of these associations[52,61,62].

Seizure incidence rate in patients treated with therapeutic doses of antidepressants and antipsychotics commonly used, varies from 0.1 to 1.5%[52], while the risk of a first unprovoked seizure in the general population ranges from 0.7 to 1 , 0%[52]. In patients who used an excessive dose, the risk of seizure increases considerably, ranging from 4 to 30%[52].

Risk of seizures in people who are treated to ADHD

There are no publications that demonstrate that the treatment with MPH in short or long-term increases the risk of epileptyc seizures[1,2,52,59]. Some authors suggest that MPH should only be considered as an option in the treatment of ADHD children with moderate or severe and well-controlled seizures, whereas, in epilepsy without seizure control it could be an option, taking into consideration the negative impact of not treating the symptoms of ADHD[3,6]. However, it is important to take into consideration before starting the use of MTF, the appropriateness of using AEDs, psychosocial interventions and alternatives to treatment[3,61].

In the first study in children and adolescents with ADHD and epilepsy who used MPH, published in 1986 by McBride et al.[63], 20 children were examined, eight had at least one seizure in the 12 months preceding the use of the MTF, and 12 children were free of seizures for over a year, and in both groups there was no increase in the frequency of seizures. After this study only 11 other studies were published: three retrospective and six prospective and two controlled double-blind trials[1,58-60,64-70]. In these 12 publications, only six included patients with uncontrolled epilepsy. The main features and results of these studies are shown in Table.

Atomoxetine, a norepinephrine reuptake inhibitor, has also shown efficacy in the treatment of ADHD[71]. Hernández and Barragán[72] in a retrospective study of 27 children, found no exacerbation of the number of seizures in none of them. Wernicke et al.[71] also reported the safety of using atomoxetine in children with controlled epilepsy .

Possible interactions between MPH and AEDs

Some studies attempt to relate drug interactions between the MPH and the AEDs, but the possible effects of the MPH were not shown in a clear way[52,59,73]. Kupferberg et al.[73] found no significant change in plasmatic levels of phenobarbital, phenytoin or primidone in 11 adults with epilepsy who also made use of MPH, while in other reported cases changes in plasmatic levels when associating MPH with phenytoin, or with carbamazepine were found[73].

Adverse effects in response to the use of AEDs and MPH has also been demonstrated, mostly in case reports. Gara et al.[74] reported two cases of children who were taking valproic acid and have developed dyskinesia immediately after association with MPH. However, Gay and Ryan[75] also reported a case of dyskinesia immediately after the start of the MPH, but the child did not use any AED.

CONCLUSIONS

The correct treatment of behavioral disorders improves the quality of life of people with epilepsy. Psychosocial factors do not contribute significantly to the etiology of ADHD, but they represent important role in the severity and persistence of symptoms[24].

For a long time it was believed that the MTF could cause seizures in susceptible patients, although there are no controlled studies demonstrating this assumption effectively. Patients with uncontrolled epilepsy more often present problems with attention, behavior and poor school achievement, and could actually benefit from the use of psychostimulants[28].

Despite the lack of double-blind and randomized trials in people with epilepsy and ADHD, to evaluate the safety of the MPH, the open-label studies and the experts opinions allow us to consider the use of this stimulant as effective and safe in patients with controlled epilepsy[3,6,28]. It is possible that the same occur with atomoxetine [71].

We emphasize the idea that to take care of people with epilepsia is much more than only get control of the seizures.

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