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Review

Comorbidity between ADHD and epilepsy: a narrative review

Carlotta Spagnoli[1], Anna Ioppi[2], Federica Di Santo[3], Dolores Rollo[2], Francesco Pisani[3,4]

[1]Child Neuropsychiatry Unit, Mother and Child Department, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy; [2]Psychobiology and cognitive neuroscience, Department of Medicine and Surgery, University of Parma, Parma, Italy; [3]Child Neuropsychiatric Unit, "Policlinico Umberto I" University Hospital, Rome, Italy; [4]Child Neuropsychiatric Unit, Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy

Abstract. *Background and aim*: Epilepsy is a common neurological disease, posing unique management challenges and opportunities in children, especially if neurodevelopmental disorder(s) coexist. The association between epilepsy and attention deficit hyperactivity disorder (ADHD) is well known. However, knowledge gaps persist, and dedicated clinical and experimental studies are not numerous. *Methods:* With this narrative literature review, we wish to describe the association between ADHD and epilepsy in children in terms of epidemiology, clinical presentation, potential pathophysiological bases, diagnostic challenges, therapies, and outcomes. Pubmed and Google Scholar were interrogated with the search terms "ADHD" OR "attention deficit and hyperactivity disorder" AND "epilepsy". We only included papers written in English and focusing on the pediatric age (0-18 years). Additional papers were retrieved by manually searching the reference lists of selected papers. No study period limitation was applied. The search ended on 24th February 2024. *Results:* ADHD in children with epilepsy is common, most often with inattentive presentation and similarly affects boys and girls. It is likely linked to epilepsy by a bidirectional association based on shared neurobiological factors, of genetic and environmental origin, only marginally understood. It significantly impacts prognosis, being associated with lower academic performances and increased risk of psychiatric comorbidities. However, comorbid ADHD is often under-recognized in children with epilepsy, with inattention being attributed to epilepsy or to antiseizure medications. It is also under-treated, due to an overestimation of the risk of lowering the seizure threshold with psychostimulants. *Conclusions*: Further research and increased awareness are warranted to improve management and outcome. (www.actabiomedica.it)

Key words: ADHD, attention, epilepsy, therapy, management, outcome

Introduction

Epilepsy is a chronic brain disorder characterized by an enduring susceptibility to generate unprovoked seizures. Its diagnosis can be formulated in case of two unprovoked (or reflex) seizures occurring more than 24 hours apart, or one unprovoked (or reflex) seizure associated with a relevant (60%) risk of a second seizure in the following 10 years, or in case of a specific epilepsy syndrome (1). Epilepsy can be classified into generalized, focal, combined focal and generalized, and unknown (2). While previous classifications focused on the anatomical bases of epilepsy and distinguished between temporal, frontal, occipital, diencephalic or brainstem seizures, subsequent research completely changed our understanding of its pathophysiological bases, and nowadays epilepsy is better viewed as a neural networks disorder, with seizures being classified as neocortical, thalamo-cortical, limbic or brainstem seizures (1). From an etiological point of view, the

causes of epilepsy can be divided into structural, genetic, infectious, metabolic, immune and unknown (2). The diagnostic work-up is based on careful history taking, general and neurologic examination, EEG and neuroimaging. According to the clinical context and first-level test results, genetic causes can be explored with CGH-array and/or next-generation sequencing techniques, next-generation sequencing techniques, or an infectious/autoimmune work-up. However, the cause still remains unknown in approximately 30% of cases (3).

Globally, it is estimated that 10.5 million children under 15 years of age have active epilepsy (4). The highest incidence is in infancy. Data from Norway report 144 per 100,000 person-years in the first year of life, 61 per 100,000 person-years in the 1-4 years group and 54 per 100,000 person-years between 5 and 10 years (5). However, not only is epilepsy common in this age group, but it is often associated with neurodevelopmental disorders (60% versus 23% of the general population) (6) and other medical comorbidities with a high potential to negatively affect the quality of life and psycho-social achievements.

In detail, neuropsychological impairment is an important comorbidity of epilepsy (7). Cognitive dysfunctions may result from more stable structural brain changes or from more dynamic epilepsy- and treatment-related dysfunctions. The importance of each of these factors may differ depending on a number of variables, including localization and lateralization of epilepsy, patient's age, age at epilepsy onset, epilepsy duration (7) and psychiatric comorbidities (8). Even patients with idiopathic epilepsy can exhibit cognitive dysfunction and academic underachievements at epilepsy onset, irrespective of their specific epilepsy syndrome, and antecedent neurocognitive impairment can be present in some of these children (9). However, in younger children, these issues need to be evaluated from a developmental perspective, acknowledging the higher potential for neuroplasticity in this age group.

According to DSM-5-TR, neurodevelopmental disorders (NDDs) are defined as a group of conditions with onset in the developmental period, inducing deficits that produce impairments of functioning. They include intellectual developmental disorder (IDD), communication disorders, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), neurodevelopmental motor disorders (including tic disorders), and specific learning disorders (*DSM*). The phenotypic heterogeneity within NDDs features variability in symptoms severity, age of onset, and comorbidity between distinct clinical phenotypes. Importantly, comorbidity is reflected in the overlap of causative genes and in the involvement of similar underlying molecular mechanisms. Notably, the majority of genes with identified de novo variation in epilepsy also have identified de novo variants in other NDDs (10), highlighting how this spectrum of disorders are likely to be related to each other, not only from an epidemiological point of view, but also etiologically and pathophysiologically.

Attention-deficit/hyperactivity disorder (ADHD) is a complex neurodevelopmental disorder (11-14), with a worldwide prevalence of 5.3% (15, 16), which is characterized by impairing levels of inattention, disorganization, and/or hyperactivity-impulsivity (11, 13, 14).

Although it is mostly diagnosed in school-aged children, it can present at any age (12). While in childhood males are more often affected than females (2.5-4:1) (17), with increasing age this gender gap tends to reduce (18). Among possible explanations, hormonal changes related to puberty might play a role, but a tendency to underdiagnose ADHD in girls is also likely, resulting in the need for their symptoms to be more severe than those required for diagnosis in males. The definition of diagnostic criteria based on cohorts of boys might have contributed to this gender-related bias.

DSM-5-TR distinguishes three ADHD presentations: predominantly inattentive, predominantly hyperactive/impulsive and combined (Table 1) (19). Among these three main ADHD categories, the inattentive presentation (ADHD-I) is the most common one, followed by the hyperactivity-impulsivity (ADHD-HI) and the combined presentation (ADHD-C) (20). Many children and teenagers with ADHD have comorbid disorders, such as depression, anxiety, disruptive behaviour disorders, learning disorders, enuresis and sleep disorders (21). Whereas in developmental age, oppositional defiant disorder and conduct disorder are the most common comorbidities,

Table 1. Diagnostic criteria for ADHD according to DSM-5-TR.

Inattention: Six or more symptoms of inattention for children up to age 16 years, or five or more for adolescents aged 17 years and older and adults; symptoms of inattention have been present for at least 6 months, and they are inappropriate for developmental level.	**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.	In addition, the following conditions must be met:
Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities.	Often fidgets with or taps hands or feet, or squirms in seat.	Several inattentive or hyperactive-impulsive symptoms were present before age 12 years.
Often has trouble holding attention on tasks or play activities.	Often leaves seat in situations when remaining seated is expected.	Several symptoms are present in two or more settings, (such as at home, school or work; with friends or relatives; in other activities).
Often does not seem to listen when spoken to directly.	Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless).	There is clear evidence that the symptoms interfere with, or reduce the quality of, social, school, or work functioning.
Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (e.g., loses focus, side-tracked).	Often unable to play or take part in leisure activities quietly.	The symptoms are not better explained by another mental disorder (such as a mood disorder, anxiety disorder, dissociative disorder, or personality disorder).
Often has trouble organizing tasks and activities.	Is often "on the go" acting as if "driven by a motor".	The symptoms do not happen only during the course of schizophrenia or another psychotic disorder.
Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time (such as schoolwork or homework).	Often talks excessively.	
Often loses things necessary for tasks and activities (e.g. school materials, pencils, books, tools, wallets, keys, paperwork, eyeglasses, mobile telephones).	Often blurts out an answer before a question has been completed.	
Is often easily distracted	Often has trouble waiting their turn.	
Is often forgetful in daily activities.	Often interrupts or intrudes on others (e.g., butts into conversations or games)	

in adulthood the most commonly diagnosed comorbid issues include substance abuse, mood disorders and anxiety. In some cases, soft neurological signs, sensory dysfunction, coordination impairment, and emotional dysregulation can also be present.

The etiology of ADHD is multifactorial, and both environmental and genetic factors are involved. Currently, the prevailing theory on ADHD aetiology considers it as a polygenic disorder, in which a high number of relatively common genetic variants in different independent loci confer an increased risk (22).

Approximately one-third of cases of ADHD will resolve in adulthood. However, one-half of patients will continue to show symptoms of inattention and hyperactivity as teenagers, often causing social and emotional issues. Approximately 15-20% of patients will

present with comorbid psychiatric disorders within adolescence or adulthood, including alcoholism, drug abuse, obsessive traits or antisocial personality disorder (23).

In this paper, we aimed to narratively review the comorbidity between epilepsy and ADHD in children, in order to highlight the epidemiological, clinical, therapeutic and prognostic issues specific to this complex population. Correctly and promptly identifying such an association is the necessary premise to adequately address management challenges since disease onset, with the aim to provide better care and, thus, better long-term outcomes to children and their families.

Methods

Our aim was to narratively describe the association between ADHD and epilepsy in children in terms of epidemiology, clinical presentation, potential pathophysiological bases, diagnostic challenges, therapeutic strategies, and outcomes. We performed a literature search on Pubmed and Google Scholar with the search terms "ADHD" OR "attention deficit and hyperactivity disorder" AND "epilepsy". We only included papers written in English and focusing on the pediatric age (0-18 years). Additional papers were retrieved by manually searching the reference lists of each selected paper. We did not apply any study period limitation. The search ended on the 24th of February, 2024.

Main body

Epidemiology

ADHD has a prevalence of 30-40% in children with epilepsy, much higher than its 5% prevalence in the general pediatric population (24, 25). Studies including children with epilepsy documented a high risk, between 2.5 and 5.5 times to have ADHD compared to healthy controls (26). Nonetheless, ADHD is often underdiagnosed in children who already have epilepsy, because attention impairments and behavioural issues can be erroneously attributed to the epilepsy itself or to the adverse effects of antiseizure medications (27).

In the pre-school and school years ADHD corresponds to one of the most common neurodevelopmental disorders, with an equal distribution between girls and boys (28, 29), thus differently from the boys prevalence observed in the general population (30).

In detail, the most frequent presentation in children with epilepsy is inattentive (31-33), which – again – is different from what we observe in the general pediatric population. However, among children with severe epilepsies, those experiencing the earliest epilepsy onset and the most drug-resistant seizures tend to show a higher occurrence of the combined presentation ADHD instead of the inattentive presentation (34).

The consequences of inattention in children with epilepsy are often clinically significant, and cause a negative impact on academic achievements (35).

Risk factors for ADHD in children with epilepsy

ADHD has been reported in association with epilepsy since the 1950s (36). However, in clinical practice, recognizing this association can still represent a challenge for pediatricians and pediatric neurologists because antiseizure medications and psychostimulants can have a reciprocal detrimental effect (37, 38). A number of different variables concur to a higher risk of ADHD in children with epilepsy, including IDD and developmental coordination disorder (39, 40), and a family history of ADHD (41). Among prenatal risk factors, a high incidence of inattention and hyperactivity was found in children of women taking valproate during pregnancy (compared to carbamazepine, lamotrigine or phenytoin) (42).

Controversial evidence has been gathered for some epilepsy-related risk factors for attention deficit in children with epilepsy. These include: early seizure onset, high seizure frequency, high burden of interictal EEG discharges or high spike index and antiseizure medications' side effects (43). For some specific epilepsy diagnoses, such as self-limiting epilepsy with centro-temporal spikes (SeLECT), both a younger age at seizure onset and a higher spike index seemed to correlate with performance in attention tests (44), but these results were not replicated in other types of epilepsy (45). Poor seizure control seems to imply a greater risk for ADHD, but based on the available

studies, it is unclear whether this is directly linked to seizure frequency and poor seizure control or rather mediated by polytherapy (27).

ADHD prevalence according to seizure and epilepsy types

ADHD symptoms are more common in certain epilepsies, including generalized epilepsies (and particularly childhood absence epilepsy [CAE]), frontal lobe epilepsy, and SeLECT. A paper comparing children with different epilepsies, found ADHD in 16.67% of children with Developmental/Epileptic Encephalopathy with Spike Wave Activation In Sleep (DEE-SWAS), in 44% of children with generalized epilepsy, in 36.36% of children with left focal epilepsy and in 35% of patients with right focal epilepsy (46).

However, it must be emphasized that the evidence of the high rates of occurrence of ADHD in certain types of epilepsy in children is partially hampered by the fact that the majority of studies did not directly compare patients with specific seizure or epilepsy subtypes. While one study documented worse performances in tests evaluating attention in children with temporal lobe epilepsy compared to children with generalized epilepsies (47), a different study comparing focal epilepsy and CAE found no significant differences in executive function performances (48). Among generalized epilepsies, CAE is associated with ADHD in 30-60% of cases depending on the analyzed cohorts, predominantly with the inattentive presentation (49).

Among focal epilepsies, SeLECT is the most common in childhood. The reported prevalence of ADHD in tertiary referral centres is as high as 60% (50, 51). Affected children have less efficient attentional control. In detail, they show greater interference from distractors moving in their visual field, compared both to healthy controls and children with generalized epilepsy (52). Of note, the presence of rolandic spikes in children with ADHD is associated with impaired inhibition of ongoing response and increased impulsivity compared to children with ADHD but without rolandic spikes and with healthy controls (53). These findings might be related to the presence of frequent discharges during waves low-wave sleep, reduced daytime awareness linked to poor sleep quality and/or transient cognitive impairment related to interictal epileptiform discharges (54). In children with SeLECT, higher levels of bilateral discharges are related to severe ADHD (50). Earlier age at seizure onset and a higher burden of interictal epileptiform discharges in NREM sleep have a negative impact on attention and impulsivity (51, 55). The association between SeLECT and ADHD has been recently reviewed (56).

Frontal lobe epilepsy is the second most common localization in children, and it is often associated with significant impairments in executive functions, including attention, due to prefrontal network involvement (57). However, the prevalence of ADHD in these children has not been systematically investigated. In a case series of 21 children with non-lesional frontal lobe epilepsy, 67% were diagnosed with ADHD (58).

A case-control study compared children between 6 and 16 years with focal epilepsy with age-matched healthy controls, using direct performance and parent ratings. Children with epilepsy performed worse than the control group on timed and complex tasks of attention irrespective of IQ, while performance on simple visual and simple auditory attention tasks was comparable. Earlier age of onset was associated with slower motor speed (59).

Pathophysiology of the association between epilepsy and ADHD

From a neurodevelopmental perspective, various hypotheses on the potential pathophysiological basis of the association between epilepsy and ADHD have been proposed (41):

1. the association between the two conditions is circumstantial and independent, but – as they represent two frequent disorders in children- on an epidemiological basis it is likely to identify a subgroup of youngsters receiving both diagnoses (60);
2. the association between the two disorders is circumstantial but dependent: it is linked to the presence of shared genetic susceptibility factors (29) or to a multifactorial origin linked to the interaction between epigenetic factors and gene/environment interactions or to a common dysfunction in the adrenergic/

noradrenergic systems. Previous research demonstrated that rats with induced epilepsy and interictal spikes show significant levels of ADHD-related symptoms (i.e. inattention and impulsivity), which were attributed to reduced noradrenergic transmission (61, 62);

3. the association between the two phenomena is due to direct causal action: seizures "per se" favour ADHD onset or worsening, which would be seemingly suggested by the highest prevalence of ADHD in children with epilepsy compared to their siblings without epilepsy (29);
4. direct effect of antiseizure medications: some drugs, such as topiramate or phenobarbital are known to cause hyperactivity and inattention (63).

Even though clinical research demonstrates that the most common presentation in children with epilepsy is inattentive, unlike what happens in the general pediatric population, ADHD with and without epilepsy seems to arise from the same pathogenic mechanisms. A growing body of evidence suggests that ADHD can precede epilepsy onset, which would favour a bidirectional relationship between the two disorders and the existence of shared neurobiological abnormalities, yet to be identified (28). In a population-based study on children with epilepsy at onset and ADHD at onset, in children with epilepsy the risk of later ADHD increased by 2.54 times, while in children with ADHD at onset, the risk of later epilepsy was increased by 3.94 times (31).

Shared risk factors between ADHD and epilepsy corroborate the presence of a bidirectional link (64). However, genetic correlation only explains approximately 40% of this phenotypic correlation (65), but shared environmental factors, including preterm birth, neonatal disease, birth weight, lower level maternal education, fewer offspring (66), and toxins (64), were detected as risk factors in clinical research.

Neuroimaging studies documented that ADHD associated with epilepsy correlates with an increased volume of grey matter within the frontal lobes and with reduced brainstem volume (30). A proposed explanation for this finding is a disruption of the physiological cortical pruning and white matter maturation processes in children with ADHD and epilepsy. Morphovolumetric changes might anatomically reflect the dysfunction of the frontal lobe observed clinically (67), and are thought to be associated with genetic or environmental factors inducing abnormal neural networks and hyperexcitability. However, other studies actually identified a marked volume reduction in all lobes and bilaterally in children with ADHD (68). The surface of cortical circumvolutions is also bilaterally reduced. These results are in keeping with an abnormal neural development, occurring between early gestation and infancy, at the time of cortical circonvolutions formation, thus in a critical period. In conclusion, at present it would be controversial to hypothesize the existence of a specific anatomical/morphometric phenotype when ADHD co-occurs with epilepsy, compared to "pure" ADHD (69), but the body of evidence available on imaging in children with ADHD and epilepsy is still scanty (70).

ADHD screening and diagnosis in children with epilepsy

From a clinical point of view, there are no studies indicating the best timing to screen children with epilepsy for ADHD. However, based on the higher risk of ADHD in children with epilepsy at the time of seizure onset or at the first epilepsy diagnosis (30), according to the ILAE Consensus paper of the Task Force on Comorbidities of the ILAE Pediatric Commission, it is advisable to first screen patients for ADHD at 6 years of age or at the time of diagnosis if older than 6 years, and to re-evaluate them yearly. Screening for ADHD is based on the use of validated scales, filled in by parents and teachers, and on DSM-5-TR criteria. Careful history taking from parents and if possible, from teachers is mandatory (27). Attention should also be re-evaluated each time antiseizure medication is changed. However, screening should not be undertaken in the first 48 hours after a seizure, especially in the case of a clinically documented post-ictal state (27). In children with new-onset epilepsy, an accurate neuropsychological and clinical evaluation is necessary before any treatment is started, especially if the child is suspected of having ADHD-related symptoms. Importantly, neuropsychological testing can allow diagnosis of IDD, a learning disorder or a psychiatric

disorder, which have a major impact on management and long-term outcomes.

Importantly, investigating the presence and severity of symptoms in all the main social contexts of a child and from various caregivers is essential, but direct and thorough neuropsychological evaluation is vital. In fact, parental ratings might be weak predictors of direct performances on attention tasks, and some aspects (i.e. speed and complex auditory attention) (59) might be better revealed than others, while there might be a risk for under-reporting of higher-order attention difficulties. Even more notably, difficulties might become clinically obvious only during follow-up, as school demands increase, stressing the need for careful follow-up with formal testing. Furthermore, evaluation of attention tasks with neuropsychological testing should be performed in children with epilepsy even when parent-reported symptoms are low, especially if academic performance is declining (59). Aside from ADHD, subsyndromal attentional issues are also detected with neuropsychological testing in children with epilepsy. While ADHD characteristically features commission errors and disinhibition on simple reaction time tests, patients with epilepsy tend to have a more generalized slowing of performance in complex decision-making tasks (71).

EEG monitoring is required to detect seizures that are not carefully quantified or correctly identified by parents and caregivers. It is essential to evaluate sleep quality and architecture and to quantify interictal discharges during sleep, especially in the context of SeLECT, in order to identify the occurrence of a continuous spike-and-wave during sleep (CSWS) pattern and diagnose DEE-SWAS, or to correlate neuropsychological changes with the spike-index. In clinical practice, it is of paramount importance to carefully examine the temporal relationship between epilepsy onset and ADHD-related symptoms onset.

ADHD per se is associated with EEG changes, including an increase in resting state theta activity over the frontal regions (72), a higher rate of alpha asymmetry) (73), and higher theta-to-beta ratio (74), although the implications of these findings in clinical practice, especially concerning seizure occurrence, is unclear (70). Additionally, children with ADHD have epileptiform interictal discharges, especially over the rolandic areas, more often than in the general population (56), even those never experiencing seizures. Furthermore, overnight EEG was associated with interictal epileptiform discharges in more than 50% of cases in a chort of 42 children with ADHD (75), which might be detrimental to cognitive and behavioural abilities.

The presence of poor sleep quality or a sleep disorder needs to be investigated and managed. In fact, sleep problems are common in children with epilepsy, especially difficulties on initiating and maintaining sleep, sleep-disordered breathing, parasomnias and excessive daytime sleepiness (76). Their presence is associated with higher rates of inattention, impulsivity and hyperactivity. The Children's Sleep Habits Questionnaire (CSHQ) is a retrospective, 45-item parent questionnaire being used to examine sleep behaviour in young children (77). In a case-control study on children and teenagers aged between 7 and 18 years with epilepsy and with minor health issues, the T-DSM-IV-S total, inattention and hyperactivity-impulsivity scores were significantly associated with a higher CSHQ total score, delineating parent-rated sleep problems (78).

Treatment in children with comorbid ADHD and epilepsy

Treatment of children with epilepsy and ADHD can represent a challenge, as antiseizure medications need to be carefully selected in order not to negatively affect the neuropsychological profile of treated children. As a typical example, phenobarbital is known to worsen behaviour (from hyperactivity to sedation) and cognition (79). Topiramate can have a detrimental effect on language and cognitive functions, including attention and memory (38), especially in patients with IDD. Valproate also has a negative impact on attention compared to lamotrigine and ethosuximide, as documented in a study based on a battery of neuropsychological tests and questionnaires administered to children with CAE (80). On the contrary, lamotrigine shows a positive effect on both cognition and behaviour (81). A similar effect was proposed for add-on lacosamide (82), but data are still limited, although it seems that the overall effect of lacosamide on cognition and mood is limited (83).

Table 2. ADHD treatment in children and adolescents (84).

Age range	First-line treatment	Second- and third-line treatment	Additional considerations
4≤x<6 years	evidence-based parent training in behaviour management (PTBM) and/or behavioural classroom.	MPH if behavioural interventions do not provide significant improvement and there is a moderate-to-severe continued disturbance in the 4- through 5-year-old child's functioning.	If evidence-based behavioural treatments are not available, the risks of starting medication before the age of 6 must be weighed against the harm of delaying treatment.
6≤x<12 years	stimulant medications + PTBM and/or behavioral classroom intervention (both if possible)	atomoxetine, extended-release guanfacine, extended-release clonidine (in this order)	
12≤x<18 years	Medications* + evidence-based training interventions and/or behavioural interventions, educational interventions and individualized instructional support		Before drug prescription, the patient should be evaluated for symptoms of substance use. * prescription of non-stimulant medications minimizing abuse potential may be considered (i.e. atomoxetine, extended-release guanfacine, extended-release clonidine)

Moreover, the presence of additional comorbidities, such as anxiety or oppositional defiant disorder, has to be carefully evaluated when selecting the most appropriate drug.

ADHD management is complex. Its treatment is based upon an evidence-based intervention in the different contexts of a child's life (mainly school and family) with behavioural therapy and stimulant and non-stimulant medications. Before 6 years of age and in case of mild functional impairment caused by ADHD symptoms, parent and teacher training are the main interventions. For children not reaching the threshold for ADHD diagnosis, psychosocial interventions can be offered (84) (Table 2).

MPH should be considered as the first treatment option in children with moderate and severe ADHD (85) from 6 years of age or if evidence-based behavioural training has failed (84). However, paediatric neuropsychiatrists are often cautious in prescribing psychotropic drugs for ADHD treatment in children with epilepsy due to the notion that they might reduce the seizure threshold. The Italian ADHD Registry includes patients aged between 6 and 18 years with ADHD, 1350 of whom were treated with metylphenidate (MPH) and 753 with atomoxetine (86), the two most widely used and most effective drugs in reducing ADHD symptoms (87, 88). In this cohort, seizures occurred in three patients in the MPH group and in 2 patients in the atomoxetine group over a five-year follow-up) (86). In a different study, EEG was performed in 244 children with ADHD before treatment initiation, and epileptiform discharges were detected in 36 (15.4%). Seizures occurred only in the treated group, in 3/30 patients with abnormal pre-treatment EEG versus 1/175 patients without epileptiform discharges (incidence: 10% versus 0.6%) (89).

A retrospective study on 105 children with epilepsy and ADHD treated with MPH found seizure exacerbation in 20% of subjects and a worsening in EEG findings in 32% of cases over a 22-months follow-up (90). However, a retrospective cohort study comparing 18166 children with epilepsy treated with stimulants and 54197 non-treated subjects did not find an increase in seizure-related hospitalizations (3.6 versus 4.3 per 100 patient-years) (91).

Data on alternative ADHD medications are more limited. Twenty-seven patients with an average seizure frequency at baseline of 7 ± 24 per month were treated with atomoxetine in a third-level centre (38). 92.5% of these patients had not previously responded to stimulants. The likelihood of treatment success in this complex group with severe epilepsy, multiple medications

and a high level of comorbidity was about 37%. Although there were no serious adverse events, 63% of patients discontinued atomoxetine, although none because of seizure exacerbation. There was no evidence of an increase in seizure frequency. Of note, atomoxetine has a risk of hepatotoxicity (92), which should be taken into account in children with epilepsy on polytherapy or on valproic acid.

According to the ILAE Consensus paper of the Task Force on Comorbidities of the ILAE Pediatric Commission, if seizures occur less than once a month and symptoms of ADHD are moderate, both MPH or atomoxetine might be used (27). If they are unsuccessful, guanfacine or clonidine might be considered, depending on ADHD severity (93, 94). The rate of improvement of ADHD-related symptoms in children with epilepsy is reported to be between 65% and l'83% (27).

Outcome of ADHD in individuals with comorbid epilepsy

Individuals with ADHD have a lower likelihood of completing school and show lower rates of access to higher levels of education. Reduced academic performance can be associated with lower opportunities to find a job and impaired social functioning. Untreated patients with ADHD have marked academic and social sequelae. Conversely, ADHD treatment has been associated positively with academic and social achievements and with increased self-confidence (95-97). However, even an effective treatment does not invariably lead to later normalization of symptoms to the general population's levels (98-100). On the other hand, complete symptom remission is associated with lowering rates of illicit drug abuse and antisocial behaviours towards those seen in the general population (101), highlighting the importance of adequate treatment and the negative prognostic implications of undertreatment, a risk which is probably higher for children with comorbid epilepsy.

An observational study investigated two cohorts of patients with ADHD twice. Sixteen boys had combined idiopathic epilepsy/ADHD and 14 boys had developmental ADHD without epilepsy. The first evaluation was performed at a mean age of 10.94 years, while the second at a mean age of 15.82 years. ADHD symptoms reduced from the time of late childhood to adolescence in both groups (102).

A controlled prospective cohort study assessed psychosocial and functional outcomes at 10-year follow-up in a cohort of uncomplicated childhood-onset epilepsy compared to healthy controls. At a mean age of approximately 23, the two groups showed similar psychosocial outcomes in educational attainment, living arrangement, employment status, personal income, marital status and quality of life. However, young adults with epilepsy had poorer functional outcomes compared to controls, and both comorbid ADHD and academic issues were identified as risk factors, while remission was not related to cognition or overall disability (103).

Conclusions

ADHD in children with epilepsy is common; it mainly presents with inattention, unlike the prevailing hyperactive-impulsive presentation in the general population; it similarly affects boys and girls rather than prevailing in boys as in the general population. These data suggest that there might be differences between the sometimes called "developmental" ADHD and ADHD associated with epilepsy. However, evidence gathered from genetic, epidemiological, and neuroimaging data at present does not allow any definite conclusions on the reasons for these observations (64, 70, 104).

ADHD and epilepsy are likely linked by a bidirectional association, based on shared neurobiological factors, of genetic and environmental origin, which are only marginally understood. The presence of ADHD in children with epilepsy significantly impacts prognosis, being associated with lower academic performances and an increased risk of psychiatric comorbidities (i.e. anxiety, depression, drug abuse, externalizing disorders). Nonetheless, it must be noted that all NDDs are on a spectrum of conditions, which also partially overlap with epilepsy, and the existence of nosographic categories, although very useful in practical terms, might not correctly identify the core etiological and pathophysiological features of these disorders

(105), which is possibly also making the concept of "comorbidity" controversial and somewhat misleading.

In spite of its common occurrence, ADHD is often under-recognized in children with epilepsy, because inattention is often attributed to epilepsy or to antiseizure medications. Even more importantly, it is also often under-treated, due to an overestimation of the risk of lowering the seizure threshold with psychostimulants.

However, based on the accumulating data on the long-term negative consequences of untreated ADHD, it is necessary to spread the correct information on ADHD management among involved clinicians, like paediatricians and child neuropsychiatrists, in order not to miss this opportunity to prevent the development of a low quality of life and associated psychiatric issues (64, 70, 104).

From a research point of view, long-term outcome data in children suffering from epilepsy and ADHD have been seldom investigated and we have limited data to compare the neuropsychological outcome of ADHD patients with and without epilepsy, or to compare children with ADHD and epilepsy with those suffering only from epilepsy, especially with respect to long-term evolution of core symptoms, effect of therapy and associated comorbidities.

In conclusion, children with epilepsy and ADHD are a complex population, and different lines of intervention, both in clinical practice and at the research level can be identified and should be implemented in the next years.

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Correspondence:
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Carlotta Spagnoli, Dr
Child Neuropsychiatry Unit, Mother and Child Department, Azienda USL-IRCCS di Reggio Emilia
Viale Umberto I, 80, 42123 Reggio Emilia, Italy
Phone: +390522296033
E-mail: carlotta.spagnoli@ausl.re.it
ORCID: 0000-0002-1828-4035