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Attention-Deficit Hyperactivity Disorder (ADHD) and Tuberous Sclerosis Complex

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The neurobiological basis of attention-deficit hyperactivity disorder (ADHD) in tuberous sclerosis complex is still largely unknown. Cortical tubers may disrupt several brain networks that control different types of attention. Frontal lobe dysfunction due to seizures or epileptiform electroencephalographic discharges may perturb the development of brain systems that underpin attentional and hyperactive functions during a critical early stage of brain maturation. Comorbidity of attention-deficit hyperactivity disorder (ADHD) with mental retardation and autism spectrum disorders is frequent in children with tuberous sclerosis. Attention-deficit hyperactivity disorder (ADHD) may also reflect a direct effect of the abnormal genetic program. Treatment of children with tuberous sclerosis complex with combined symptoms of attention-deficit hyperactivity disorder (ADHD) and epilepsy may represent a challenge for clinicians, because antiepileptic therapy and drugs used to treat attention-deficit hyperactivity disorder (ADHD) may aggravate the clinical picture of each other.

Keywords: ADHD; tuberous sclerosis complex; antiepileptic drugs; methylphenidate; autism

Attention-deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder with onset in early childhood, caused by the presence of many genetic and environmental risk factors.[1] Attention-deficit hyperactivity disorder is subserved by many brain structures, and neuroimaging studies show evidence of at least 3 anatomic networks that function separately and together to support various aspects of attention.[2] These interacting networks are (1) a vigilance network comprising the right frontal and right parietal lobes; (2) an executive attention network including the left lateral frontal areas and the anterior cingulate gyrus; and (3) an orienting network consisting of parietal, midbrain, and thalamic circuits.[2-4] Different impairment of these systems may cause inattention, hyperactivity/impulsivity, or both.

Sometimes, symptoms of ADHD are associated with severe neurogenetic disorders, such as neurofibromatosis 1, Turner syndrome, Williams syndrome, velocardiofacial syndrome, Prader-Willi syndrome, and fragile X syndrome.[1] Attention-deficit hyperactivity disorder is also common in individuals with tuberous sclerosis complex, a multisystemic genetic disease caused by a mutation in 1 of the 2 tumor suppressor genes, *TSC1* on chromosome 9q34 or *TSC2* on chromosome 16p13.3.[5] In tuberous sclerosis complex, abnormalities of neuronal migration and cellular differentiation and excessive cell proliferation, all contribute to the formation of various brain lesions including cortical tubers, subependymal nodules, subependymal giant cell tumors, and widespread gray and white matter abnormalities.[6]

Patients with tuberous sclerosis often show attention deficits, most notably in dual tasking/divided attention. Although this association between ADHD and tuberous sclerosis complex has been widely described, little is known about the possible pathogenesis underlying it.[7] Furthermore, this comorbidity may represent a challenge for child neurologists because antiepileptic therapy may aggravate ADHD, and drugs used to treat ADHD may aggravate epilepsy. In this article, we discuss the current understanding of the pathogenesis and the neurobiological links between ADHD and tuberous sclerosis complex and review some of the major considerations that guide child neurologists to tailor treatments according to clinical needs.

Epidemiology of ADHD and Tuberous Sclerosis Complex

In patients with tuberous sclerosis complex, ADHD has been reported as being more frequent than in the general

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Table 1. Frequency of ADHD in Tuberous Sclerosis Complex

Authors	Patients With Tuberous Sclerosis Complex (N)	Patients With ADHD (N)	% of Patients With ADHD
Hunt[8]	300	85	28
Gillberg et al[9]	32	20	62
de Vries et al[7]	250	139	55
Muzykewicz et al[10]	241	73	30

population, ranging from about 30% to 60%[7-10] (Table1). In a large population-based study, Hunt observed that hyperactive behavior was significantly more frequent in children with tuberous sclerosis complex experiencing at least 1 seizure than in patients without seizures at all.[8] Moreover, although ADHD is more frequently observed in severely affected individuals with tuberous sclerosis with autism spectrum disorders, it also affects patients with tuberous sclerosis complex with normal intelligence.[7-9]

Why ADHD Is Associated With Tuberous Sclerosis Complex

The pathogenesis of ADHD in tuberous sclerosis complex is still largely unknown, and many different hypotheses have been raised to explain this comorbidity. The commonly accepted etiological model is that the damage resulting from tubers causes the cognitive and behavioral impairments in tuberous sclerosis complex.[11] It is also well known that children with epilepsy, independently of etiology, have an increased risk for ADHD,[12,13] and that certain epilepsy syndromes, such as frontal lobe epilepsy, may also predispose to ADHD-like behavior. Finally, ADHD in tuberous sclerosis complex can also reflect a direct effect of the abnormal genetic program.

Localization of Central Nervous System Lesions in Associative Areas

In tuberous sclerosis complex, the localization of tubers, the abnormalities of neuronal migration, and widespread gray and white matter abnormalities could be the basis of the dysfunction that leads to ADHD symptoms. Cortical tubers can disrupt the brain networks that control different types of attention,[14,15] as well as frontal brain systems, thus leading to abnormalities in regulatory and goal-directed behaviors.[14] Fewer tubers in the frontal regions might be a favorable predictor for mental development[16]; however, more recent data indicate that the proportion of total brain volume occupied by tubers is a better predictor of cognitive function than tuber number.[17]

The presence of subependymal nodules, which are typically located along the walls of the lateral ventricles often adjacent to the caudate nucleus, has been reported to be associated with hyperactive and aggressive/disruptive behavior[10]; the growing of these lesions could interfere with the frontostriatal circuits.

Comorbidity With Epilepsy

Different hypotheses have been generated regarding the possible pathophysiology of the comorbidity between ADHD and epilepsy in the context of brain development, including the effects of chronic seizures, electroencephalographic epileptiform discharges, as well as the effects related to the antiepileptic drugs.[18-20] Epilepsy occurs in about 90% of patients with tuberous sclerosis complex, with onset often in the first year of life, and in a sizeable proportion of patients, seizures tend to persist and are refractory to antiepileptic drug treatment.[21] Frontal lobe epilepsy shares behavioral features with ADHD, presenting in some patients with impulsivity, disinhibition, and excitement/irritability.[22] Children with tuberous sclerosis complex with frontal lobe electroencephalographic foci show deficits on tasks assessing impulse control and planning, as well as impaired inhibition and set shifting relative to controls (Figure 1). Side of the seizure focus may contribute to executive dysfunction in patients with epilepsy, particularly a left frontal focus can interfere with inhibitory processes.[23] Part of the behavior and social problems observed in children with tuberous sclerosis complex with frontal lobe epilepsy is probably attributable to their attention problems, their lack of inhibitory control, and their impaired ability to disregard nonrelevant information. Frontal lobe dysfunction continues to interfere with the child's mental activity even when adequate seizure control is achieved[24] (Figure 2). Executive functions seemed to be particularly vulnerable to interictal electroencephalographic spikes during critical stage of brain maturation; their disruption possibly interferes with the normal development of learning processes.[25] There is a critical early stage of brain maturation during which frontal lobe epileptiform electroencephalographic discharges perturb the development of brain systems that underpin attentional and hyperactive disorders.[26]

Comorbidity With Mental Retardation and Autism Spectrum Disorders

Patients with tuberous sclerosis complex range from intellectually normal to severely retarded: 30% of patients are profoundly impaired, with the remaining 70% having a distribution pattern ranging from 40 to 130 intellectual quotient, the mean intellectual quotient being shifted slightly down (mean intellectual quotient = 93).[27] Although the high incidence of learning disability reported in patients with tuberous sclerosis complex can confound studies of ADHD, conservative estimates indicate that about 60% of children with tuberous sclerosis complex with mental retardation have ADHD.[9]

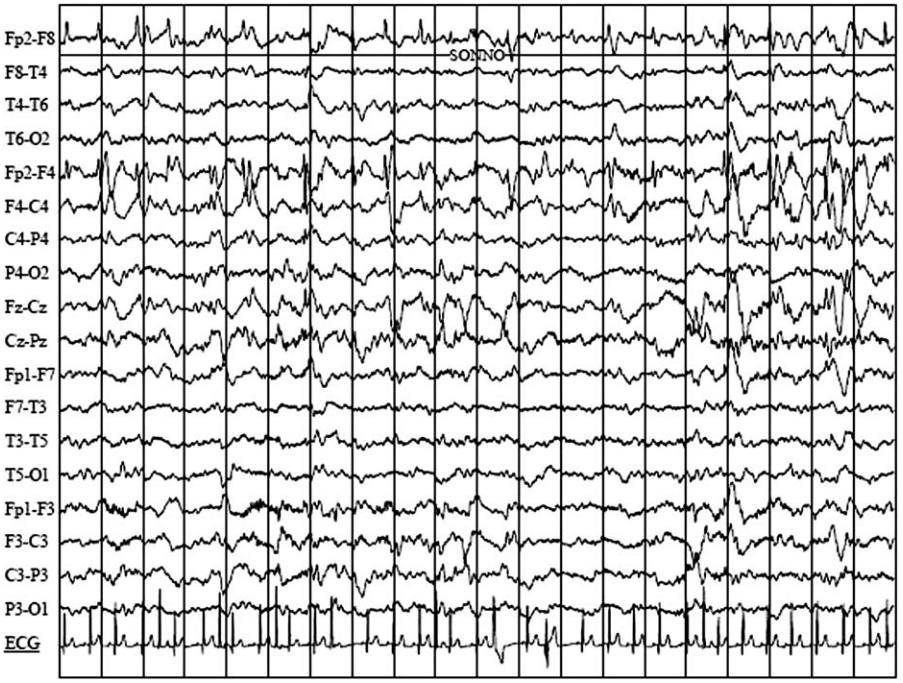

Figure 1. Sleep electroencephalographic recording epileptiform abnormalities prevalent in the right frontal region in a hyperactive 6-year-old boy with tuberous sclerosis complex.

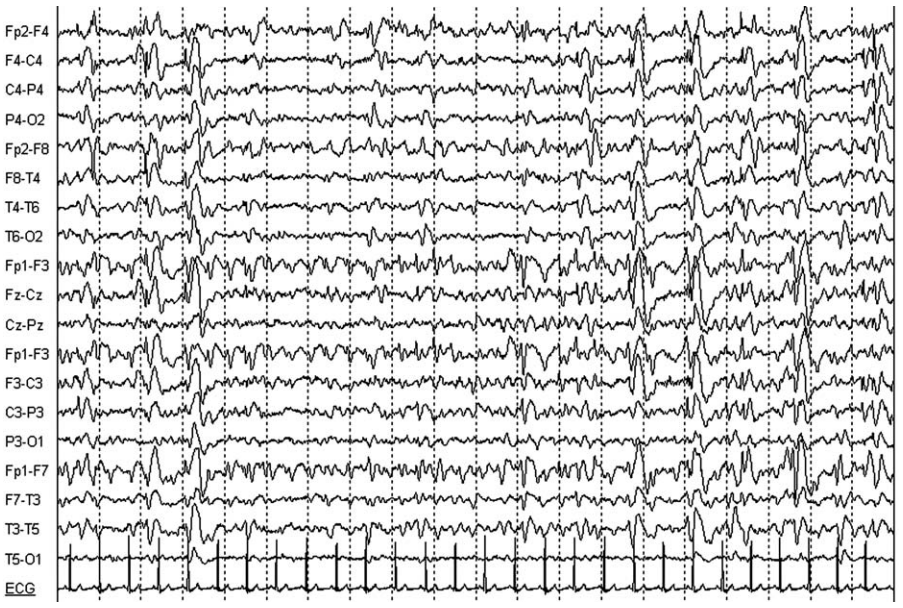

Figure 2. Frontal discharges with secondary bilateral synchrony in a seizure-free 9-year-old girl with marked inattention and lack of inhibitory control.

There is strong evidence for high rates of autism spectrum disorders in children with tuberous sclerosis complex, with up to 50% to 60% of individuals affected.[9,28,29] Autistic symptoms seem to be more common in mentally retarded patients with tuberous sclerosis complex.[7,30] It has been suggested that an early dysfunction in the associative areas owing to the location of cortical tubers may be responsible for the autistic

features.[15] Younger children and those with a diagnosis of autism spectrum disorder were rated as having more ADHD/hyperactivity symptoms.[31] There is in fact a high percentage of children with tuberous sclerosis complex affected by both autistic symptoms and ADHD, thus suggesting a possible neurobiological link between these conditions.[32]

Genotype–Phenotypes Relationships

Recently, molecular genetic studies have provided convincing evidence for multiple interacting genes as the main causative determinants of ADHD and support dysregulation of neurotransmitter systems as the basis of genetic susceptibility to the disorder. In ADHD, genome scan studies have demonstrated linkage on several chromosomes, including the 16p13 region, where the *TSC2* gene is located.[33-35] In a North American study that retrospectively assessed all the psychiatric comorbidities in a wide population with tuberous sclerosis, a higher frequency of ADHD was observed in patients with tuberous sclerosis complex 2 rather than in those with tuberous sclerosis complex 1.[10] Furthermore, a locus of susceptibility to autism has been identified in the 16p13 chromosome region that encodes for the *N*-methyl-D-aspartate glutamate receptor 2A.[35-38] Although the glutamatergic signaling pathway represents an ideal candidate susceptibility system for ADHD, there are contrasting results about the association between this polymorphism and ADHD.[38,39] An association between variations in the *N*-methyl-D-aspartate glutamate receptor 2B subunit gene and ADHD has been also suggested.[40] New data from animal models emphasize the role played by an anomalous glutamatergic pathway in the prefrontal-striatal circuits.[41] In addition, greater concentrations of striatal glutamate, glutamate/glutamine, and creatine have been detected by magnetic resonance spectroscopy in patients with ADHD compared to controls.[42]

In frontal and temporal regions, the *TSC2* gene product tuberin is highly expressed; these brain areas are involved in the behavioral phenotypes of autistic disorder and ADHD. Tuberous sclerosis complex 1 and tuberous sclerosis complex 2 messenger RNA and proteins have also been detected in the cerebellum, which has been shown to play a part in ADHD.[1,6] *TSC1* and *TSC2* genes have a central role in the integration of multiple signaling pathways through numerous putative phosphorylation sites and interaction domains on hamartin and tuberin. Therefore, the variability of neurocognitive manifestations observed in tuberous sclerosis might depend on which structural and functional features and phosphorylation sites are impaired by an individual mutation.[43]

Treatment Options

Psychotropic agents can be useful for behavior and psychiatric problems in addressing target symptoms including aggression, impulsivity, hyperactivity, and obsessive-compulsive symptoms in individuals with tuberous sclerosis complex.[30] Several antiepileptic drugs are known to cause behavioral activity that may exacerbate underlying ADHD symptoms. Additionally, stimulant medications used in patients with ADHD may lower the seizure threshold in patients with tuberous sclerosis. Therefore, treatment of children with tuberous sclerosis with combined symptoms of ADHD and epilepsy can represent a challenge for clinicians.

Effects of Antiepileptic Drugs on ADHD

Some of the newer antiepileptic agents, such as topiramate and levetiracetam, which have proved to be highly effective antiepileptic drugs in patients with tuberous sclerosis complex, may cause relevant behavioral changes, so they must be used with caution in children with tuberous sclerosis with ADHD and epilepsy comorbidity.[44] In a recent series of patients with tuberous sclerosis treated with levetiracetam, the most frequently reported side effects were behavioral problems, with agitation being the most common.[45] However, levetiracetam in autistic children can improve behavior, by reducing hyperactivity, impulsivity, mood instability, and aggression.[46,47] Lamotrigine has been demonstrated to improve behavior and attention in epileptic children with a specific positive psychotropic effect on mentally retarded and autistic children.[48,49]

Effects of ADHD Treatments on Epilepsy

For children with tuberous sclerosis complex with epilepsy plus ADHD, the safety and efficacy of many of the standard treatments for ADHD remain to be studied, because no controlled studies have been published. There is some evidence for the short-term efficacy of methylphenidate in decreasing ADHD symptoms in children with epilepsy, and several studies have reported that methylphenidate does not increase seizure frequency in children with epilepsy.[50-53] In a single open-label trial, only 1 of 17 patients with ADHD and epilepsy showed an increase in the number of epileptic seizures in the first 2 weeks of treatment with atomoxetine.[54] Only 1 isolated case of atomoxetine-induced seizure, following a drug overdose was reported.[55] A more recent meta-analysis confirmed that there was no significant difference in the rates of seizures between those taking atomoxetine, methylphenidate, and placebo.[56]

If the seizures are occurring less than once per month, and there is at least moderate impairment from the ADHD, then either methylphenidate or atomoxetine should be started, keeping in mind that methylphenidate has the strongest evidence for efficacy and safety in this population. If these fail, then a trial of guanfacine or clonidine can be considered depending on the severity of the ADHD.[57,58] According to the knowledge available

currently, modafinil and tricyclic antidepressants should be reserved for children with marked impairment from ADHD plus epilepsy whose ADHD symptoms have failed to improve with other treatments.[44] Bupropion has a documented risk of increasing seizure frequency and should be avoided in epileptic comorbidity.[59]

Clinicians should periodically reassess for the possibility that ADHD medications are no longer needed for selected patients with tuberous sclerosis.

Conclusions

In preschool children, incidence of ADHD associated with tuberous sclerosis complex can be significantly higher than the rates of cardiac or renal abnormalities, for which screening is routinely conducted. The high rate of ADHD symptoms among individuals with tuberous sclerosis complex requires patients to be regularly monitored to plan tailored educational, social, and clinical strategies.[60] Early diagnosis of ADHD obviously allows for earlier treatment and has the potential for a better outcome in children with tuberous sclerosis complex. Treatment for both ADHD and tuberous sclerosis complex requires a multidisciplinary comprehensive and individualized approach. Both the child and the family may benefit first from an early and intensive cognitive and behavioral intervention; however, pharmacotherapy also has a crucial role. Certain antiepileptic drugs may provide indirect benefits on the ADHD symptoms associated with tuberous sclerosis complex.

Tuberous sclerosis complex is a greatly informative model for studying the link between brain and behavior. Hopefully, advances in identifying the pathogenesis of ADHD symptoms in tuberous sclerosis complex will pave the way for the development of more thorough and effective treatment strategies.

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