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Attention-deficit/hyperactivity disorder, Tourette's syndrome, and restless legs syndrome: The iron hypothesis

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Summary Preliminary but increasing evidence suggests that attention-deficit/hyperactivity disorder (ADHD), Tourette's syndrome (TS), and restless legs syndrome (RLS) may be comorbid. In the present article, we hypothesize that ADHD, TS, and RLS may be part of a spectrum, and that iron deficiency contributes to the pathophysiology underlying this spectrum. Iron deficiency might lead to ADHD, RLS and TS symptoms via its impact on the metabolism of dopamine and other catecholamines, which have been involved into the pathophysiology of ADHD, TS, and RLS. We speculate that the catecholaminergic systems are differently impacted in each of the three disorders, contributing to a different specific phenotypic expression of iron deficiency. MRI studies assessing brain iron levels in ADHD, TS, and childhood RLS, as well as genetic studies on the specific molecular pathways involved in iron deficiency, are greatly needed to confirm the iron hypothesis underlying ADHD, TS, and RLS. This body of research may set the basis for controlled trials assessing the effectiveness and tolerability, as well as the most appropriate dose, duration and type (oral vs. intravenous) of iron supplementation. In conclusion, the iron hypothesis may help us progress in the understanding of pathophysiological links between ADHD, RLS, and TS, suggesting that iron supplementation might be effective for all these three impairing conditions.

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Introduction

Attention-deficit/hyperactivity disorder (ADHD) is characterized by consistent and age-inappropriate levels of inattention, impulsivity, and/or hyperactivity [1]. Onset before the age of seven and impaired functioning in two or more settings are essential for the diagnosis [1]. ADHD is one of the most common childhood neuropsychiatric disorders, estimated to affect 5—10% of school-aged children [2]. Impairing symptoms of ADHD may persist into adulthood in up to 60% of the cases [3].

Tourette's syndrome (TS) is a childhood-onset movement disorder characterized by both motor and phonic tics that fluctuate in severity and last for more than one year [4]. Current estimates of the prevalence of TS are approximately 4—6/1000 children [5—7]. About 20% of children with TS continue to experience a moderate level of impairment of global functioning by the age of 20 years [8,9].

Restless legs syndrome (RLS) is a common sensorimotor disorder, characterized by an irresistible urge to move the legs, often accompanied by uncomfortable sensations, relieved by movement and worse in the evening or night and at rest [10]. Periodic limb movements in sleep (PLMS) may be associated with RLS in about 80% of the patients [10]. Reported prevalences of RLS range between 5% and 20% of the general population [10]. Although RLS has been traditionally considered a disorder of middle to older age, it may occur in children. In 2003, the International Restless Legs Syndrome Study Group (IRLSSG) proposed a set of criteria specific for children [10]. In the first population-based study using these criteria, Picchietti et al. [11] recently found that 1.9% of 8 to 11-year-olds and 2.0% of 12 to 17- year-olds presented with definite RLS.

Several studies reported that ADHD may be associated with TS: comorbid ADHD has been observed in up to 70% of patients with TS in clinical settings and in a substantial proportion of subjects with TS in community samples [4].

Preliminary but increasing evidence suggests that both ADHD and TS may be associated with RLS.

As for ADHD, in a review of the published clinical reports completed in 2005 [12], we concluded that up to 44% of subjects with ADHD have been found to have RLS or RLS symptoms, and up to 26% of subjects with RLS have been found to have ADHD or ADHD symptoms. Although some of the included studies presented methodological issues, the reviewed literature suggests a potential comorbidity which deserves further investigation.

With regard to TS, in a large clinical study, Lesperance et al. [13] reported that RLS was present in 10% of 144 probands with TS or chronic tics and 23% of their parents. Interestingly, tics and compulsions found in TS may be preceded by urges or sensations similar to RLS. Moreover, in another small clinical study, Voderholzer et al. [14] found a high number of PLMS (15—32/h of total sleep) in five of the seven patients with TS but in none of the matched controls.

Therefore, increasing evidence suggests that ADHD, TS, and RLS may co-occur.

In the present paper, we hypothesize that ADHD, TS, and RLS may be part of a spectrum, and that iron deficiency contributes to the pathophysiology underlying this spectrum.

Background

Iron deficiency and ADHD

A preliminary open trial by Sever et al. [15] reported partial effectiveness of iron supplementation (5 mg/kg/day for 30 days) in a small sample of ADHD children (significant improvement as rated by the parents but no significant improvement on teachers' ratings).

In a further study conducted on 53 ADHD children and 27 matched controls, our group [16] found significantly lower serum ferritin levels (the most widely used marker of total body iron stores) in children with ADHD vs. controls, suggesting that iron deficiency might contribute to ADHD. In addition, serum ferritin levels were correlated with ADHD symptoms severity. Clearly, the cross-sectional nature of this study could not establish causality but prompted the interest for iron metabolism dysfunction in ADHD.

Iron deficiency and TS

In a study on 14 adult TS subjects and 14 matched normal control subjects, Peterson et al. [17] found significantly lower ferritin levels in the TS group. In a further larger study on children and adults (63 TS, 44 comparison), Gorman et al. [18] replicated these findings, showing significantly lower ferritin and serum iron levels (although still within the normal range) in the TS subjects. Moreover, the caudate and putamen (which have been involved in the pathophysiology of TS) were smaller in the TS subjects who had lower ferritin levels than in the comparison subjects who had lower ferritin levels. However, no association was found between tic

severity and either serum ferritin or iron levels. These two studies suggested that iron metabolism might be implicated in the pathophysiology of TS.

Iron deficiency and RLS

Evidence on iron deficiency in RLS is now well documented. Two studies showed that serum ferritin levels inversely correlated with RLS severity [19,20]. Researchers in this field have gained further insight using MRI to estimate iron levels in the brain. Two MRI studies [21,22] and a B-mode transcranial ultrasound imaging study [23] showed reduced nigral iron in patients with RLS compared to controls. Furthermore, two CSF studies [24,25] reported that patients with RLS, compared to matched controls, had significant decreases in CS ferritin. Finally, decreased iron and H-ferritin have been reported in stained sections of substantia nigra of patients with RLS [26]. Therefore, there is evidence, both from peripheral and central measures, supporting a significant iron deficiency in patients with RLS.

The hypothesis

Given the evidence on iron deficiency in RLS and the preliminary data on low serum ferritin levels in ADHD and TS, as well as the newly described comorbidity among these three disorders, we hypothesize that ADHD, RLS, and TS are part of a spectrum and that iron deficiency contributes to their pathophysiology. To our knowledge, these three disorders have never been considered as being part of the same spectrum and iron deficiency has seldom been considered a factor involved in the comorbidity between RLS and other neurodevelopmental disorders.

The exact mechanisms explaining how iron deficiency contributes to the pathophysiology of these three disorders need further investigation. However, it is possible that iron deficiency leads to ADHD, RLS and TS symptoms via its impact on the metabolism of dopamine and, possibly, of other neurotransmitters.

Dysfunctions in the dopaminergic systems have been consistently reported in ADHD [27], RLS [28], and TS [4].

It is well known that iron deficiency can affect the dopaminergic systems, as well as other neurotransmitters, in several ways. Animal models suggest that iron deficiency leads to a decrease in striatal D1 and D2 receptors and dopamine transporter (DAT) density [29,30]. Moreover, iron is a cofactor for tyrosine hydroxylase, the rate limiting enzyme for catecholamine synthesis [31]. Finally, iron is required for myelination [32].

However, it is likely that the dysfunction in the dopaminergic systems is not the same for the three disorders in question. For example, the fact that RLS can be treated by dopaminergic agonists and TS usually responds to dopaminergic antagonists [14] suggests that clearly the dopaminergic pathways are not altered in the same way in these two disorders. However, it has also been reported that TS patients who are resistant to several neuroleptic drugs (D2 blockers) remarkably improved on a dopaminergic agonist (pergolide), suggesting that direct and indirect dopaminergic pathways could be differentially involved in different cases of TS [33].

How iron deficiency can impact the dopaminergic systems in each of the three disorders needs further investigation. We speculate that the impact of iron deficiency is different according to some not yet understood factors specific of each disorder or according to each subgroup of patients with the same disorder, given the above-mentioned variability in dopaminergic pathways within the same disorder.

With regard to the impact of iron deficiency on the dopamine systems in RLS, Allen and Earley [28], after reviewing the literature on iron deficiency and RLS, concluded that iron deficiency leads to an increased dopamine production and an increasing of extracellular dopamine. They further hypothesized that reduced DAT and D2R would reduce the information provided to the presynaptic cell regarding extracellular dopamine levels. This would lead both to abnormally increased dopamine production and also to abnormally increased circadian amplitude in the amount of extracellular dopamine. Thus, the amplitude of the RLS circadian pattern for dopamine remains increased but its low point or trough may be decreased with its peak levels increased relative to normal. Postsynaptic receptors may not adequately adjust to such an abnormally large circadian variation, producing abnormally decreased dopamine stimulation during the circadian trough of dopamine activity. This trough roughly corresponds to the period of RLS symptoms.

We speculate that this dopaminergic pattern is different in ADHD as well as in TS because of some disorder-specific factors, contributing to a different specific phenotypic expression of iron deficiency.

Implications

If confirmed, the hypothesis of iron deficiency as a common factor contributing to the pathophysiology of ADHD, RLS, and TS, might have relevant

implications for the treatment of patients presenting with these conditions, suggesting that iron supplementation might be effective for all of these disorders. Therefore, the same treatment could address three different diseases, making more simple the management of these disorders when they are comorbid, which is, nowadays, quite challenging.

Further studies

The iron hypothesis underlying the pathophysiology of the spectrum including ADHD, RLS, and TS needs to be confirmed by several lines of research.

1. First, iron deficiency should be better investigated in these three disorders, especially in ADHD and TS, as well as in childhood RLS. More specifically, brain iron levels should be better investigated. Indeed, while studies on SNC iron levels have been conducted in adult patients with RLS [21,22], no such studies are available for ADHD, TS, and childhood RLS. In fact, studies on iron deficiency in ADHD [16] and TS [17,18] have determined serum levels of ferritin. Although this is considered a marker of total iron stores, how well peripheral iron indices correlate with central iron content is still unclear. For example, whereas some investigators have reported a positive correlation between serum and CSF ferritin in individuals with RLS [24], others have found that the quantity of nonheme iron in the human brain is largely independent of body iron stores [34]. Moreover, it may be important to consider both peripheral and central levels of iron markers and their interaction, as pointed out by Allen and Earley [28]. These authors suggested that patients with RLS have marginal CNS iron status that can become insufficient when deprived of normal access to adequate peripheral iron or may be insufficient even with normal access to adequate peripheral iron. Thus, RLS has both reduced brain iron status and also impaired ability to gain brain from peripheral iron. Whether this applies also to ADHD and TS remains unexplored. Therefore, MRI and autopsy studies aimed at measuring central iron levels in ADHD, TS, and childhood RLS are greatly needed. A better insight into the SNC iron levels in the three disorders would contribute to a better understanding of why peripheral measures have provided somewhat contrasting results. For example, while the above-mentioned study by our group found significantly lower serum ferritin in ADHD vs. controls, Millichap et al. [35] did not replicate this finding. If the mechanism hypothesized by Allen and Earley [28] for RLS applies also to ADHD, and potentially to TS, one can understand that peripheral iron normal levels may coexist with a central iron deficiency and that low iron peripheral iron levels may further aggravate central iron deficiency.
2. Once potential peripheral as well as central iron deficiency is confirmed in ADHD, RLS, and TS, genetic studies on the molecular pathways involved in iron deficiency would allow us to improve our knowledge in the field.
3. Finally, once we have gained insight into the molecular bases of iron deficiency and its consequences on the neurotransmitter systems, we will be able to design potentially effective iron therapy trials and target the specific molecular pathways influenced by iron deficiency. One question is whether or not a large increase in peripheral iron, for example, via IV iron delivery or via oral iron, would provide sufficient iron to overcome the limitations in making it available to brain tissue. Another question is how long iron supplementation should be continued. In the field of RLS, researchers have already begun to answer these questions. Earley et al. [36] recently showed the effectiveness of 1000 mg of IV iron dextran in adult patients with RLS. They reported that six out of 10 patients with RLS had almost complete or complete relief from all RLS symptoms for at least 2 weeks, and for most patients the relief lasted longer than 2 months. Our group recently published a pilot double blind trial showing the effectiveness of oral iron supplementation in ADHD [37]. However, no studies using IV iron have been conducted in children presenting with RLS, ADHD, and TS. Such studies would contribute to significant advances in our therapeutic options for patients with these disorders, establishing the dose, duration, and type (oral vs. intravenous) of appropriate and effective oral supplementation, as well as its tolerability. Finally, studies on iron supplementation would be particularly informative if they included MRI scans to measure iron content in brain tissue before and after treatment. No such studies have been conducted.

This body of research would help us progress in the understanding of pathophysiological links between ADHD, RLS, and TS, suggesting effective and specific treatment for these impairing conditions.

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