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A Gut Feeling: A Hypothesis of the Role of the Microbiome in Attention-Deficit/Hyperactivity Disorders

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Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a neurologic disorder characterized by hyperactivity/impulsivity and/or inattentiveness, with genetic and environmental factors contributing to the disorder. With the growing recognition of the microbiome's role in many neurological disorders, the authors propose that it may also be implicated in ADHD. Here, we describe several evolving areas of research to support this hypothesis. First, a unique composition of gut bacteria has been identified and linked to behaviors in ADHD. Second, our research found an increased incidence of 2 gastrointestinal symptoms (constipation and flatulence) in children with ADHD, as compared to controls. Finally, emerging data may be interpreted to suggest that immune dysregulation in ADHD be associated with an altered microbiome, low-grade inflammation, and gastro-intestinal dysfunction. Although more studies are needed to elucidate exact mechanisms and causality, we propose that an altered microbiome, gastrointestinal symptoms, and immune dysregulation may be associated with the ADHD phenotypes.

Keywords

attention-deficit/hyperactivity disorder (ADHD), microbiome, gastrointestinal (GI) disorders, immune dysregulation

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental and neurobehavioral disorder characterized by hyperactivity/impulsivity (ADHD, predominantly hyperactive/impulse type), inattentiveness (ADHD, predominantly inattentive type), or both (ADHD, combined type).[1] Despite being one of the most prevalent neurodevelopmental conditions, affecting approximately 6% of United States children aged 4 to 17 years old, the etiology of the disorder remains unclear.[2,3] It is widely accepted that ADHD is heritable, although only a small number of genes have been reported to have a relatively small effect in predicting ADHD.[4–6] At the same time, studies have shown that children with a parent diagnosed with ADHD have a greater than 50% chance of having ADHD; twin studies have suggested a heritability of 71% to 90% for the various subtypes of ADHD.[7] Concurrently, it is estimated that between 10% and 40% of the variance in heritance may be due to environmental factors.[3] For example, perinatal stress, maternal smoking, and alcohol use during pregnancy, lead exposure, and micronutrient and mineral deficiencies have all been noted as increasing the risk of developing ADHD.[8] Nonetheless, these known environmental factors do not account for all of the variance in heritability.

In recent years, the gut microbiome has been associated with many psychiatric and neurodevelopmental disorders, including autism spectrum disorders, depression, anorexia nervosa, and Rett syndrome.[9–13] Consisting of several trillion commensal microbes, the microbiome plays an active role in maintaining health throughout life. In a system known as the gut–brain axis, the gut microbiome continuously "converses" with the central nervous system through hormonal, immune, and innate neuronal pathways.[14] These pathways, established through

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microbiota metabolites, may be critical to the development of the central nervous system, including the brain.[15] Murine models mimicking an environment devoid of a gut microbiome, such as the murine germ-free models, demonstrate abnormal neurotransmitter profiles and abnormal neuroanatomy. In one study of murine germ-free models, postsynaptic density protein 95 and synaptophysin were found to be increased, suggesting increased excitatory synapse and synaptic vesicle maturation in regions of the brain associated with motor control and anxiety-like behaviors.[15,16] In another study, germ-free mice developed hypermyelinated axons which normalized following subsequent colonization with conventional microbiota. Furthermore, defects in microglia cells were also partially restored following colonization with conventional microbiota.[17,18] Similarly, in humans, it is hypothesized that dysbiosis (eg, imbalance of the microbiota) may have a negative effect on the most critical moments of cerebral development, leading to lasting or permanent modifications to the CNS and its function.[19]

Studies have shown that, in addition to roles in digestion and detoxification, gut flora is critically involved in immunoregulation. In dysbiosis, there may be a disproportionate quantity of pro-inflammatory microbes, leading to increased intestinal permeability and inflammation as well as a resultant shift of microbes into the systemic circulation, which may lead to low-grade systemic inflammation and immune dysregulation.[20] Literature has generally supported the relationship linking autoimmune disorders with dysbiosis.[21–23]

Immune dysfunction has been speculated to be associated with ADHD. In general, it has been proposed that low-grade systemic inflammation may lead to gradual destruction of the blood–brain barrier and possibly the neuroinflammation seen in ADHD.[24,25] Supporting this theory, a review profiling cytokine levels in cerebral spinal fluid and serum along with related gene polymorphisms found evidence to suggest that there is low-level inflammation present in children with ADHD. The authors acknowledge a high level of variability in the findings, though it is possible that this may result from the heterogeneity of ADHD itself.[26] Other studies have found that environmental stresses in pregnancy, such as poor maternal diet, infection, antibiotic use, or stress, lead to an increased incidence of offspring with behavior problems, including ADHD; again, inflammation due to these stresses may be implicated in the pathogenesis of ADHD.[27–31] Finally, the increased incidence of immune-mediated disorders such as asthma and atopic dermatitis among patients with ADHD likewise suggests immune dysfunction in children with ADHD.[32] Although these links are tenuous and speculative, they may be deserving of further investigation.

Hypothesis

We hypothesize that perturbations in the host gut microbiome, increased gastrointestinal symptoms, immune dysregulation, and alterations in metabolomic markers may be present in some children with ADHD.

Evaluation of the Hypothesis

Altered Microbiome in ADHD

Although gut microbiome studies in ADHD are in their early days, there is emerging interests in differences between the microbiome in patients with ADHD as compared to that of neurotypical controls. Using 16S rRNA marker gene sequencing, Aarts et al noted a slight increase in *Bifidobacterium* genus in patients with ADHD. With the bacterial gene functionality encoding cyclohexadienyl dehydratase, an enzyme utilized in the synthesis of phenylalanine (itself a dopamine precursor), the authors sought to indirectly correlate *Bifidobacterium* prevalence with its effect on neural reward anticipation (a known functional target of dopamine), as suggested in ventral striatal fMRI responses to reward anticipation. Indeed, the authors noted a diminished neural reward anticipation as being correlated with increased *Bifidobacterium* in the gut.[33] Given the known association between ADHD and dopamine dysregulation,[34] as well as abnormally decreased reward anticipation pathways,[35] this study speculated that dysbiosis may contribute to the clinical phenotypes of ADHD.

Prevalence of Gastrointestinal Symptoms in ADHD

An altered gut microbiome can be associated with gastrointestinal symptoms, such as constipation, diarrhea, abdominal pain, and flatulence. A number of studies have also documented an increased incidence of gastrointestinal symptoms in neurodevelopmental disorders.[36–39] Establishing whether children with ADHD have more symptoms of gastrointestinal dysfunction than their neurotypical counterparts may be a first step toward determining whether there are clinical manifestations of dysbiosis in ADHD.

We administered the 6-item Gastrointestinal Severity Index (see Table 1) to 68 children with ADHD (aged 3-16 years old) and 72 healthy controls (aged 3-16 years old). Mean age of the cohort was 9.96 $\pm$ 3.24 years (see Table 2). Patients were recruited from general pediatric clinics (for neurotypical controls) and from pediatric neurology clinics (for patients with ADHD) at University Hospital in Newark, New Jersey. A diagnosis of ADHD was based upon the clinical criteria in the *DSM-IV-TR* and/or *DSM-V* criteria with consideration of developmental level. Children with comorbid disorders, such as an autism spectrum disorder, Tourette syndrome, learning disability, or speech delay, were excluded from the study. Thirty-three of the 68 children were on a sympathomimetic stimulant. Twelve patients were on an α-adrenergic agonist such as clonidine. Among the medication users, 3 were on both categories of medications. Gastrointestinal Severity Index was validated in children with autism spectrum disorders in our prior study[40]; to our knowledge, its use in ADHD has not been validated.

Control participants were recruited during their wellness visits and were screened for medical and developmental disorders prior to enrollment. Specifically, any children with symptoms of ADHD were excluded. Informed consent was

Table 1. The 6-Item GSI Score.

	Score		
Category	0	1	2
Constipation	≥5 stools per week	3-4 stools per week	0-2 stools per week
Diarrhea	0-1 loose stools per day	2-3 loose stools per day	≥4 loose stools per day
Average stool consistency	Formed	Loose/unformed ≥3 days per week	Watery ≥3 days per week
Stool smell	Normal	Abnormal ≥3 days per week	Unusually foul ≥3 days per week
Flatulence	Normal	Frequent ≥ 3 days per week	Daily
Abdominal pain	None	Mild discomfort ≥3 times per week	Moderate to severe discomfort ≥3 times per week

Abbreviation: GSI, Gastrointestinal Severity Index.

Table 2. Demographic Features of the Participants.

Variable	ADHD	Control
Male (% of group)	51 (75%)	33 (46%)
Female (% of group)	17 (25%)	39 (54%)
Mean age (SD)	10.3 years (± 2.97)	9.7 years (3.24)
Mean BMI (SD)	20.3 kg/m^2 (± 4.99)	20.4 kg/m^2 (5.27)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; SD, standard deviation.

Table 3. Mean GSI Total and Symptom Scores for ADHD and Control Groups[a,b].

	ADHD (N=68)		Control (N=72)				
Variable	M	SD	M	SD	*t*	*df*	*P*
GSI total score	1.13	1.48	.38	1.04	3.248	119	<.001
Constipation	0.34	0.66	0.13	0.41	2.28	110	.024
Diarrhea	0.01	0.12	0	0	1.00	67	.321
Consistency	0.01	0.12	0.01	0.12	0.04	138	.968
Smell	0.13	0.42	0.08	0.32	0.77	138	.443
Flatulence	0.28	0.62	0.08	0.32	2.33	126	.019
Abdominal pain	0.34	0.64	0.07	31	3.15	95	.269

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; *df*, degrees of freedom; GSI, Gastrointestinal Severity Index; M, mean; SD, standard deviation.
[a]Total N = 140.
[b]If *df*s = 138, then an independent *t* test for equal variances was used to compare the mean scores. If the *df*s are <138, Welch *t* statistic for unequal variance was employed to compare the mean scores.

obtained from parents/guardians according to the protocol approved by the institutional review board of our institute. The Gastrointestinal Severity Index was administered to the patients at the time of visit for ages 5 years old and above; for patients below 5 years old, the parents were asked to complete the survey. The Gastrointestinal Severity Index allows for rating the severity of gastrointestinal symptoms using a 3-point Likert rating scale ranging from 0 ("none/normal") to 2 ("severe/significant") for 6 gastrointestinal symptoms (constipation, diarrhea, average stool consistency, stool smell, flatulence, and abdominal pain) (Table 1). Children with ADHD had significantly higher mean Gastrointestinal Severity Index total, constipation, and flatulence scores than the healthy controls (Table 3). These gastrointestinal symptoms were not severe in the majority of children with ADHD in this cohort. Aside from a small correlation of total Gastrointestinal Severity Index scores with sex (0 = male, 1 = female) in the ADHD group ($r = 0.271$; $P = .026$), there were no significant correlations for the total Gastrointestinal Severity Index score with sex, age, and BMI in either group.

Despite previous reports that use of stimulant medications, such as methylphenidate, may contribute to abdominal pain,[41] we did not find any significant relationship between medication use and constipation, flatulence, or total Gastrointestinal Severity Index score (ie, stimulant, nonstimulants, both stimulant and nonstimulant, or no stimulant/nonstimulant use groups).

Discussion

Our findings contribute to a small but growing body of literature describing gastrointestinal disturbance in patients with ADHD. One large study of parental reports (n = 6483) of comorbidities in ADHD found significantly increased rates of "serious stomach or bowel problems" (defined as problems such as gastritis or ulcers) in ADHD, even after adjusting for demographics and other medical/mental disorders of a nationally representative sample. Interestingly, gastrointestinal disturbances and enuresis were the only 2 comorbidities found to be significantly more likely in this large cohort of ADHD.[42] In parsing out specific gastrointestinal symptoms, Duel et al[43] found increased rates of constipation in a group of 28 children with ADHD. In a large, retrospective study using a military database, children with ADHD (n = 32 773) were more likely to have fecal incontinence and constipation than those without ADHD.[44] In terms of abdominal pain, one study found a 2-fold increased risk of recurrent abdominal pain among children with ADHD.[45] A comparison of these studies with ours is illustrated in Table 4. Gastrointestinal symptoms could be associated with anxiety, mood disorders, dietary intake, and many other factors; these confounders were not considered in the studies. However, Almog et al[46] found no significant correlation between gastrointestinal symptoms and ADHD in a cohort of 62 Israeli children.

Table 4. Comparison of Studies of GI symptoms in ADHD.

Study		Average Age, year (Range)	n	Male %	GI Symptoms Assessed and Conclusions	Study Comments
Jameson et al.[42]	ADHD	15.2 (13-18)	550	51.2%	Serious stomach and bowel problems (eg, gastritis or ulcers) strongest correlate of ADHD	Large samples. Interview and parent self-administered questionnaire. No distinction of specific GI symptoms
	Control	NA (13-18)	5933	NA		
Duel et al.[43]	ADHD	M: 9.4 (6-12); F: NA	28	82%	Constipation more common in children with ADHD	Small sample sizes. Parent and child competed surveys. GI symptoms not the focus of the survey
	Control	M: 10.1 (5-14); F: NA	22	45.5%		
McKeown et al.[44]	ADHD	8 (6-9)	32 773	73.7%	Constipation and fecal incontinence more likely in children with ADHD	Large retrospective chart review
	Control	7 (5-9)	710 166	50.1%		
Holmbergand Hjorn[45]	ADHD	10 (10)	96	71.5%	Recurrent abdominal pain associated with ADHD	Modest sample size. Interviewed child, a parent, and a teacher. Did not specify medication use
	Control	10 (10)	420	46.5%		
Our current study	ADHD	10.3 (3-16)	68	75%	Significantly higher mean GSI scores (especially constipation and flatulence) in ADHD	Small sample sizes with broad age range. Interview. Quantifies GI symptoms
	Control	9.7 (3-16)	72	46%		

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; GI, gastrointestinal; GSI, Gastrointestinal Severity Index; NA, not available.

Conclusion

Increased gastrointestinal symptoms among patients with ADHD may be suggestive of an altered microbiome. Practical approaches to testing the hypothesis would include controlled studies to further characterize the microbiome in ADHD, as has been done in autism spectrum disorders. Investigating any correlation between clinical gastrointestinal symptoms and gut dysbiosis may address the increased prevalence of gastrointestinal symptoms in children with ADHD. Further basic science and clinical studies are then needed to understand the neurotransmitter, neurometabolic, neuroanatomic changes, if any, that dysbiosis may cause. Furthermore, any potential gut dysbiosis would need to be correlated with immunological profiles. If there is gut dysbiosis causing neurotransmitter, neurometabolic, neuroanatomic, and/or immunologic abnormalities in children with ADHD, our treatment paradigm of ADHD could expand to treat gut dysbiosis and immunologic disturbances, and not just the presenting neurological symptoms. Of course, the contribution of gastrointestinal dysbiosis to ADHD symptomatology, if any, would need to be viewed within a greater framework that addresses broader genetic and environmental etiologic factors.

We propose that gut dysbiosis should be explored for a potential role in contributing symptoms of ADHD, supported by our finding of a modest increased prevalence of gastrointestinal dysfunction (namely, constipation and flatulence) in children with ADHD. These differences are consistent with recent literature suggesting an association between ADHD and gastrointestinal disturbance as well as gut dysbiosis (such as a slight increase in *Bifidobacterium* genus in patients with ADHD). Furthermore, a role of immune dysfunction in ADHD should be further investigated and an association with gut dysbiosis, if present, should likewise be explored. These findings may, in turn, shed light on a previously uncharted piece of the ADHD puzzle.

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Author Contributions

XM conceived the study and wrote final manuscript. NC collected data and wrote first manuscript. CR and GB collected data. JK aided in subject recruitment. RAS analyzed the data. All authors discussed the results and commented on the manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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