The Role of Gluten in the Etiology of Neurodevelopmental Disorders: Opioid and Immunological Mechanisms

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Abstract

Gluten, a protein found in most cereal grains, is perhaps the protein consumed in greater quantizes than any other protein. It has long been known that a small percentage of the population is intolerant to gluten, and gastrointestinal upset, including diarrhea, bloating and flatulence result from its consumption. Less widely known is that gluten intolerance actually affects a larger population than originally thought and the gastrointestinal effects may not be present until further along in the course of the disease. Initial presenting signs may be far removed from the small intestine, and may affect any other body system. Most common systems to be effected are the central and peripheral nervous systems, the dermatological system and the endocrine system. Neurodevelopmental disorders in children have reached almost epidemic proportion, and have been linked to gluten intolerance. This paper explores the mechanism by which gluten effects the clinical presentation in neurodevelopmental disorders, ranging from ADD to autism.

Background

Gluten is a protein found in the class of plants called Monocotyledonae, also known as monocots. Gluten is found in the seeds, also called grains, of the grass family of plants, including wheat, rye, barley, spelt, triticale, kamut and oats. There is no gluten present in the grass before emergence of the seed. [1] There is, however, gluten still present in sprouted grains, although in lesser amounts, since the sprouting begins the enzymatic breakdown of gluten into peptides and amino acids. [2]

Gluten containing foods are very prevalent in the diet of most Americans and modern day inhabitants of the Western world. Gluten grains are found in breads, noodles, crackers, cookies

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and other baked goods. Derivatives of gluten containing grains include malt, hydrolyzed plant proteins, textured vegetable proteins, grain vinegars, soy sauce, grain alcohol, natural flavorings, and binders and fillers found in many nutritional supplements and medications.[1] Comprehensive lists of gluten containing foods are available online. According to Drs. Braly and Hoggan, bread makes up over half the calories of the average diet of people in most countries.[3] Analysis of patient dietary intakes over the past 15 years confirms that gluten containing foods constitute a major portion of the average American's caloric intake.

Gluten Intolerance

Intolerance to gluten, a condition that has come to be known as celiac disease, was first described back in the first century AD, in a book of chronic diseases by Aretaeus the Cappadocian, one of the most distinguished ancient Greek doctors of his time. This chapter, entitled "on the coeliac diathesis", described the condition as follows: "*. . .the stomach being the digestive organ, labours in digestion, when diarrhea seizes the patient. . .and if in addition, the patient's general system be debilitated by atrophy of the body, the celiac disease of a chronic nature is formed".*[4]

Gluten is a mixture of individual proteins including prolamines and glutelins. Gliadin is a prolamine found in wheat. Different grains have different prolamines. The variability of reactions to different gluten containing grains is influenced by the amount and kind of prolamine in the gluten of that particular food. The gliadin prolamine found in wheat is a major cause of problems in celiac disease [5]

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Most people, even those in the medical profession, still consider Celiac Disease to be primarily a disorder of the small intestine, in spite of a large body of evidence that extra-intestinal manifestations are quite common. As early as 1908, in his book entitled *Sprue and its Treatment*, Carnegie Brown described two patients who developed "peripheral neuritis". Later , in 1925, Elders reported the association between "sprue" and ataxia.[6.7] Since then, gluten intolerance has been associated with a wide variety of neurological and psychiatric conditions, with or without intestinal pathology. This includes, but is not limited to, cerebellar ataxia, peripheral neuropathy, epilepsy, dementia, schizophrenia, depression, migraine, seizures, encephalopathy, chorea, brain stem dysfunction, Parkinson's, Alzheimer's, myelopathy, mononeuritis multiplex, Guillain-Barre-like syndrome, Huntington's disease and neurodevelopmental disorders including autism, ADHD, Aspersers and PPD. Histological and vascular changes in the CNS have been associated with gluten intolerance, including perivascular inflammatory changes, cerebellar atrophy, cerebral hypoperfusion, and Purkinje cell loss. [,8,9,10,11,12,13,14,15,16,17,18,19,20,21]

Several mechanisms have been proposed to explain how gluten affects the neuromuscular systems. The mechanisms include autoimmune reaction and inflammation, malnutrition and opioid excess.

Autoimmunity as an Expression of Gluten Intolerance

Autoimmunity as a mechanism for the neurological expression of gluten intolerance is supported by the work of Vodjani, et al and Hadjivassiliou, et al , amongst others. In studying autistic children, Vodjani, et al found that gliadin peptides in individuals with predisposing HLA molecules may bind to different aminopeptidases and induce autoantibodies to peptides and tissue antigens. They measured such autoantibodies targeted towards brain tissue, as well as

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small intestine.[22] Hadjivassiliou et al concludes from his research that "an immunological role may be important in the genesis of the neurological dysfunction associated with celiac disease. Our finding that neuromuscular disorders can be the presenting feature of celiac disease implies that the immune response triggered by sensitivity to gluten may find expression in organs other than the gut and that the central and peripheral nervous systems are particularly susceptible."[23] Rather than being defined by small bowel histology, he suggests that celiac disease be defined as an abnormal immunological response to ingested gliadin in genetically susceptible people.

The damage to intestinal mucosa observed in celiac disease is the result of both humoral and T cell mediated inflammation.[24] Both antigliadin antibodies and gliadin specific T cells are found systemically. Antigliadin antibodies are also found in the CSF.[25] Inflammation in the white matter of the cerebellum has been observed in gluten sensitive patients presenting with ataxia, along with antibodies against Purkinje cells, suggesting that IgG antigliadin antibodies cross react with epitopes on Purkinje cells from human cerebellum.[8,26]

Malabsorption of Nutrients as an Expression of Gluten Intolerance

It may be plausible that gluten induced symptoms outside the small bowel are a result of malabsorption of nutrients due to celiac manifestations in the small bowel and subsequent nutritional deficiencies and imbalances. Hadjivassiliou explains that nutrient deficiencies (B 12, folate, vitaminD, vitamin E) are rare and are an unlikely explanation for neuromuscular disorders in the patients he studied for the following reasons: firstly, many of the neuromuscular disorders described clearly have an inflammatory or autoimmune basis, including polymyositis, mononeuropathy multiplex, acute polyneuropathy, and neuromyotonia. Secondly, the neurological disorders in these patients preceded the gastrointestinal disorder by many years, and the patients had no physical or biochemical

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evidence of malabsorption at the onset of neurological disease. Thirdly, neurological disorders associated with gluten sensitivity but normal small bowel mucosa,' makes appreciable malabsorption unlikely. [8,23]

Opioid Overload as an Expression of Gluten Intolerance

Another mechanism by which gluten can affect the brain and central nervous system is by opiate overload. Opioid active peptides have been found in wheat gluten and bovine and human milk.[27] These peptides have been referred to as exorphins, because they have similar activity as that of morphine and endorphins. Those derived from gluten are referred to as gluteomorphins or gliadinomorphins. The peptide produced from milk is known as casomorphine. [28]

To determine the origin of the peptides exhibiting opioid activity, Huebner et al fractionated wheat proteins, hydrolyzed them, separated the resulting peptides and tested them for opioid-like activity by competitive binding to opioid receptor sites in rat brain. The most active peptides were those that had been derived from the gliadin fraction of gluten. [29] Zioudrou et al similarly extracted the opiate like peptides and found them to have activity and potency akin to that of morphine. [30]

Four opioid peptides were isolated by enzymatic breakdown of wheat gluten. Their structures were Glycine(Gly)-Tyrosine(Tyr)-Tyrosine-Proline(Pro)- Threonine(Thr), Gly-Tyr-Tyr-Pro, Tyr-Gly-Gly-Trp-Leu and Tyr-Gly-Gly-Trp, which were named gluten exorphins A5, A4, B5 and B4, respectively. Gluten exorphin B5, which corresponds to [Trp4,Leu5]enkephalin, showed the most potent activity among these peptides. [31] The gluten exorphin A5 has been found to

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affect both the peripheral and central nervous system of mice. [32] A unique opioid peptide named gluten exorphinC was isolated from gluten by Fukudome, et al. in 1993. [331] The opioid peptides found in wheat gluten are extremely powerful. A single wheat-gluten protein-molecule can contain up to 15 opioid peptides. Some of the wheat gluten peptides are 100 times more powerful than a morphine molecule. [34, 35]

In order for exorphins from gluten to affect the central nervous system, they must be produced in the digestive tract by incomplete enzymatic breakdown of gluten, be absorbed through the brush border of the small intestine, and cross the blood brain barrier. The exorphins produced from gluten have been shown to be resistant to breakdown by intestinal proteases trypsin and chymotrypsin. Further, the work of Hemmings et al on rats verified that many of the peptides do indeed reach the brain. [36] Shattock and Savery report that in healthy individuals, small amounts of the exorphins reach the brain, but more significant quantities of the peptides reach the central nervous system in those with compromised digestion, increased permeability of the gut wall, as in celiac and other small bowel disorders, and blood brain barrier defects,. [36]

Figure 1 demonstrates the ways in which levels of the opiod peptides from gluten can enter the brain. Figure 1a represents the clinically normal subject, in which the number of peptides in the gut is relatively small, the intestinal lining is fairly intact, and only allows for the passage of a small percentage of the peptides into the blood, and the blood brain barrier is effective at keeping most of the peptides from entering the brain. In figure 1b, there is an increase in the number of peptides in the gut, and given the same degree of leakiness of both the gut wall and the blood brain barrier, there is an increase in the number of peptides entering the CNS. In figure 1c, the

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number of peptides in the small intestine is the same as in the "normal" example, but there is increased permeability of the brush border so an increased number of molecules enters the CNS. Figure 1d is the most problematic in there is both an increase in the number of exorphins in the gut and an increased permeability of the intestinal lining, resulting in a much greater concentration of opioid peptides entering the CNS. [36]

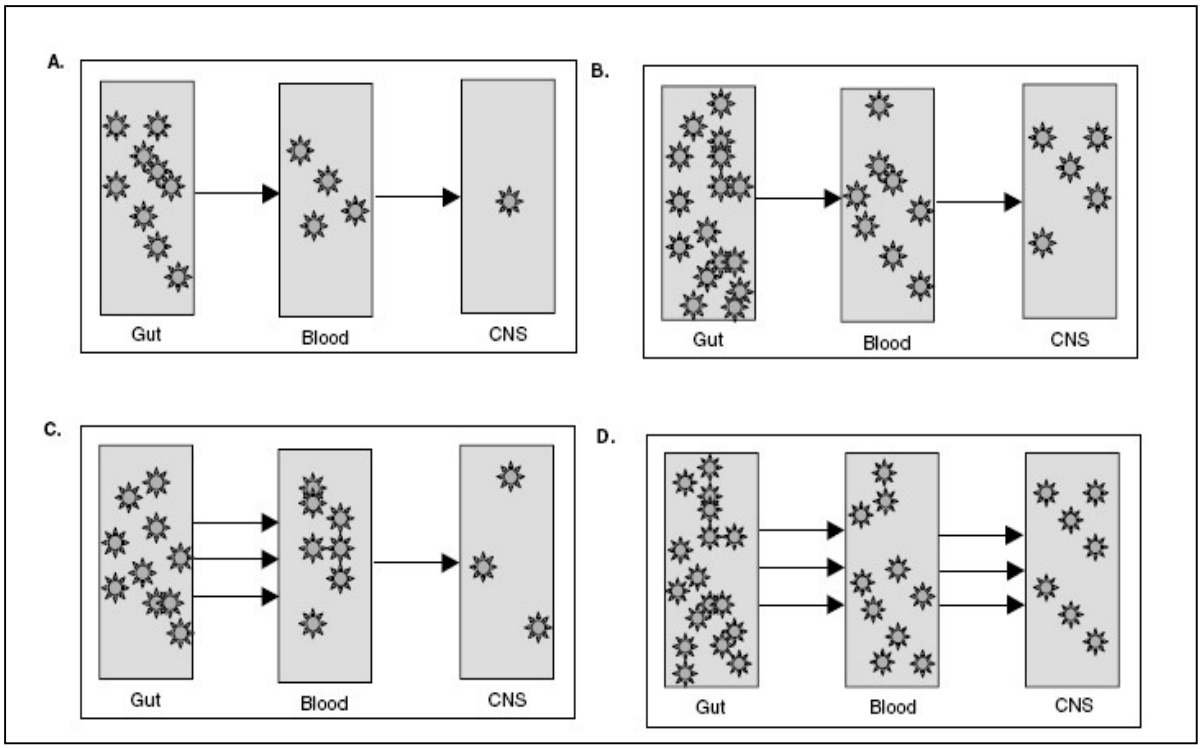

Figure 1

That opioid peptides are produced as a result of incomplete breakdown is clearly demonstrated in the literature. Support is present for the resistance of these peptides to enzymatic breakdown by intestinal peptidases. It has also been clearly demonstrated that these molecules indeed enter the CNS. The effect of these molecules on the neuromuscular and cognitive systems has recently been explored in depth. This mechanism of action has been linked not only to neurodevelopmental and psychiatric conditions, such as autism [37,38] and schizophrenia [39], but to

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endocrine and cardiovascular dysfunction as well. [40]

Neurodevelopmental Disorders

Neurodevelopmental disorders in children have reached almost epidemic proportion. The full spectrum, from least to most serious, of neurodevelopmental disorders are illustrated in Figure 2.[41] Collectively, these disorders are often referred to as Autistic Spectrum Disorders (ASD).

ADHD without/with LD :	OCD/Tourette's PDD/NOS	Asperger's Autism
Fewer problems	**More significantly impacted**	**Most severe**

Key:
ADHD = Attention deficit/hyperactivity disorder
LD = Learning disability
OCD = Obsessive compulsive disorder
PDD/NOS = Pervasive developmental disorder /"not otherwise specified"

Figure 2

While each of these conditions is shown to be on a continuum, and have some overlapping signs, symptoms and treatments, they are considered to be distinct disorders.

Many theories exist about the etiology of the neurodevelopmental disorders, including the Autistic Spectrum disorders (ASD). Several of these theories propose mechanisms that are consistent with the mechanisms by which gluten affects the neuromuscular systems. The etiologies discussed here are the opiate excess theory and the immunological theory, including both autoimmunity and allergy. As autistic spectrum disorders are complex and symptomatology inconsistent, it is probable that the etiology is multifactorial and variable from person to person. Genetics clearly play a large role and influences the environmental factors.

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Great strides have been made in the understanding and treatment of ASD, in the area of behavioral intervention, nutrient balancing, and decreasing the toxic load, especially with regards to mercury. These areas are well documented and researched, but are beyond the scope of this paper. This paper will tie together the immunological and biochemical effects of gluten and the etiology of ASD.

The Immune System and Neurodevelopmental Disorders

There is a substantial body of evidence to support the role of the immune system in the pathogenesis of autism and ASD. [43] According to Edelson and Cantor, autistic patients consistently show abnormalities in the limbic and cerebellum areas. These abnormalities include stunting of dendrites and abnormal branching of dendrites and reduced numbers of Purkinje cells. [42,] Purkinje cell loss and brainstem abnormalities in autism are confirmed by a number of authors, as are diffuse cortical abnormalities and megaencephaly. [43, 44] While these abnormalities can be linked to exposure to toxic agents, the evidence presented earlier in this paper establishes a link between cerebellar and Purkinje cell damage to anti-gliadin antibodies, and autoantibodies produced as a result of antigliadin antibodies. Evidence is presented by Kidd that autistic children manifest abnormally low blood flow in the temporal cortex, which could explain many of the perceptive, cognitive and emotional symptoms.[43] Cerebral hyperperfusion has been demonstrated to be a manifestation of autoantibodies in celiac disease.[10,14] Further support of autoimmunity as a causative factor in autism is that brain autoantibodies to myelin have been found in up to 58% of autistic children. [44]

Researchers at the University of Minnesota have found T-cell reactivity to the dietary proteins in soy, milk, and wheat in 75 to 80% of a group of 83 children with autism. [44] Gastrointestinal

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problems are found in a majority of children with autism and ASD. Some studies show as many as 98% of all children on the autistic spectrum demonstrate gastrointestinal and immune dysfunction. Numerous studies link gastrointestinal problems, celiac disease and food allergy to ASD. [22,28,41,43,44,46,47,50]

Opioid Excess in Neurodevelopmental Disorders

The opioid excess theory of autism states that symptoms of autism can be caused by an excess of opioid activity in the brain. Autistic like symptoms, such as decreased pain sensitivity, reduced crying, reduced desire for social interactions and diminished clinging behavior have been induced in animals with the administration of exogenous opioids. Self injurious behaviors resulted when the opioids were withdrawn from the addicted animals. Mechanisms are speculated by which an increase in endogenous opioids may be produced. Prenatal opioid exposure is also a possibility. [36] Exogenous opioids from dietary proteins, especially gluten and casein have also been implicated.[45,46]

Social interaction difficulties, language development challenges, and pain sensitivity deficiencies are major problems for autistic children. It is postulated that exposure of the developing brain to higher than normal levels of opioid peptides results in a lag in the normal flowering in the developing nervous system and results in developmental immaturity. [36] Research as early as the 1970's, reported by Panskeep and Sahley, suggests that endogenous opiates control development. Early exposure, either prenatally or developmentally, to higher levels of either endogenous or exogenous opioids results in significant physical and cognitive impairment. Opioids have been shown to be involved in the pruning of central nervous system nerve cells. This occurs in-utero and in early infancy. Excessive pruning can result from elevated levels of opioid peptides at critical developmental stages, leading to manifestations of autistic behaviors. [47]

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Exposure to exogenous opioids is considered to be a result of excessive exposure to dietary peptides coupled with deficiencies in intestinal enzyme activity and failure of intestinal mucosal or blood brain barriers to keep the peptides out of circulation. Defective sulphation has been suggested as a mechanism for hyperpermeability of the mucosal barrier. More recently, it has been discovered that lymphoid hyperplasia in the area of the ileocecal valve may be involved. On biopsy, measles virus was detected in almost all specimens, suggesting a link between immunization and autism.[45]

Evidence to support the opioid theory of autism is readily available. In the 1980's, Gilman et al measured elevated levels of opiod peptides in the cerebrospinal fluid of autistic children. [48] Reichert et al measured elevated levels of urinary peptides in about 50% of people with autism.[49,50]

Summary

The mechanisms by which gluten affects the brain and nervous system and the anatomic and histological presentations of the nervous system in people with Autism and ASD clearly overlap. Reactions to gluten and casein have been associated with adverse reactions not all of which involve allergen-specific immune response. Adverse reactions to these proteins involve allergic type reactions as well as the possible toxic effect of exorphins on behavior and learning. In many cases of ASD, anti-gliaden antibodies are measurable by laboratory assessment. These antibodies may affect the small intestine and manifest as true celiac disease. If these antibodies are present, it is probable that they will cross react with CNS tissue, resulting in cerebellar, cortical and/or Purkinje cell damage. As previously reported, most people who demonstrate symptomatology of autistic spectrum disorders demonstrate some degree of gastrointestinal dysfunction, whether or not it is associated with celiac disease.

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Even in the absence of true celiac disease, the neurodevelopmentally challenged individual may be adversely affected by the opioid peptides produced by incomplete digestion of gluten proteins. It is likely that those who have antigliadin antibodies and small intestinal manifestations have significantly compromised gut permeability that facilitates the passage of opioid peptides into the blood stream and across the blood brain barrier. It has been noted that antigliadin antibodies can affect the blood brain barrier as well as the small intestine lining and the brain tissue we have previously discussed, resulting in an influx to the brain of large quantities of exogenous opioids.

In light of both the immunologic and biochemical evidence that gluten plays a role in the manifestation of neurodevelopmental disorders, mainstream acceptance of the gluten free diet as part of the treatment protocol for ASD would be expected. This, however, is not the case. While some are skeptical, others are outright opposed to such intervention on the basis of the difficulties in carrying it out and the risks associated with omitting wheat from the diet. Clearly, given the cultural dietary norms, a gluten free diet is a challenge to undertake. [52] But, as most of the gluten foods consumed by the average person are highly refined, it is unclear how omitting these foods could result in nutritional deficits. That said, the typical gluten free, casein free diet is not highly nutritious, not due to the exclusion of gluten, but, rather, due to the inclusion of a large quantity of refined flour, albeit non gluten, sugars and fillers in an attempt is replace breads.

While the efficacy of the gluten and casein free diet has not yet been demonstrated by a placebo controlled double blind study, the clinical results seen by many individual practitioners has been very promising. Those who are waiting for the results of the placebo controlled study will likely be long in waiting; as such an intervention does not easily lend itself to even single blind, let

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alone double blind methodologies.

Parents of children with autism have reported that avoidance of gluten and casein had a significant impact on their child's behavior [54] The Autism Research Institute's parent ratings indicated that upon removal of wheat from their child's diet, 2% got worse, 51% had no effect, and 47% got better. The ARI observed "Gluten and/or casein free diet has been implemented to reduce autistic behavior, in addition to special education, since early in the eighties. The reported results are more or less identical: reduction of autistic behavior, increased social and communicative skills, and reappearance of autistic traits after the diet has been broken." [57]

A summary by Lahey and Rosen describes a 2001 trial of seven group studies, plus three case studies and two surveys on dietary intervention with autistic children, which reports positive changes in autistic behavior in all but one study. [5]

Lewis Mehl-Madrona, MD, PhD, Coordinator for Integrative Psychiatry and System Medicine Program in Integrative Medicine at the University of Arizona College of Medicine says "Nutritional therapies are first on my list. The gluten-casein free diet has helped many children and is where I begin. Gluten, and the structurally related casein from dairy, are incompletely digested and pass through the gut as molecules with opioid-like properties. The effects of opioid-like compounds are, in part, the symptoms seen in autism, Asperger's, and other developmental disorders. [51]

Norwegian researcher Kallie Reichelt has published data which support the effectiveness of gluten and casein avoidance. He has written about the results extensively, both in peer reviewed journals and online. [52,59]

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Elimination of gluten from the diet helped 80% of children who met the DSM-IV criteria for ADHA improve by at least 50% in 2 weeks. [60]

Many more examples of positive outcomes from gluten free diets as part the protocol for autism are cited in both peer reviewed journals and online [44 – 60] Like anything else, the diet is not a magic bullet, nor will it result in improvement for all neurodevelopmentally challenged individuals. The treatment approach must be multifaceted and tailored to the individual needs of the patient. Diet, targeted nutritional supplementation, including fatty acids, amino acids, digestive enzymes, intestinal repair nutrients, amino acids, vitamins, minerals, and herbs, behavior therapies, hands on therapies including manipulation and CranioSacral therapy, detoxification programs, including chelation, methylation defect intervention, and antioxidant support have all been shown to benefit when used carefully, thoughtfully, and in proper combination. I have personally seen and talked to parents who have experienced dramatic improvement using a diet and nutritional approach to neurodevelopmental disorders.

As far as the diet is concerned, a major improvement, both in terms of taste and nutritional content, over the typical gluten free approach which seeks to replace all the flour products with non-gluten versions, is a diet which emphasizes fresh, raw fruits, vegetables, nuts and seeds. The response to classes on this topic has been very positive. [61]

Conclusion

In conclusion, research and clinical trials have identified a mechanism by which gluten plays a role in the etiology of neurodevelopmental disorders. Removing gluten from the diets of

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affected persons can result in improvement of the condition. Gluten intolerance can no longer be viewed as a disease of the small bowel. Its widespread affects on the the body in genetically predisposed individuals is a major contributor to many diseases, and especially should not be overlooked in neurodevelopmental disorders of the autistic spectrum, including ADHD, OCD, Aspperger's and Autism.

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