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FOODS AND SOCIAL PROBLEMS IN CHILDREN WITH AUTISM SPECTRUM DISORDERS

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ABSTRACT: *Autism is a complex disorder with no specific diagnostic test so the disease is defined by its characteristics including cognitive defects, social, communication and behavioral problems, repetitive behaviors, unusual sensitivity to stimuli such as noise, restricted interests, and self stimulation. Exploration into the role of the immune system, genetic susceptibility, and environmental factors such as infections, vaccines, and diet has led to the emergence of numerous theoretical models to explain the biological basis for autism. Individuals with Autism Spectrum Disorders (ASD) often suffer from gastrointestinal problems which may contribute to ASD behavioral symptoms. Developmental disabilities (DDs) are chronic physical, cognitive, speech or language, psychological, or self-care conditions that typically originate during childhood, are likely to continue indefinitely; and require additional coordinated services, support, or other assistance for an extended duration or during a lifetime. Developmental disabilities profoundly affect children's health and functioning. Additional study of unmet needs and access to care is needed.*

KEYWORDS: *Autism, gastrointestinal problems, social problems, probiotics*

INTRODUCTION

Autism is a complex disorder with no specific diagnostic test so the disease is defined by its characteristics including cognitive defects, social, communication and behavioral problems, repetitive behaviors, unusual sensitivity to stimuli such as noise, restricted interests, and self stimulation. The incidence of this disease has increased remarkably in recent years and was 110/10,000 children (~1%) in multiple areas of the US in 2007. The financial burden on families and communities is enormous (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators and CDC, 2012) [4]. ASD can be devastating to families who are often ill-equipped to meet the challenges of caring for a child with autism [28]. Particularly difficult is communicating with the autistic child. Much research on ASD has focused on genetic, behavioral, and neurological aspects of disease, though the contributions of environmental risk factors [24], immune dysregulation [38], and additional peripheral disruptions [30] in the pathogenesis of ASD have gained significant attention. Exploration into the role of the immune system, genetic susceptibility, and environmental factors such as infections, vaccines, and diet has led to the emergence of numerous theoretical models to explain the biological basis for autism. In turn, a growing number of parents are implementing a variety of still unproven treatment modalities with their autistic children [28].

The implications of this rise in prevalence is on the scale of an epidemic, but as yet no definitive cause has been determined, and the efficacy of specific interventions are not yet clear. Parents

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of children with autism spectrum disorders report many challenges with children's daily activities, behavior, and communication. Parents also frequently express concern related to meal times. Parents of children with autism spectrum disorders often report that their children are highly selective eaters, with very restricted repertoires of food acceptance. Picky eating, also referred to as food selectivity, is a considerable problem because it can be associated with inadequate nutrition as a result of the restricted diet [12; 18; 25; 31; 40; 44; 50]. Food refusal and introduction of new foods were cited as the most difficult problems faced by parents. There is growing interest in possible dietary involvement in the aetiology and treatment of Autistic Spectrum Disorders (ASD). Research has focused on the physiological and behavioural effects of dietary change but has not examined the effect of exclusion diets on nutritional intake. No significant differences in the energy, protein and micronutrient intakes were found between the two groups of children. A longitudinal prospective study is suggested to examine whether differences in food choice are the result of dietary intervention or the prerequisite for the successful application of diet in this special group of children [13].

Despite recently emerging as the most increasingly prevalent and most heavily researched neurodevelopmental disorder in the United States, autism spectrum disorder (ASD) is still largely incurable. ASD has traditionally been viewed as a neurological disorder, as its symptoms include deficits in language and social behavior, but new research has brought focus onto the many disorders associated with ASD, including diabetes, sleep disorders, and — of particular interest — gastrointestinal (GI) defects. Individuals with Autism Spectrum Disorders (ASD) often suffer from gastrointestinal problems [9]. The exact percentage suffering from gastrointestinal (GI) problems varies from study to study and depends on the age of the study population, but there is a general consensus that GI problems are common in autism. In a study of 137 children with ASD, 24% had a history of at least one gastrointestinal symptom, with diarrhea being the most prevalent one – occurring in 17% of individuals [35]. Similarly, a study of 172 children with autism spectrum disorder found 22.7% were positive for GI distress, primarily with diarrhea and constipation [42]. A characterization study of 160 children with ASD found 59% had GI dysfunction with diarrhea or unformed stools, constipation, bloating, and/or gastroesophageal reflux (GERD) [34]. A study of 51 children with ASD compared to 40 typical controls ages 3-15 found that 63% of children with autism were reported to have moderate or severe chronic diarrhea and/or constipation, vs. 2% of the control children [3]. In summary, these studies demonstrate that GI symptoms are common in autism.

GI problems in children with autism may contribute to the severity of the disorder. Abdominal pain, constipation, and/or diarrhea are unpleasant and likely to produce frustration, decreased ability to concentrate on tasks, behavior problems, and possibly aggression and self-abuse, especially in children unable to communicate their discomfort. These problems also result in a decreased ability to learn toilet training, leading to increased frustration for the child and their parents/ caregivers [2]. The cause of these GI problems is unclear, but it appears to partly relate to abnormal gut flora and possibly to the excessive use of oral antibiotics which can alter gut flora. Commonly used oral antibiotics eliminate almost all of the normal gut microbiota, which play an important role in the breakdown of plant polysaccharides, promoting gastrointestinal motility, maintaining water balance, producing some vitamins, and competing against pathogenic bacteria. Loss of normal gut flora can result in the overgrowth of pathogenic flora, which can in turn cause constipation and other problems. Finegold et al. 2002 [19] studied fecal samples from 13 children with late-onset autism and 8 controls. The number and type of *Clostridium* and *Ruminococcus* species in children with autism differed from the control children. Song et al. 2004 [45] found that *Clostridium cluster* groups I and XI and *Clostridium*

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boltae had mean cell counts significantly higher than those of control children. Parracho et al. 2005 [39] levels of the *Clostridium* histolyticum group of bacteria were higher in the ASD children compared to typical children. *C. histolyticum* bacteria are recognized toxin producers and may contribute to gut dysfunction. Finegold et al. 2010 [20] studied gut bacteria in children with autism vs. controls, and found several differences at the phylum level, including higher levels of Bacteroidetes in the severely autistic group, and higher levels of Firmicutes in the control group. Finegold 2008 [21] hypothesized that 1) the relapse of some autistic kids after antibiotic treatment is caused by the presence of *Clostridium* spores, 2) the incidence of autism is related to the widespread exposure to *Clostridium* spores, and 3) the increase of multiple autism cases within a single family is also related to contact with spores. Finegold also discussed the fact that propionate has been shown to have severe neurological effects in rats [32; 46] and *Clostridia* species are propionate producers [16]. No human studies have been conducted to test whether the relative proportion of propionate and/or its absolute concentration correlates to autistic symptoms. There have also been reports of decreased activity of digestive enzymes in children with autism. One study by Horvath and Perman 2002 [26] reported that 44 of 90 (49%) children with autism who underwent endoscopy (because they had significant gastrointestinal problems) had deficiencies in one or more disaccharidase enzymes, especially lactase and maltase. They reported that all of the children with low enzyme activity had loose stools and/or gaseousness. A recent study of children with autism and their first degree relatives found that 37% and 21%, respectively, had increased intestinal permeability based on a lactulose/mannitol test, compared to 5% of normal subjects [2]. They also found that autistic patients on a gluten-free, casein-free diet had significantly lower intestinal permeability [17].

Additionally *Desulfovibrio* species and *Bacteroides vulgatus* were present in higher numbers in autistic than controls Treatment studies using a minimally absorbed oral antibiotic (vancomycin) to treat abnormal gut flora showed significant temporary improvements in behavior for children with late-onset autism [43], but the benefits were lost after treatment stopped. In terms of predisposing factors, heredity plays a role in some subjects, but it is clear that environmental factors are also important. Environmental toxins can affect the immune system adversely. Intestinal bacteria are recognized by a few investigators as potentially important and certain antimicrobial drugs may be a key factor in modifying the intestinal bacterial flora adversely, selecting out potentially harmful bacteria that are normally suppressed by an intact normal intestinal flora. The clostridia in the gut might be involved in autism because they are virulent organisms and spore-formers; spores would resist antibacterial agents so that when antibiotics were discontinued the spores would germinate and by toxin production or another mechanism lead to autism. *Desulfovibrio* is an anaerobic bacillus that does not produce spores but is nevertheless resistant to aerobic and other adverse conditions by other mechanisms and is commonly resistant to certain antimicrobial agents (such as cephalosporins) often used to treat ear and other infections that are relatively common in childhood. This bacterium also produces important virulence factors and its physiology and metabolism position it uniquely to account for much of the pathophysiology seen in autism. If these results on *Desulfovibrio* are confirmed and extended in other studies, including treatment trials with appropriate agents and careful clinical and laboratory studies, this could lead to more reliable classification of autism, a diagnostic test and therapy for regressive autism, development of a vaccine for prevention and treatment of regressive autism, tailored probiotics/prebiotics, and important epidemiologic information [22]. Among several comorbidities in ASD, gastrointestinal (GI) distress is of particular interest, given its reported prevalence [8; 14 and correlation with symptom severity [3]. While the standardized diagnosis of GI symptoms in ASD is yet to be clearly defined, clinical as well as epidemiological studies

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have reported abnormalities such as altered GI motility and increased intestinal permeability [6; 17]. Moreover, a recent multicenter study of over 14,000 ASD individuals reveals a higher prevalence of inflammatory bowel disease (IBD) and other GI disorders in ASD patients compared to controls [30]. GI abnormalities are also reported in other neurological diseases, including Rett syndrome [36], cerebral palsy [10], and major depression [23]. The causes of these GI problems remain unclear, but one possibility is that they may be linked to gut bacteria.

Human gut microbiota plays a crucial role in host health, both as a source of infection and environmental insult and, conversely, in protection against disease and maintenance of gut function. Although little is known about the health impact of the dominant groups of gut bacteria it is generally accepted that bifidobacteria and lactobacilli are important components of what might be termed the beneficial gut microbiota. Hsaio and colleagues link gut microbes to autism spectrum disorders (ASD) in a mouse model. They show that ASD symptoms are triggered by compositional and structural shifts of microbes and associated metabolites, but symptoms are relieved by a *Bacteroides fragilis* probiotic. Thus probiotics may provide therapeutic strategies for neurodevelopmental disorders [27]. The authors find that treating mice with a probiotic known as Bacteroides fragilis not only corrects gut defects but also improves behavioral abnormalities, by decreasing anxiety-like behavior and increasing communication. These results strongly suggest that the behavioral abnormalities seen in ASD are in fact caused by gut defects. The authors strengthen their claim by proposing that these gut defects may stem from changes in the levels of certain metabolites (small molecules) in the gut, and they point specifically to a metabolite known as 4-ethylphenylsulfate (4EPS), which produces anxiety-like behavior in mice and has a close parallel to a human metabolite known to be increased in ASD patients [27].

Indeed, dysbiosis of the microbiota is implicated in the pathogenesis of several human disorders, including IBD, obesity, and cardiovascular disease [5], and several studies report altered composition of the intestinal microbiota in ASD [2; 20; 29; 48; 49]. Commensal bacteria affect a variety of complex behaviors, including social, emotional, and anxiety-like behaviors, and contribute to brain development and function in mice [11; 15] and humans [47]. Long-range interactions between the gut microbiota and brain underlie the ability of microbe-based therapies to treat symptoms of multiple sclerosis and depression in mice [7; 37], and the reported efficacy of probiotics in treating emotional symptoms of chronic fatigue syndrome and psychological distress in humans [33; 41]. Elaine Y. Hsiao, 2013 [27] studies herein that offspring of maternal immune activation (MIA) mice, which display behavioral abnormalities, have defects in intestinal integrity and alterations in the composition of the commensal microbiota that are analogous to features reported in human ASD. While a number of studies support a role for GI complications in ASD, additional prospective population-based studies are needed to evaluate the frequency of GI symptoms in ASD and the interesting possibility that GI conditions are enriched in particular ASD subtypes. The role of GI abnormalities and their contribution to symptoms in other neurodevelopmental disorders warrants further investigation as well.

In summary, gastrointestinal problems are common in children with ASD and may contribute to ASD behavioral symptoms. Developmental disabilities (DDs) are chronic physical, cognitive, speech or language, psychological, or self-care conditions that typically originate during childhood, are likely to continue indefinitely, and require additional coordinated services, support, or other assistance for an extended duration or during a lifetime.

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