Review Article

Potential Etiologic Factors of Microbiome Disruption in Autism

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ABSTRACT

Purpose: The primary purpose of this article was to consider the candidate disruptors of the development of a healthy microbiome in patients with autism. The reported abnormalities in the microbiome of individuals with autism are discussed.

Methods: This selected review used data from published articles related to the assessment of microbiota in autism. Evidence-based support of factors known to affect the intestinal microbiome in individuals with autism are presented. Proposed interventions are evaluated and discussed.

Findings: Studies that have investigated the intestinal microbiome in patients with autism have reported significant differences versus unaffected controls. Increased clostridial species in autism have been reported in several studies. These differences may have resulted from a number of environmental factors. Microbiome alterations that might contribute to the development of autism include altered immune function and bacterial metabolites.

Implications: Efforts to modify microbial imbalances through a variety of interventions are addressed. Focusing on mechanisms that drive imbalances in the microbiome may affect the development of disease. Altered intestinal health may contribute to the development of autistic behaviors or autism itself. Interventions aimed at improving intestinal health may favorably affect the microbiome and autism. (*Clin Ther*. 2015;37:976–983)

Key words: autism, intestinal microbiome, microbiota, pediatrics.

INTRODUCTION

Autism is a medical condition originally described by Kanner[1] in 1943. In <75 years since the recognition of the condition, the prevalence of autism has exploded from 1 in 5000 individuals to 1 in 68.2. The prevalence is 4- to 5-fold greater in boys than in girls.[2] For obvious reasons, there is an effort to address the potential factors that account for this rising prevalence. Although genetic factors have been closely associated with the condition, especially in families with >1 affected individual, in most cases of autism, a cause has not been identified.[3] There is speculation about maternal immune factors,[4] prenatal or environmental toxicity (reviewed by Rossignol et al[5]), and metabolic derangement[6] contributing to the development of autism.

We should add gastrointestinal (GI) and dietary factors to the list of speculation. Interest in GI abnormalities in autism goes back to the original descriptions of affected individuals. These included remarkable differences in dietary intake and the requirement for feeding support in some patients.[1]

Since then, a growing literature supports a high frequency of GI symptoms in individuals with autism. The symptoms do mirror the general pediatric community in terms of the nature of concerns such as constipation, acid reflux, and diarrhea, but consistently seem to have a greater frequency in autistic patients than in the control populations reported in

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most studies.[7,8] Recognizing underlying GI conditions or other medical problems may be difficult in individuals with no or limited verbal capability. Pain may trigger behaviors such as aggression or self-injury in individuals with autism, and caregivers may manage these issues as behavioral without considering the underlying disease.[9]

Autism may contribute to GI issues directly because of altered eating patterns, which might change the stool pattern or microenvironment. Sensory factors that may alter feeding patterns and toileting behaviors are common, although not universal, in autism.[10] Is it possible that an altered GI state could contribute to the neurologic state of autism in some individuals? This concept was suggested by Adams et al,[11] who reported that in patients who had GI symptoms, were identified as having more severe impairment from autism features by autism-testing tools.

We have become more capable of addressing some questions as our understanding of autism has grown and our ability to assess the GI microbiome and the metabolic gut environment, the *metabolome,* has developed. From a clinician's perspective, the discussion of intestinal microbiome and disease has been rather esoteric to this point. However, with available interventions such as probiotics and fecal microbiota transplantation (FMT) available, patients with conditions known to affect the intestinal microbiome such as autism, inflammatory bowel disease and celiac disease are asking for advice from providers how to fix these abnormalities.

MATERIALS AND METHODS

This selected review used data from published articles related to the assessment of microbiota in autism. Data from studies that compared the intestinal microbiome in patients with autism to that in healthy controls were included. The selection of articles used in this review include selected earlier literature. The primary review comes from key words, autism, autism spectrum disorders, microbiota, microbiome from 2000-present. It included prospective author initiated, retrospective and review papers in this period. All papers were considered for use without an exclusion based on the limited available literature.

RESULTS

What Is Reported Regarding Microbiome Abnormalities in Autism?

Our intestines contain tens of trillions of microbes. Although bacteria are predominant, Archaea, Eukarya, as well as viruses are cohabitate in this complicated ecosystem of the human host. In each individual, a unique microbiome typically made up of ~1150 bacterial species is established.[12] In disease, there is a characteristic decrease in the number and diversity of these species.[13] The development of this microbial community begins even before birth[14] and continues for up to the first 3 years of life. There are differences that occur in the makeup of the colonies present based on infant nutrition; in breast-fed infants, the microbiome established is different from that in formula-fed infants.[15] Between 2 and 3 years of age, there is stabilization of a child's microbiome that seems consistent with an established adult community.[16] It is quite clear that dietary changes or other nutrient-based changes, such as supplementary fiber, can alter the composition of the microbiome[17] in individuals of all ages.

Children are typically diagnosed with autism between ages 1 to 3 years.[18] This coincidence of timing makes consideration of the developing microbiome and immune system worthy of study. There are many examples in nature of intestinal microbes altering host behavior. One such example involves the eukaryotic pathogen *Toxoplasma gondii* when it infects the rodent, causing the animal to lose its innate fear of the odor of bobcat urine. By not avoiding territory inhabited by the predator, rodents are more often caught, and *T gondii* is then excreted in the bobcat stool where it is able to infect other rodents.[19,20] Infection with *T gondii* is also associated with behavioral changes in humans, who may exhibit poor self-control and increased high-risk behavior.[21–23] Similarly, neuropsychiatric disorders have been associated with infection with *Brucella suis*, *Leptospira* spp, *Mycobacterium tuberculosis*, and streptococci (coined the *PANDAS* [pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection]).[24–28]

In addition to these specific examples of behavioral changes caused by single organisms, there are compelling data that alterations in the entire microbial ecosystem may also affect behavior in mice. Mice that are reared in a germ-free environment have increased movement in a maze, suggesting decreased anxiety.[29] The metabolic product of enteric bacteria, propionic acid, has been reported to affect behavior and cognition in mice.[30]

A recent seminal report in *Cell* describes improvement in a mouse model of autism in animals treated with the commensal organism *Bacteroides fragilis*. Not only was intestinal permeability corrected but