New Study Confirms Link Between Gut Microbes and Autism — But Stops Short of Answering Which Comes First

Research reported in Nature Neuroscience strongly links the gut microbiome to autism spectrum disorder (ASD), identifying four bacterial species tied to ASD and fueling hopes of microbiome-targeted treatments. But experts caution against expectations of a quick cure.

By Angelo DePalma, Ph.D.

The connection between the gut microbiome and behavioral health has been the subject of intense investigation. But even when the link appears indisputable, associating the microbiome's thousands of bacterial, yeast, fungal and virus species to specific symptoms or diseases may be challenging.

Now, results from a study reported in Nature Neuroscience in June support the connection between the microbiome and autism spectrum disorder (ASD), and provide clues about the microbes involved.

These data may eventually lead to "natural interventions" that promote a healthy microbiome and, it is hoped, relieve some of the burden of ASD on those affected, according to the study authors.

The difficulty with comparing studies

The authors of the Nature Neuroscience paper reviewed results from more than 70 studies investigating the microbiome-ASD connection.

A major problem with drawing conclusions from a large number of studies is that the sheer diversity of study designs, aims, methods and even investigators raises the possibility that the analysis will compare "apples to oranges."

One paper may look at kindergarten-age girls while another studies adolescent boys. Some investigations may include an intervention — requiring subjects to eat certain foods or take a drug or dietary supplement, for example — while others are purely observational.

Additionally, not all "microbiome" studies focus on the same microorganisms or use the same analytical methods to find them. One study may look at proteins generated by bacteria while another measures genes from yeast. Both studies qualify as microbiome investigations but their conclusions may not be comparable.

This is a common problem with microbiome research as there are potentially thousands of species involved and a dozen ways to detect and characterize them.

An innovative approach

In the case of the Nature Neuroscience paper, lead researcher Gaspar Taroncher-Oldenberg, Ph.D., and his team solved this dilemma by using an innovative study design first described in

2019 by researchers at the University of Nevada, Reno, and Wayne State University in Detroit, Michigan.

The method involves two steps: identifying a factor common to both data sets, and comparing those data (and assigning their relative significance) based on that relationship.

Take as an example a hypothetical review of studies on the effect of diet on the ability to hit a baseball. Let's say half the studies measured protein consumption and the other half tallied the number of meals subjects consumed per day.

Both groups qualify as "diet" studies but they are not directly comparable because protein consumption and eating schedule are totally unrelated.

However, if it were possible to relate protein and meal frequency to a third factor that is easily measured and critical to hitting a baseball — say, visual acuity — it then becomes possible to compare the results.

In the case of the Nature Neuroscience study, researchers connected seemingly unrelated studies to the known, well-established connections between bacterial species and the biological "pathways" or mechanisms through which ASD develops.

They then used the strength of those associations to develop a system for ranking and comparing microbial species for their potential involvement in ASD.

In all, they drew data from 25 studies on individual microbiome species, dietary patterns, bacterial metabolites, inflammatory proteins and alterations in brain chemistry associated with ASD.

They found the strongest associations to ASD in the chemical profiles of bacterial metabolites consisting of fats, carbohydrates and protein breakdown products. Four bacterial species were primarily involved: Prevotella, Bifidobacterium, Desulfovibrio and Bacteroides.

The authors also noted "a strong association between temporal changes in microbiome composition and ASD phenotypes," meaning that changes in a person's microbiome can affect the type and severity of ASD symptoms.

It's probably not all 'in your genes'

ASD, which involves mild-to-severe impairments in cognition, behavior and communication, affects approximately 2.8% of American children. Its occurrence in boys is almost 4 times higher than in girls (4.3% versus 1.1%).

Parents usually notice symptoms by age 2, and as children mature, their cognitive and behavioral deficits often affect their performance in school or work and their ability to socialize.

Distinguishing vaccine injury from genetic and other developmental disorders has been difficult for a variety of reasons. Funding priorities and technology trends (like using knockout mice — mice in which researchers have inactivated, or "knocked out," an existing gene by replacing it or disrupting it with an artificial piece of DNA) have resulted in a strong emphasis on investigating potential genetic vulnerabilities related to ASD.

So far, more than 100 genes have been linked to the disorder. However, these observations come with the caveat that many of the same genes are implicated in other neurologic processes or in broader childhood development — so the preponderance of studies looking for genetic causes for ASD needs to be understood in this context.

One previous study looked directly at abnormalities in brain structure for clues. Such abnormalities are subtle and, according to Taroncher-Oldenberg, their causal relationship with ASD has not been established.

"One comorbidity that has been linked to ASD with high confidence is the occurrence of gastrointestinal (GI) symptoms, such as constipation, diarrhea or abdominal bloating" even though "causal insights" have not been clear, wrote Taroncher-Oldenberg.

But this evidence, along with the observation that the severity of GI symptoms often correlates with ASD severity, makes this idea a reasonable starting point, and the basis of current investigations on the "gut-brain axis" and ASD.

The original article in The Lancet — which was retracted — connecting the MMR (measles-mumps-rubella vaccine) to ASD looked specifically at 12 children who presented with both acute onset ASD and severe gut symptomatology.

The gut-brain axis is a bidirectional chemical communication channel between a person's digestive and nervous systems, particularly the brain. Communication occurs primarily through the release of chemicals by the brain and the trillions of microbes comprising the gut microbiome.

In addition to ASD, disruptions in the gut-brain axis have been associated with anxiety, obesity, schizophrenia, Parkinson's disease and Alzheimer's disease.

Gut microbes a factor, not a cause

Although the association between the gut microbiome and ASD is strong, one cannot conclude, based on the evidence, that certain bacteria definitively cause autism.

Many possible contributors to the ASD-bacteria link remain uninvestigated. For example, children with ASD could simply be fussy eaters and be less likely to consume nutrients that promote a healthy microbiome. Their diets alone or some other unknown factors — or both — may be responsible for their behavioral problems.

Future investigations should also look into the possibility that ASD is the cause, and not the effect, of microbiome issues.

Other possible factors confounding the ASD-microbiome link are differences in study population demographics — including number of subjects recruited, race, age or sex — and that studies often collect data only from one point in time.

Since the characteristics of both ASD and the gut microbiome change over time, connections between microbial populations and the disorder are often difficult to pin down.

Taroncher-Oldenberg commented on this point in a July interview in FoodNavigator:

> "So you don't really know what came before, or what came after. All you know is that while you're having the symptoms or whatever it is you're measuring phenotypically, you know that you have this microbiome versus that microbiome composition. That's all you know.
>
> "So it's very hard to infer any kind of mechanistic insights from this, other than to say

there is a difference in the microbiome."

"Phenotypically" refers to the observable, diagnostically-relevant symptoms of ASD.

Phenotypic variations between the sexes are also common. Taroncher-Oldenberg's study corrected for both age and sex.

One problem this study could not address was the "time point" factor. Significant changes in symptoms are evident as subjects age, from infancy through their teenage years.

Taroncher-Oldenberg told FoodNavigator:

> "In order for us to know if any of those signals were relevant or what they could mean, therapeutically or just in terms of disease, mechanistically, we needed to 'ground-truth' our results with longitudinal data, that had five or six data points over time that correlated with some kind of change in the autistic phenotype."

The significance of this study lies in the potential to improve ASD symptoms in children or perhaps, should the brain-microbiome connection prove causative, even cure ASD.

Although Taroncher-Oldenburg dismissed the idea of an easy cure, his group did re-analyze data from a two-year, 18-subject open-label (i.e., without a control group) fecal matter transplant study with children with ASD.

Fecal transplants involve giving people beneficial bacteria they lack by having them ingest a capsule containing a small quantity of stool from a healthy donor.

The technique has been used, with positive results, to treat dangerous bacterial infections of the GI tract, Type 2 diabetes, multiple sclerosis and Crohn's disease.

In the study, the children were first purged of resident gut bacteria through a two-week antibiotic treatment and a bowel cleanse, followed by daily fecal dosing for eight weeks.

Based on one common measure of ASD symptoms, the Childhood Autism Rating Scale, investigators noted significant improvements that persisted for two years post-treatment.

Taroncher-Oldenberg suggests interventions like fecal transplants "are consistent with a potential role of the microbiome in improving autism symptoms, but how the underlying changes in microbiome composition [are] related to those seen in other studies remains unknown."

In other words, we should not expect a cure or even a universally accepted treatment for ASD until scientists sort out which factors and which bacterial species are responsible — and which ones are merely bystanders.

SUGGEST A CORRECTION

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