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Does pica potentiate autism?: Developing a research agenda

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Introduction

The past two decades have provided groundbreaking research in the biology of autism in children. Among the papers most contributory are studies of metabolic biomarkers of increased oxidative stress and impaired methylation capacity;1 understanding how an alteration of the gut ecosystem (microbiome) may lead to improvement in gastrointestinal and autism symptoms[2-5] and most recently how saliva RNA biomarkers of gastrointestinal dysfunction can potentially have bearing on precision medicine.[6] These research teams are architects of new and promising approaches.

The same cannot be said of biological advances in pica research. Pica is the ingestion of non-foods (e.g., plastics, rubber, screws and nails), which can perforate or wrap around organs, require surgeries, and even lead to death. Though considered the most dangerous form of self-injurious behavior in the literature on developmental disabilities, pica has received relatively little (biological) research.[7]

Ironically, pica looms as a serious problem for children and adults with autism. A recent study[8] supported by the CDC reported that 23.2% of children ages 3-5 demonstrated pica behavior. A 1985 investigation by Kinnell[9] reported that 60% of clients with autism (ages 9-76, mean 31; N=70) engaged in pica compared to 4% of adults with Down Syndrome (ages 21-75, mean 42; N=70). He considers pica a diagnostic feature of autism. While lacking more recently formulated tests for diagnostic corroboration (ADOS, ADI, CARS), Kinnell's description of autism is comprehensive and convincing. From any viewpoint, pica is a "stakeholder" in autism.

Phenotypic subgroups as a way forward

A 2020 study by these authors[10] looked across adult clients in four groups: autism, pica, autism/ pica, and developmental disability without secondary diagnosis (ages 24-58, mean 42; N=64). Based on chart review covering a 10 year period by "blind" UCLA graduate school interns, the clients with autism/ pica showed the highest average number of gastrointestinal diseases (2.88) per individual, while the autism (only) clients were the lowest of the four groups (0.53 diseases on average). Pica clients were second highest (2.25 diseases), with an average of 1.31 diseases for clients with developmental disabilities only. Our separate autism/pica and autism groups were on the extreme ends of our data sets. When groups were combined into "pica" (autism/ pica and pica) and "no pica" (autism and developmental disability only) conditions, the adults with pica showed higher prevalence for each of the 10 (of 19) most frequently recorded GI diseases. Why? How?

The prospect of better understanding the pathophysiological processes driving GI disturbances may be facilitated by distinguishing specific subtypes of ASD, which might impact treatment.[6,11] Our study suggested that individuals with both autism and pica disorders may be a phenotypic subgroup on the autism spectrum characterized by GI symptomatology, requiring a clinical algorithm for categorization and effective treatment. Pica may largely explain a link between autism and GI problems.[12] We advocate for the application of those groundbreaking methods described above and below as critical steps toward understanding the pathophysiology of pica, autism, and their interaction. Does pica potentiate autism? We believe so. Accordingly, we hypothesize greatest disturbance in function, i.e., deviation on biological measures, for A/P clients compared to other groups.

Methods highlighted: descriptions, contributions, considerations, hypotheses

Saliva RNA biomarkers of GI dysfunction

As with stool analysis and oxidation/ methylation studies described below, research on saliva RNA biomarkers[6] seeks to understand biological differences between children with ASD and control groups, here children with non-ASD developmental delay (DD) and typical development (TD). The primary goals of this study included:

a) identify human and microbial RNA levels in saliva that were associated with GI disturbance

b) investigate whether these relationships were impacted by child developmental status

c) determine if specific RNA "biomarkers" displayed unique expression patterns in particular GI disturbances (e.g., constipation) or with particular treatments (e.g., probiotics)

Procedural outline for saliva RNA transcriptomes

a) saliva obtained from participants in non-fasting state via swab

b) nucleic acid extraction

c) RNA sequencing

d) alignment and quantification of known RNA sequences to reference data base

e) assignment to microbial genes, quantified to a microbial identity (e.g., genus, species, strain)

Results summarized

a) Compared to children with TD, a higher proportion of children with ASD reported GI disturbances (22% vrs 10%); constipation (11% vrs 3%); reflux disorder (6% vrs 0.5%)

b) There were no differences between children with ASD and DD in rates of constipation, reflux, food intolerance, chronic abdominal pain, diarrhea, or eosinophilic esophagitis

Considerations

Comparing the adult autism/ pica group[10] in our study to our autism group we found higher symptomatology on similar measures: GERD (35% vrs 7%); abdominal pain (29% vrs 0%); constipation (94% vrs 80%). Also consistent were vomiting (41% vrs 27%); and alternating diarrhea/ constipation (29% vrs 7%).

Hypothesis

Utilizing measures associated with saliva RNA transcriptome analysis, adult clients with pica and autism/pica will show a higher percentage of GI symptoms and diseases than ASD, DD, or TD clients.

Bacteria genera in the gut

Beneficial bacteria in the gut, or microbiome, can affect body weight, the body's susceptibility to infection, aid in food digestion, produce vitamins, and protect against harmful bacteria.[13] If left unchecked, harmful bacteria can excrete dangerous metabolites that can affect the gut, the brain, and the rest of the body. Interventions for rebalancing human and gut microbiota to treat disease have included diet, probiotics, prebiotics, and fecal microbiota transplants.

Procedural outline for bacteria genera analysis

a) microbial DNA extracted from feces, swabs

b) "library" preparation and next generation sequencing

c) build a phenotypic tree of representative sequences for use in phylogenetic diversity analyses

d) taxonomically annotate representative sequences

e) isolate and sequence viral DNA

NOTE: Beversdorf[6] discusses the more readily obtained salivary transcriptome as a proxy for the primary pathological site of most GI disturbances, the lower GI tract- captured by stool analysis.

Results

In their meta-analysis of nine studies of the gut microflora in ASD and TD children, Xu et al.[5] report that participants with ASD had:

a) a lower abundance of ("healthy") Akkermansia, Bacteroides, Bifidobacterium, ("good") E. coli, and Enterococcus

b) a higher abundance of ("unhealthy") Faecalibacterium and Lactobacillus

c) a slightly increased abundance of ("unhealthy") Ruminococcus and Clostridium

NOTE: Krajmalnic –Brown et al.[14] report a lack of diversity in the gut bacteria strains of children with autism spectrum disorder.

Considerations

While Microbiota Transfer Therapy represents a direct effort to rebalance the microbiome, that intervention- even while demonstrating success- has and continues to receive much scrutiny. On the other hand, dietary supplementation/nutritional interventions, particularly with key vitamins and minerals, has led to observable improvement for persons with autism in several studies[15,16] (see also[17-19] cited in[20]). Moreover, improvement is noted for persons with pica in small scale studies,[21,22] and single-subject case reports.[15,23,24] That such nutritional interventions can modulate gut microbiota – at least in ASD- is made clear by Ristori and her colleagues.[25] But comparable data on bacteria genera for pica, and autism/pica are again lacking.

Hypothesis

Using measures associated with bacterial taxonomy, percentage, and relative abundance, adult A/P clients and clients with pica only will show higher percentages and greater relative abundance of "unhealthy" bacteria, and lower percentages and less relative abundance of "healthy" bacteria, as well as less diversity in bacteria strains, than ASD, DD, or TD clients.

Oxidative sress and impaired methylation

Methylation is critical in suppressing viruses, processing toxins in the liver, controlling inflammation and oxidation, regulating genes, and generating sufficient neurotransmitters in the brain. The body must constantly balance in lockstep activating methylation and synthesizing the highly potent antioxidant glutathionine. Hypomethylation can suppress these processes, whereas too little production of glutathianine results in oxidative stress.

James and her colleagues[1] wanted to determine if the genetic component of primary autism could be expressed as a chronic metabolic imbalance that impairs normal neurodevelopment and immunologic function. That they were able to correct observed metabolic imbalance in children with autism with targeted nutritional intervention "implies that certain aspects of autism may be treatable" (p. 1615). The possibility that autism has a METABOLIC PHENOTYPE is raised by examining subclinical perturbations in physiological pathways (see also).[26]

Procedural outline for improving the metabolic profile

a) obtain baseline concentrations of plasma metabolites in the methionine cycle and transsulfuration pathway

b) establish whether the metabolic profiles of the children under study (here ASD and TD) differ significantly

c) based on observed abnormalities in plasma metabolites, first administer oral supplements of folinic acid and betaine BID

d) after three months compare each metabolite concentration with baseline blood samples

e) provide an injectable form of methylcobalamin twice weekly in addition to folinic acid and betaine

f) have each child serve as his or her own control

Results

a) Relative to the control children, the children with autism had significantly lower concentrations of methionine, SAM, homocysteine, cystathionine, cysteine, and total glutathionine, and significantly higher concentrations of SAH, adenosine, and oxidized glutathione.

b) Ratios associated with this metabolic profile are consistent with impaired capacity for methylation and increased oxidative stress in children with autism.

c) The intervention was effective in normalizing the metabolic imbalance in the autistic children.

Considerations

The authors offer an explanation for autistic anomaly based on oxidative inactivation of methionine synthase in combination with

a decrease in SAH hydrolase activity secondary to the increase in adenosine. They further suggest that the metabolic pattern observed in the transsulfuration pathway is linked to imbalance in methionine cycle metabolites. Balance vs imbalance.

Hypothesis

Based on plasma concentrations of metabolic biomarkers, adult clients with pica and autism/pica will show greater oxidative stress and impaired methylation capacity than ASD, DD, or TD clients.

Concluding considerations

There are many empirical directions that can help to explore the relationship between autism and pica. Straightforward correlations are a good starting point. Does autism/pica predict higher autism severity scale scores than autism only? Compared to autism does pica or autism/pica predict higher Gastrointestinal Symptom Rating Scale (GSRS) scores? Higher anxiety/ impulsivity scores? Higher food selectivity scores? Do clients with pica show patterns of clinically significant suboptimal nutrient intake that even exceed those for children with autism?[27] Some of these answers have been provided to this author by Stephen M. Edelson Ph. D.,[28] Director of the Autism Research Institute in San Diego based on survey of almost 2300 children with autism. To illustrate, of 217 autistic children with IBS, 58% engaged in pica while 42% (autism only) did not; of 438 children with GERD, 55% engaged in pica while 45% (autism only) did not. Similar values for A/P children include: eats large amounts of food (59%), demonstrated craving for certain foods (58%), had smelly (55%) or loose stools or diarrhea (53%), and abdominal pain (52%). Interestingly, a lower percentage (42%) of A/P children liked to be held.

The road is plowed to measure and compare saliva RNA transcriptomes, bacteria genera, and metabolic profiles across autism, pica, autism/pica, developmental disability, and neurotypical groups. Doing so would follow the the recommendation for subgroup categorization and analysis offered not only by Beversdorf et al.,[6] but also by Alexander et al.,[10] Buie et al.,[29,30] Coury,[27] James et al.,[1] Ousley and Cermak,[31] and others. We may discover unique or shared metabolic phenotypes as well as behavioral phenotypes; and be well on our way to specific targeted nutrition treatment for maldigestion, malabsorption, and presumably dysbiotic gut flora, inflammation, and increased gut permeability.[32-34] A gut out of balance may be rebalanced.

Each of the three methodological approaches adds to a "whole person " approach. While investigators may choose which test groups to focus on, it would be optimal to include all three sets of dependent measures – salivary, bacterial, and metabolic. To do so would permit more direct within- subject comparisons. The power of statistical analysis can be increased by utilizing a common complaint, e.g., gastritis or H .Pylori (diagnosed by a physician) across all study participants.[35] A study employing children would permit comparison to most studies cited here, while focus on adult populations would complement the findings by Alexander et al.[10] and Kinnell.[9] The latter approach may yield more striking results since age, disease, and other factors can impact the gut microbiota ecosystem.[4] Investigators may then work backward in time to study younger populations.

Architects have given us "plans" for a comprehensive and holistic research agenda. Advances in technologies and analysis have streamlined once cumbersome methods. We are now better positioned to address the "why" and "how" accounting for discrepancies between autism and autism/pica. The stage is set to consider quantitative and/ or qualitative potentiation.

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None.

Conflicts of Interset

None.

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