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THEORIES OF GUT-BRAIN AXIS INVOLVEMENT IN CHILDHOOD DEVELOPMENTAL DISORDERS

BY ARTHUR KRIGSMAN, MD

In clinical medicine, the concept of brain function being dependent upon activities occurring in the gastrointestinal (GI) tract is not a novel one. In the setting of gastrointestinal health, this unidirectional gut-brain link is seen upon ingestion of various foods and pharmaceuticals. For example, when one ingests substances containing alcohol, there is rapid absorption of alcohol molecules from the gastrointestinal tract. These molecules are transported within minutes to the brain via the blood. Similarly, when one ingests pharmaceutical substances such as narcotics, there is rapid absorption from the healthy gastrointestinal tract into the bloodstream with transport of the ingested opioid molecules to the brain via the peripheral circulation. Both of these examples serve to illustrate the simple concept of the direct and rapid effect of absorbed intestinal contents on the brain and its function.

From a strictly conceptual standpoint, it is critical to understand that the gastrointestinal tract serves primarily as a biologic interface with the larger environment in which the human organism resides. When speaking of the absorption of “outside molecules,” the gastrointestinal tract is by far the single organ most responsible for internalization of substances that are exogenous to the body. Because of the potential detrimental impact upon the brain of the wide variety of ingested foods (and non-food items), the mammalian body has evolved a variety of protective mechanisms designed to make gastrointestinal absorption as selective a process as possible. This serves to ensure physiologic homeostasis within the body, allowing the body as a whole to function within the very narrow physiological parameters necessary to ensure optimal health. Deviation from these optimal parameters due to inappropriate absorption of gastrointestinal luminal contents usually results in disease.

THE DIGESTIVE PROCESS

The highly evolved and selective process of absorption begins immediately after ingestion of foods and is referred to as the process of digestion. In this process, ingested foods are broken down into simpler molecules by the combination of physical chewing activity, salivary enzymes, gastric enzymes, gastric acid, duodenal brush border enzymes, pancreatic enzymes, and bile. Together, these numerous and complex processes serve to transform large ingested molecules into smaller simpler substances that then come in contact with the surface of the small bowel villi responsible for absorption. The actual passage of these simple molecules through the villi is also a highly selective process, the success of which relies heavily upon the intact architectural structure of the villi.

An elaborate transport system exists in which some molecules move across the villous membrane without expenditure of energy (passive transport), whereas other molecules require the expenditure of energy (active transport). Once absorbed, these molecules enter the lymphatic system and are transported to the body’s systemic circulation. During their movement through the most superficial layers of the intestinal lining (epithelium), they encounter a highly evolved immunologic defense that is designed to remove molecules that it deems foreign or does not recognize. (In fact, the gastrointestinal tract is the organ that contains the most heavily concentrated system of lymphoid tissue, a fact that further attests to the enormity of the body’s exposure to external influences via the gastrointestinal tract and the importance of maintaining its integrity.) When the immunologic defense system is functioning in health, any protein antigens that manage to circumvent the initial degradation phase occurring within the lumen of the bowel are prevented from entering the systemic circulation. Those molecules that somehow succeed in penetrating the immunologic defense system will encounter additional immunologic activity within the circulating portion of the blood to prevent them from causing harm. The focus of this article is on the digestive and immunologic activity on the luminal surface of the bowel and within the lining of gastrointestinal tissue that interfaces the GI tract and the lumen—the epithelium. It proposes a mechanism explaining how the inflammatory disease of this epithelial lining may be viewed as the initial step in a cascade of gut-brain axis leading to development delay.
Because autism-associated enterocolitis presents exclusively in the critical developmental period of infancy or early toddlerhood, existing data relating to its unique inflammatory characteristics provide a scientifically intriguing window onto its impact not only on neurologic function but also on developmental, behavioral, and fundamental cognitive processes.

DOWNSTREAM EFFECTS OF DIGESTIVE DYSFUNCTION
Deficiencies or disease in any of the individual systems of digestion, absorption, and surveillance result in disease states that are thought to have neurologic and immunologic consequences. Examples of this are celiac disease, Crohn’s disease, and classic IgE-mediated food allergy. These examples are similar in that damage to the highly evolved system of selective intestinal villous absorption leads to pathologic absorption of food and consequent systemic downstream effects, including effects on the central and peripheral nervous systems. In all three examples, the inflammatory disease state has been well characterized on a cellular and molecular level and, to a lesser extent, on a genetic level.

In the case of celiac disease, immunologic destruction of the villous barrier function results in inappropriate absorption of a variety of intact food-derived macromolecules, with a consequent increase in systemic elevations of IgG and other immunoglobulins. Importantly, from a neurologic standpoint, seizure activity and peripheral neuropathy have both been linked to untreated or inadequately treated celiac disease, suggesting that the immunologic activity occurring in the intestinal lining of these patients is having a downstream effect on neurologic function. The precise mechanism of this downstream effect is unclear. Leading theories include immunologic activity directed against the central and peripheral nervous systems and/or the products of inappropriately absorbed gluten molecules or their derivates acting as neurotransins.

In the case of Crohn’s disease, there is also ample data demonstrating the presence of food-specific IgG in active versus quiescent intestinal inflammation. Interestingly, numerous publications have noted the presence of an altered affect in adult patients with Crohn’s disease as compared with other chronic diseases; it is entirely plausible that pathologically absorbed molecules from the gut are acting on the adult brain, negatively impacting affect and personality.

In the third example, that of classic IgE food allergy, an intense immunologic response to pathologically absorbed foodstuffs further contributes to pre-existing immunologic sensitization at the mucosal level, triggering specific immunologic activity involving eosinophils and mast cells. This results in potentially multifaceted pathologic such as respiratory distress or failure, hives, capillary dilatation and leakage, edema, arthritis/arthralgia, and gastrointestinal bleeding. Neurologic consequences of classic food allergy are not as common as those in celiac disease and Crohn’s disease but may include encephalopathy and peripheral neuropathy.

AUTISM-ASSOCIATED ENTEROCOLITIS
In the context just described, one can consider the more commonly encountered and unique disease entity of autism-associated enterocolitis and its attendant impact on brain function. However, there is one important distinction to be made between autism-associated enterocolitis and the three examples listed above. Whereas Crohn’s disease, celiac disease, and IgE-mediated food allergy have known effects on immunologic and neurologic systemic dysfunction in adults (and less often in children), these diseases do not appear to have developmental sequelae. In contrast, because autism-associated enterocolitis presents exclusively in the critical developmental period of infancy or early toddlerhood, existing data relating to its unique inflammatory characteristics provide a scientifically intriguing window onto its impact not only on neurologic function but also on developmental, behavioral, and fundamental cognitive processes.

The focus of the ensuing paragraphs is twofold. First, I synthesize what is known about the mucosal pathology of autism-associated enteritis/enterocolitis (with enteritis defined as inflammation of the small intestine and enterocolitis defined as inflammation of both the small and large intestines), discussing mucosal inflammation, villous destruction, brush border disaccharidase deficiencies, increased intestinal permeability, and elevated antibody production to clostridial floral species. Second, I formulate a mechanistic hypothesis that demonstrates the cumulative role of these processes in the breach of intestinal mucosal integrity and the attempts of the gastrointestinal immunologic response to contain this breach. Extension of this hypothesis leads to the question of whether failure to adequately contain the breach could result in more systemic involvement, including that of delays in brain development and function.

1. MUCOSAL INFLAMMATION
The earliest significant description of the cellular infiltrate present in autism-associated inflammatory bowel disease (IBD) was authored by the Inflammatory Bowel Disease Study Group at the Royal Free Hospital in London, England, and was published in the American Journal of Gastroenterology in September 2001. The nine authors of this retrospective controlled study demonstrated a number of significant findings:

- Active ileitis was present in 8% of GI-symptomatic children with autism spectrum disorder (ASD) but not in controls. 
- Chronic colitis was present in 88% of GI-symptomatic ASD children compared with 45% of non-autistic controls. This chronic colitis was patchy in distribution, displaying a pattern distinct from ulcerative colitis but similar to that seen in Crohn’s disease.
- Eosinophil infiltration of the lamina propria was present significantly more frequently in GI-symptomatic ASD children than in either children with ulcerative colitis or non-autistic controls.
- Frequency and severity of inflammation was significantly greater in affected ASD children as compared with non-autistic controls but less intense than that seen in ulcerative colitis.
- Endoscopic features of mucosal inflammation in GI-symptomatic ASD children were less frequent and intense than those seen in ulcerative colitis but significantly more frequent than in non-autistic controls.

Subsequent to this 2001 publication, two additional papers have looked specifically at the frequency and cellular characterization of enterocolitis in GI-symptomatic ASD children. The first, published in 2005 by a group of Venezuelan researchers led by pediatric gastroenterologist Dr. Lenny González, won second prize in the scientific category at the Venezuelan Congress of Pediatrics 2005. In the study, GI-symptomatic ASD children demonstrated duodenal intraepithelial lymphocytosis and colonic lymphoplasmacytosis. Frequent esophagitis, gastritis, duodenitis, and ileocolitis also were noted.

In a second paper, my colleagues and I reviewed histopathologic findings at ileocolonoscopy in 143 consecutive GI-symptomatic ASD children. We found ileitis to be present in more than a third of the children (34.6%) and colitis...
in more than two-thirds (69.2%). In addition, we noted inflammation of both the ileum and colon together in over one-fourth of GI-symptomatic children (29.1%). When ileitis was present, it was most frequently associated with colitis as opposed to presenting as an isolated small bowel histologic entity. When colitis was present, it tended to be multifocal. Significantly, the presence of histologic ileal and/or colonic lymphoid nodular hyperplasia (LNH) statistically predicted was present, it tended to be multifocal. Significantly, the presence of histologic ileocolonic inflammatory activity. This distinction between LNH accompanied versus unaccompanied by mucosal inflammation is critical and resolves the longstanding misconception that GI mucosal LNH, when encountered, may be immediately dismissed as being of no clinical import.

Taken together, our data and the data of Dr. González's group replicate the original observations of Professor John Walker-Smith and his Inflammatory Bowel Disease Study Group team regarding the presence of pathologic mucosal inflammatory cellular infiltrates in conjunction with lymphonodular hyperplasia in GI-symptomatic ASD children.

In 2001, in an effort to further define specific cell populations of colonic lymphocytes in inflamed colonic tissue obtained from GI-symptomatic ASD children, Furlano and colleagues performed immunohistochemical evaluation on colonic biopsies to determine cell lineage and functional markers, and histochemical study to evaluate the presence of glycosaminoglycans and basement membrane thickness. As compared with normal control subjects, the GI-symptomatic ASD children were found to have:

- significantly more intraepithelial lymphocytes in the surface epithelium
- a significantly higher number of lamina propria eosinophils
- a lymphocyte population with significantly higher proportions of CD3+, CD8+, gamma delta T cells, plasma cells, and proliferating epithelial cells on immunohistochemical analysis of the transverse colon

The gamma delta T cell counts were higher in the GI-symptomatic ASD children than in the children with ulcerative colitis, whereas the ulcerative colitis children had higher proportions of CD3+, CD8+, gamma delta T cells, plasma cells, and proliferating epithelial cells than the GI-symptomatic ASD children.

These immunohistochemical findings correlated well with the histologic findings by these same researchers as described in their 2001 review of the histopathology of the ASD GI disease described above. In addition, the paper noted that basement membrane thickness of GI-symptomatic ASD children was significantly greater than that seen in normal control subjects. Perhaps of even greater interest, the basement membrane thickening in ASD children far exceeds what is seen in Crohn’s disease and ulcerative colitis. In addition, glycosaminoglycans were decreased in GI-symptomatic ASD children as compared with normal control subjects but not as much as in children with ulcerative colitis. This again correlates well with the concept of a less intense degree of mucosal destruction in autism-associated colitis as compared with ulcerative colitis. However, the exceedingly thickened basement membrane in ASD as compared with both Crohn’s disease and ulcerative colitis suggests a unique attempt at architectural construction of a physical barrier against epithelial injury “known” by the immune system to be even more systemically harmful to the host than the inflammation seen in ulcerative colitis and Crohn’s disease.

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### 2. VILLOUS DESTRUCTION

In GI-symptomatic ASD children, we frequently encounter an as-yet-unpublished but readily identifiable endoscopic lesion of the small bowel. The lesion appears visually as a white spot, usually less than 1 mm in diameter, that is superficial to the small bowel mucosa and appears adherent to the mucosal surface. Indeed, this white spot is typically easily displaced from the mucosa upon contact with the tip of the endoscope. Examined at light microscopy with routine H & E staining, the lesion appears to consist of a decapitated single villus (or occasionally two
under 5 years of age.

of lactase deficiency (58%) in GI-symptomatic ASD children following 5-6 hours. The inert property of the ingested carbohydrates allows for administered orally after a brief fast, and urine samples are collected over the various organs of the body and are excreted in the urine. The carbohydrates are those molecules that are absorbed remain structurally intact as they traverse the intestinal health, neither of these compounds is particularly well absorbed, and the subsequent measurement of urinary recovery of each molecule. The most

lactulose and mannitol in 40 children with ASD. Importantly, the study excluded, among other things, clinical (that is, symptomatic) evidence of gastrointestinal disease. Despite the exclusion of children with GI symptoms, a significantly higher proportion (p<0.001) of ASD children demonstrated abnormal intestinal permeability of lactulose (but not mannitol) as compared with a non-autistic control group. None of the children had undergone gastrointestinal endoscopy. Speculating on the significance of abnormal lactulose permeability versus the normal permeability seen with mannitol, the authors concluded that the paracellular pathway may be more affected because of alterations of tight junctions between adjacent cells of the bowel mucosa.

This preliminary finding of villous architectural damage is exciting in that it potentially provides a simple anatomic explanation for the increased intestinal permeability found in ASD children (see Increased intestinal permeability).

BRUSH BORDER DISACCHARIDASE DEFICIENCIES

In 1999, Horvath and colleagues demonstrated decreased activity of at least one duodenal brush border disaccharidase or glucoamylase in nearly three-fifths (58%) of GI-symptomatic ASD children and decreased activity of two or more enzymes in approximately one-fourth (24%) of these children. Disaccharidases and glucoamylases are enzymes that help break down larger carbohydrate molecules into simpler carbohydrate molecules. In the Horvath study, lactase (the enzyme involved in the hydrolysis of lactose) was the most frequently deficient brush border enzyme. More recently, Kushak and colleagues found strikingly similar proportions of lactase deficiency (58%) in GI-symptomatic ASD children under 5 years of age. Again, lactase was the most frequently deficient enzyme, followed by sucrase and maltase. Interestingly, light microscopic evidence of cellular mucosal inflammation was absent in the vast majority of children studied (N=199). When present, however, cellular mucosal inflammation was strongly predictive of deficiency of at least one brush border disaccharidase. The frequent presence of disaccharidase deficiency in the absence of light microscopic cellular histopathology is reminiscent of the findings of Torrente described above, in which significant inflammatory activity (and mucosal damage) was present in the absence of cellular infiltrates as seen on conventional light microscopy.

INCREASED INTESTINAL PERMEABILITY

It is well established within the current body of medical literature that conditions involving mucosal inflammation and diminished intestinal mucosal barrier function often lead to the appearance of inappropriately absorbed intestinal luminal contents within the blood. Although the precise mechanisms by which the pathologically absorbed luminal contents enter the blood may vary from disease to disease, the phenomenon of their presence within the systemic circulation is collectively referred to as increased intestinal permeability. Intestinal permeability has recently been shown to be involved in the pathogenesis of both intestinal and even extraintestinal autoimmune diseases such as Crohn’s disease, celiac disease, and type 1 diabetes mellitus.

Formal testing to determine whether increased intestinal permeability from any cause is present in a given patient is most frequently accomplished using a simple test. The procedure involves the simultaneous oral administration of two biologically inert carbohydrates of different molecular sizes and absorption routes and the subsequent measurement of urinary recovery of each molecule. The most commonly used inert carbohydrates are lactulose and mannitol. In situations of intestinal health, neither of these compounds is particularly well absorbed, and those molecules that are absorbed remain structurally intact as they traverse the various organs of the body and are excreted in the urine. The carbohydrates are administered orally after a brief fast, and urine samples are collected over the following 5-6 hours. The inert property of the ingested carbohydrates allows for detection and quantification of the degree of intestinal absorptive dysfunction.

Importantly, because lactulose is a relatively large molecule, it is absorbed via a paracellular route. In contrast, mannitol, a relatively small molecule, is absorbed via a transcellular route. Further analysis of the urinary lactulose:mannitol ratio is therefore thought to reflect the disease-specific underlying pathophysiologic processes responsible for the abnormal absorption and permeability.

In 1996, D’Eufemia and colleagues evaluated intestinal permeability of lactulose and mannitol in 40 children with ASD. Importantly, the study excluded, among other things, clinical (that is, symptomatic) evidence of gastrointestinal disease. Despite the exclusion of children with GI symptoms, a significantly higher proportion (p<0.001) of ASD children demonstrated abnormal intestinal permeability of lactulose (but not mannitol) as compared with a non-autistic control group. None of the children had undergone gastrointestinal endoscopy. Speculating on the significance of abnormal lactulose permeability versus the normal permeability seen with mannitol, the authors concluded that the paracellular pathway may be more affected because of alterations of tight junctions between adjacent cells of the bowel mucosa.

A more recent study by de Magistris and colleagues evaluated intestinal permeability as measured by urinary excretion of lactulose and mannitol in children with ASD and their adult first-degree relatives as compared with non-ASD healthy children and their adult first-degree relatives. As compared with the D’Eufemia study, this study excluded only those patients in whom a gastrointestinal disease had been confirmed but did not exclude patients on the basis of the presence of gastrointestinal symptoms. As a result, the study would be expected to identify a larger proportion of children with abnormal intestinal permeability. The researchers found that more than a third (37%) of ASD children showed abnormal intestinal permeability as compared with zero healthy child controls. Interestingly, one-fifth (21%) of the first-degree adult relatives of ASD children also demonstrated abnormal intestinal permeability, as compared with only about 5% of the healthy adult controls. The presence of abnormal intestinal permeability within the ASD group did not predict the presence of GI symptoms as reported by the parents. It would be interesting to perform the reverse analysis to see whether patients with GI symptoms are more likely than those without GI symptoms to have increased intestinal permeability. Regardless, this study confirmed the earlier 1996 report of increased intestinal permeability and is entirely consistent with disruption of mucosal barrier function in children with ASD and their first-degree relatives as compared with non-ASD children and their first-degree relatives.

ELEVATED ANTIBODY PRODUCTION TO CLOSTRIDIAL FLORA SPECIES

It is well established that there are serum antibodies to microbial flora of the intestine in both adult and pediatric patients with Crohn’s disease, including antibodies to *Saccharomyces cerevisiae*, *Escherichia coli*, and Clostridia species. More recent data has associated the presence of some of these antibodies with a more complicated disease course, including fistulization and perforation. When combined with known Crohn's disease gene associations, the presence of these serologic antibodies may even provide prognostic information as to the statistical risks of developing these potential complications. The association between these antibodies and severity of disease takes into account both the number of different species to which antibodies are being produced as well as the actual amount of antibody to each individual species. Thus, risk of progression to severe disease may be indicated by low levels of numerous species-specific antibodies or, conversely, by exceedingly high levels of antibody to even a single species. The significance of these findings lies in their statistically predictive value. For example, if one knew that a given patient’s serologic status was associated with a statistically higher chance of a more severe disease course, this would support earlier and more aggressive treatment.

No published data exist regarding the frequency of these serologic markers in GI-symptomatic children with ASD. However, in my experience with antibody serologies in over 500 GI-symptomatic children with ASD, a pattern has emerged. The pattern involves marked elevation of the cBir1 antibody early
Figure 1. Schematic of proposed mechanistic origins of pathologic ASD-enteritis gut-brain axis

Luminal Surface

Legend:
1: Mucosal villi
2: Lamina propria
3: Basement membrane
4: Submucosa
5: Muscularis mucosa
6: Serosa
7: Fibrinous plume arising from truncated villi coating exposed surface (aka “white spot” microerosion as described by Krigsman)

Detail of Immunologic Response to Mucosal Breach

Legend:
Disaccharidase deficient zone (Horvath, Kushak)
IgG
C1q
Thickened basement membrane (Torrente)
Further adding to the inflammatory cascade at the luminal surface is the presence of bacterial and fungal flora which, as a result of the loss of intestinal mucosal barrier integrity, are now in direct contact with the high concentration of protective gastrointestinal lymphoid tissue that normally lines the gastrointestinal tract.

in the course of the bowel disease, with negligible antibody presence against *E. Coli* and *S. cerevisiae*. The cBrl antibody is an antibody to the flagella protein on clostridial bacterial species. In the absence of treatment of bowel inflammation, there is a gradual and much smaller rise in the other antibodies over time, but their absolute values do not approach those seen for cBrl. Importantly, retrospective pooled analysis in our patient group demonstrates that the presence of elevated serum cBrl antibody is statistically predictive for the presence of histologic ileocolitis as seen upon conventional light microscopy. Of further interest is a pattern of cBrl antibody normalization in patients who, upon receiving pharmaceutical and dietary interventions for their IBD, achieve GI symptom resolution coupled with evidence of mucosal healing on follow-up biopsies. cBrl appears to enhance the proinflammatory cytokines IL-6 and IL-1 in peripheral blood monocytes, and studies to determine further cytokine associations are under way.

When discussing the presence of serologic antibodies in the setting of inflammatory bowel disease (both ASD-associated and non-ASD-associated), it is important to understand that current data have not demonstrated that the antibodies’ presence stems from infection or overgrowth of the organism to which antibodies are being produced. Therefore, no therapeutic interventions should be based on their presence. It is thought that an immunologic intolerance to normal intestinal flora develops as a result of the increased intestinal permeability in IBD. Identifying the presence of serologic antibodies to gut flora is used primarily as a way to distinguish between Crohn’s disease and ulcerative colitis and to offer prognostic information as to the likelihood of aggressive disease. The relevance of this information for ASD-associated enterocolitis lies in the clues these antibodies may hold for understanding the immunologic mechanisms at play and how these mechanisms affect both bowel and brain function.

**PROPOSING A CONCEPTUAL MODEL**

By synthesizing the aforementioned mucosal immunohistochemical, histochemical, histopathologic, permeability, and serologic data with the clinical observations seen in countless ASD children over the years by parents and clinicians, it is possible to put forth a conceptual model that links these various processes in ASD as follows (Figure 1):

1. **At some point within the first year of life**, an autoimmune process is triggered, targeting the mucosal lining of the bowel. The autoimmune nature of this inflammatory activity is strongly supported by the specific lymphocyte subpopulations seen with immunohistochemical and histochemical staining in both the small and large bowel. Light microscopy severely underestimates the presence of this inflammatory activity. The antigen source is likely both exogenous to the body and strongly antigenic.

2. **As a direct consequence of this T-cell inflammatory activity** (and to a lesser extent neutrophilic activity), individual villi are decapitated focally but in cumulatively great numbers. Again, and significantly, light microscopy often fails to identify inflammatory cellular infiltrate, or identifies only mild neutrophilic or lymphocytic invasion, in regions of villous damage and associated superficial mucosal erosion.

3. **In an effort to maintain barrier function integrity of the now-exposed subepithelial compartment**, a fibrinous proteinaceous material is exuded from the truncated villi, covering the exposed surface and forming a white spot lesion, which is the endoscopic hallmark of autism-associated inflammatory bowel disease. Surrounding these white spot lesions is a well demarcated area of superficial mucosal erosion that is enough to decrease the concentration and activity of the most superficially located disaccharidase (lactase) and, less frequently, other disaccharidases.

4. **T cells cluster around the crypts**, perhaps in a further effort to prevent what the immune system recognizes as potentially devastating pathologic absorption of inadequately processed luminal material.

5. **Additional architectural protective action undertaken by the immune defenses involves the thickening of the basement membrane with heavy concentration of IgG and complements C1q.**

Considering these processes together, it is tempting to view the autistic GI mucosal immunologic response as one that attempts to confine the damage to the epithelium and contain any pathologically absorbed luminal products within the inflamed epithelium. The products of this intense inflammatory activity, including cytokines, remain local to the mucosa but also are transported systemically via the blood. It is entirely conceivable that the proinflammatory molecular products of mucosal cellular-mediated inflammation are transported via the blood to extraintestinal locations such as the brain and the large joints, causing encephalitis and arthritis, respectively.

Further adding to the inflammatory cascade at the luminal surface is the presence of bacterial and fungal flora which, as a result of the loss of intestinal mucosal barrier integrity, are now in direct contact with the high concentration of protective gastrointestinal lymphoid tissue that normally lines the gastrointestinal tract. This exposure triggers production of particularly high levels of serum anticolonial antibodies (anti cBrl), well above those seen in Crohn’s disease and ulcerative colitis. Antibody production against other flora species occurs as well but to a significantly lesser extent. Our data showed that the presence of elevated levels of serum anticolonial antibody is predictive of enterocolonic inflammation, and the cBrl antibody is associated with production of proinflammatory cytokines. Additional inflammatory cytokine activity occurring in the intestinal mucosa has been documented as well. The contribution, if any, of abnormal flora to this ASD-GI mucosal inflammatory process is less well understood.

The ability of luminal contents to bypass selective absorptive pathways is reflected most simplistically in the permeability studies of D’Euflenia and de Magistris. The observation that lactulose, rather than mannitol, is the predominant abnormally absorbed analyte is consistent with the concept of disrupted mucosal integrity in the manner described above.

Despite immunologic attempts at repair and containment, the primary autoimmune inflammatory process is ultimately ineffective. Luminal products such as incompletely digested food and products of microbial degradation succeed in reaching the systemic circulation, where further immunologic activation occurs, though at least some of this observed activity may be the result of immune activation occurring at the aforementioned luminal surface. Proinflammatory cytokine activity within the peripheral blood of GI-symptomatic ASD children...
has been noted in response to specific dietary antigens such as gluten and cascin.21,22 Because of the young age of the child and the critical developmental window during which this process occurs, the successful penetration of luminal bacterial and fungal degradation products, luminal diet-derived products, and the degradation products of the destroyed cells themselves could then potentially serve as catalysts for a variety of mechanisms described elsewhere in this publication, resulting in developmental delay, arrest, or regression.

From the standpoint of clinical gastroenterology, the inflammatory processes described above result in such “conventional” symptoms as diarrhea, constipation, abdominal pain, abdominal distention, and failure to thrive. The phenomenon of neurodevelopmental dysfunction as the result of gut-brain axis involvement within the setting of gastrointestinal disease allows for the specific neurodevelopmental disease, in this case autism, to be considered no less a GI symptom than diarrhea.

This mechanistic approach provides a unifying explanation for some intriguing clinical observations frequently made by those who care for ASD patients. Clinical observations point to improvement in cognitive and gastrointestinal function when patients are on one of the following:

- a clear liquid diet (in preparation for colonoscopy)
- a diet that excludes protein (i.e., an exclusively elemental formula)
- a regimen of regular bowel cleansouts

Perhaps the most intriguing observation of all is that improvement in gastrointestinal function frequently correlates with improvement in cognitive and behavioral function. Conversely, worsening of gastrointestinal function is frequently associated with a decline in cognitive and behavioral function.23,24 Parents often report that when they see the first morning stool, they immediately know what kind of “autism day” lies ahead.

From a treatment standpoint, the presence of chronic gastrointestinal symptoms in the face of demonstrable mucosal pathology warrants treatment for the IBD. In the absence of any data to the contrary, it is clinically reasonable to treat autism-associated IBD in identical fashion to the IBD observed in conventional, non-ASD Crohn’s disease. To the extent that this unifying theory of gut-brain axis involvement is correct (i.e., that the neurodevelopmental disorder called “autism” is a gastrointestinal symptom), primary treatment of the IBD holds great promise as a potential treatment for ASD and possibly other neuropsychiatric disorders with known bowel mucosal pathology.

The phenomenon of neurodevelopmental dysfunction as the result of gut-brain axis involvement within the setting of gastrointestinal disease allows for the specific neurodevelopmental disease, in this case autism, to be considered no less a GI symptom than diarrhea.

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