Autism and the Digestive System

Autism is multi-factorial but an intriguing clue lies in the gut.

By Derrick MacFabe, M.D.

Autism spectrum disorders (ASD) are a rapidly increasing problem in western society. Autism is a spectrum of severe neurodevelopmental disorders, frequently consisting of profound language impairment, repetitive motor behaviors, impaired socialization, sensory disturbances, severely restricted interests, and self-injury. Seizure disorders also frequently accompanies autism. The prevalence of autism is now 1 in 150. This alarming increase, rising from between seven and 20 per 10,000 just a few decades ago, cannot be accounted for merely by increased surveillance.

Autism was originally thought to be due to environmental influences such as poor parenting. However, recent research from human autopsies, brain imaging, and clinical biochemistry are now seeing autism as a definable systemic disorder involving a number of factors that may affect brain development both pre- or post-natally. Neuropathological work being pioneered by Margaret Bauman and recent imaging studies by Martha Herbert at Harvard University have shown subtle disorders in brain development, involving language, facial expression, movement, and social behavior.

Studies suggest that persons with autism have enlarged brain size, particularly in the first few years of life. A recent neuropathological study by Carlos Pardo at Johns Hopkins University has revealed evidence of inflammatory processes in the brains of young patients as well as adult patients.

The cause of autism is as yet unknown and is likely due to many factors. Genetic factors undoubtedly play a major role. The relative risk of first degree relatives is 100 fold higher, and concordance in identical twins is 60 percent. However, even though genetics is suspected as a major factor, a purely genetic link remains elusive and is over-simplistic. Indeed, factors in the uterus may also play a role, given the many similarities with neurological abnormalities from intrauterine exposure to ethanol, valproic acid, terbutaline, or thalidomide, and prenatal infections. Supportive of this notion are studies that have examined the effects of early prenatal exposure to these agents in rodents. Administration of these agents near the time of neural tube closure have shown brain structural changes and altered social behavior similar to aspects of human autism.

Anecdotal reports from parents and other family members note that the symptoms first occur after apparently normal development in the first few years of life, often following either acute gastrointestinal infections, upper respiratory infections, or vaccination for childhood viral diseases. Regarding vaccination, the link between autism and the Thimersol-containing measles, mumps, rubella vaccine (MMR) has received tremendous media attention but has not been proven. This raises the strong possibility that other factors during early childhood may be involved. The current consensus is that autism may comprise a family of disorders, resulting from genetic sensitivity to intrauterine or early post-natal exposure to a variety of environmental toxic or infective factors.

A link between autism and seizure disorders is great and may be under-reported. Autism is a major component in tuberous sclerosis, which also results in severe cortical development problems and seizure disorder, and the Landau-Kleffner syndrome of acquired aphasia and seizure. In particular, the symptomology of non-convulsive seizures resembles many aspects found in autism, including aggression, repetitive motor activity, and inattention.

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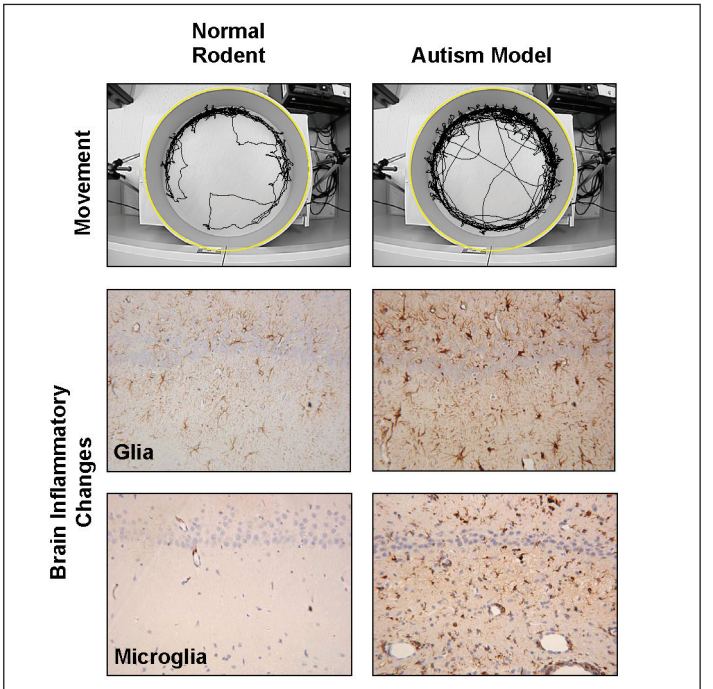

Automated tracking of rodent model of autism shows hyperactivity and repetitive movement. Microscopic examination of brain tissue (hippocampus) from autism model shows inflammatory changes (increased staining density) in glia and microglia (connective tissue of the brain) similar to tissue obtained from brains of human autism patients (modified from MacFabe et al, 2007, Behavioural Brain Research).

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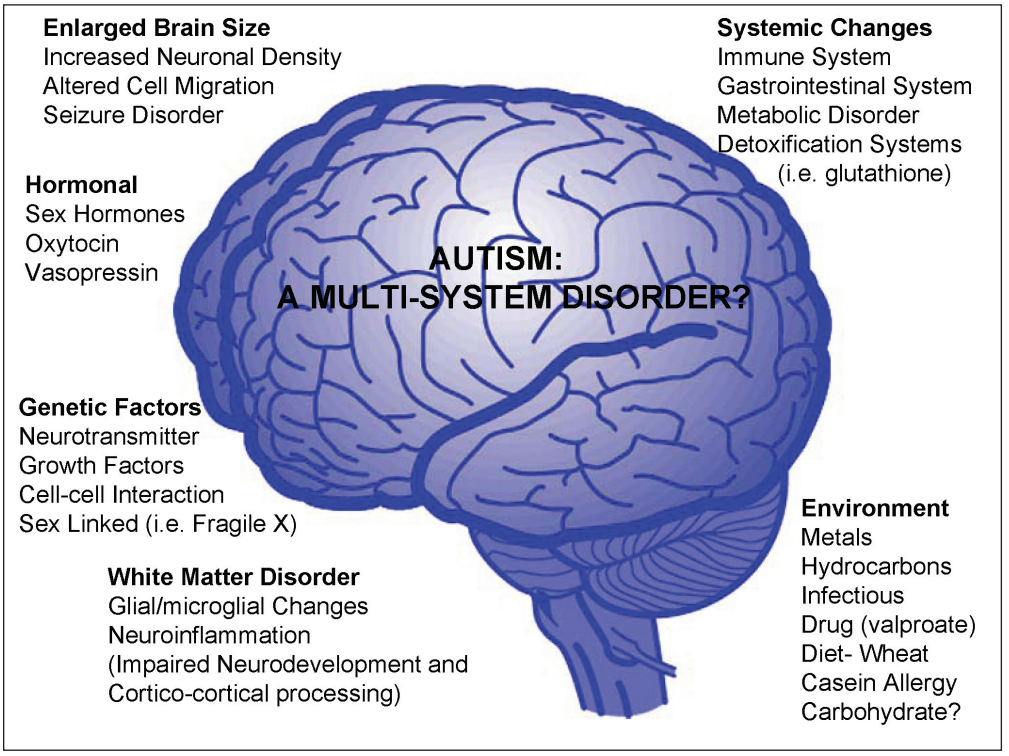
Many investigators are looking at autism as a general metabolic disorder involving environmental factors such as metals or environmental organic compounds or, more likely, a genetic sensitivity to these compounds in specific sub populations. These may result in increased oxidative stress through cumulative production of reactive oxygen free radicals and the resultant inflammation which cause widespread damage to the central nervous system both before and after birth.

Work by Jill James at the University of Arkansas and Abha and Ved Chauhan at Staten Island have found evidence of elevated free radicals, reductions in detoxifying agents (glutathione), antioxidant metal binding proteins (transferrin and ceruloplasmin), and impairments in brain methylation pathways in autism.



Research at the M.I.N.D. Institute at the University of California, Davis focused on systemic immunological abnormalities in autism. It is thought that neuroimmune interactions, particularly in the formation of the embryo and persisting throughout the lifetime of the individual, contribute to the neuromigratory abnormalities, increased innate neuroinflammatory response, and anti-brain antibodies. However, oxidative stress and neural inflammation is common in a number of neurological disorders of very different clinical presentation and pathophysiology. It is unclear if these responses are causative to autism or a compensatory response to some other factor. Nevertheless, this finding may lead to some promising future treatments utilizing current available immune system modulating agents in autism.

However, amidst all the current discussion about possible causal factors, an intriguing possible piece of the puzzle is emerging, which, heretofore, has not been looked at closely—that significant clues to autism may be found in the digestive system and in the relationship between the digestive system and the brain.

In the fall of 2006, the Kilee Patchell-Evans Research Group, located at the University of Western Ontario in London Ontario, published a significant paper in the international biomedical research journal, *Behavioral Brain Research*, pointing to an intriguing link between the digestive system and autism. The Kilee-Patchell Evans Autism Research Group was founded by a generous donation from GoodLife Fitness Clubs' CEO, David Patchell-Evans, whose daughter has autism.

The brain-gut connection is an interesting and emerging area of research, focused on the role of diet and gut function in autism spectrum disorders. It is often forgotten that the human digestive system hosts a plethora of bacteria and enzymes, all contributing to gut function but which can easily go awry. Gut disorders, including dysmotility and altered gut permeability, along with pathological lesions resembling (but not identical to) gluten or casein enteropathy have been seen in many patients.

Parents of children with autism often report that their children have frequent digestive upsets. These upsets, and the child's behavior, seem to worsen when the child eats wheat or dairy products. As well, some affected children paradoxically crave such foods, suggesting that some gut-borne factor with neuroactive properties may contribute to this disorder.

Some clinicians and researchers have begun to suspect that the digestive upsets in autism may be directly linked to brain function and thus perhaps play a causal role in autism. Further, clinical reports and studies by Finegold, indicate an association with pre- or post-natal infectious diseases, antibiotic exposure, and gut clostridial species in a subset of autistic patients. To the Kilee Patchell-Evans Autism Research Group, this is of particular interest because of the increasing emergence of antibiotic resistant strains in both hospital and outpatient populations.

Core members of the Kilee Patchell-Evans Autism Research Group include this article's author as Director (Dr. Derrick MacFabe), Drs. Klaus-Peter Ossenkopp, Peter Cain, Martin Kavaliers, Elizabeth Hampson, and Fred Possmayer. The Group's mandate is to combine the expertise of various disciplines in looking at the many aspects of autism, specifically neurodevelopment, seizure, neurochemistry, obsessive compulsive disorder, anxiety disorders, social behavior, cellular metabolism, neuroimmunology, genetics, and infectious disease.

There are ethical limitations in doing direct studies on human children incapable of giving informed consent. It is also extremely costly and time consuming. The development of a suitable animal model was absolutely necessary.

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It is particularly important to quantify analysis of many aspects of motor output in experimental systems. Rodents are the most extensively studied experimental mammals in brain development, physiology, and behavior. Rodents' rapid development and large litter sizes make possible developmental and interventional studies that are virtually impossible to do in humans.

Recent work performed by the Group concerns the role of a panel of gut-borne factors in autism spectrum disorder through using a novel rodent model. The most recent work concerns the short chain fatty acid propionate (PPA), a compound present in human diets, a component of normal fatty acid metabolism, and also a major by-product of gut bacteria, particularly those associated with diarrhea occurring during antibiotic use.

PPA is also elevated in the condition known as human propionic acidemia, one of a family of inherited paediatric disorders, which produce developmental delay, seizure, movement disorder and gut dysfunction as well as following ethanol, valproate exposure, and disorders of biotin and B12 metabolism.

PPA readily enters the systemic circulation and is known to affect gut, immune, and brain function. Regarding brain function, PPA affects the general brain energy metabolism, cellular pH, calcium signaling, gene induction, neurotransmitter release and intercellular communication via cytokines and gap junctions. Together, these factors play a major role in neurodevelopment, seizure, learning and movement, and sensitivity to a variety of environmental stresses, all plausibly linked to autism. PPA produces behavioral and developmental abnormalities when administered to rodents. Thus, PPA is an ideal target compound linking diet and gut function to autism-implicated brain physiology and behavior.

We are currently examining the effects of PPA and related gut metabolic compounds at the electrical, behavioral, neuropathological, and biochemical levels. Research by graduate students Jennifer Hoffman and Sandy Shultz has shown that PPA, when infused in small amounts into the brains of rodents, immediately produces hyperactivity, repetitive behavior and social impairment, strongly resembling the symptoms of autism spectrum disorders. Interestingly, the animals also display brain electrical changes resembling some types of human epilepsy, which often co-exists with autism. Repeated exposure to the PPA compounds increases the severity and duration of these effects, suggesting that PPA can exert permanent effects on brain and behavior.

Brain tissues from animals show an innate inflammatory process consisting of reactive astrogliosis and activated microglia, resembling that found in brain tissue donated from deceased persons who had autism. In addition, there is an increase in the protein known as phosphoCREB, which is associated with widespread gene expression implicated in learning, memory, and addictive behavior.

The major brain changes appear to involve the glia, the non-neural component of the brain. These glia are critical in maintaining a stable environment for neurons, learning and memory, the rapid transmission of information throughout the brain, neurodevelopment, and brain repair. Biochemical analysis of brain tissue from PPA treated rodents by post-doctoral fellow, Karina Rodriguez-Capote, showed increased oxidative stress and impaired glutathione metabolism, similar to that found in human autism. The reduced levels of glutathione are of particular interest, and could explain a possible mechnism where the PPA afected brain could become sensitive to a wide variety of toxic environmental compaounds, including metals. Thus, the abnormalities found in these experimental rodents may lead to problems in information processing, movement as well as brain electrical, immunological, and metabolic activity. They may provide a link to some environmental risk factors involving the diet or digestive tract found in human autism.

The Group is now in the process of further investigating the molecular mechanisms by which PPA and related compounds produce their biochemical, electrophysiological, and behavioral effects before and after birth.

A crucial next step will be the assessment of the environmental and genetic risk factors in large populations of persons with autism and their families. With the assistance of Dr. Jeanette Holden of Queens University, Director of the Canadian American Autism Research Consortium http://www.asdcarc.com), a patient registry of over 7000 participants is being created. Persons with autism, with or without digestive symptoms, are encouraged to participate in these and related studies.

The complexity and enormous social burden of autism spectrum disorders present an enormous challenge to Western medicine. When one considers the lifelong duration of the disease and the possible link with other similar disorders, including aggression and mood disorders, the total social and financial effects on society are immense and may rival Alzheimer's disease.

There is an urgent need for early diagnosis to develop effective, evidence-based treatments. This can only be accomplished with rational examination of animal models, which link directly to clinical observation. The recent research and information exchange in the fields of genetics, neurodevelopment, immune function, energy metabolism, infectious disease, and gastroenterology have resulted in a major paradigm shift where autism is no longer considered only as a brain disorder but rather as a systemic disorder affecting many organ systems. These organ systems, such as the digestive system, may indeed hold important clues as to how the disease comes about. With the multidisciplinary collaboration of the molecular, behavioral, and clinical medical sciences, effective solutions to this immense problem are attainable and will eventually bring new hope to children with autism and their families.

For references that accompany this article, please make request to jhollingsworth@eparent.com •

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