

Is Autism the Coal Miner's Canary of America's Health Status?

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Possibly because of the reported 556% increase in the pediatric prevalence of autism between 1991 and 1997,¹ the classical presentation of autistic spectrum disorders (ASD) is currently an area of widespread study. In addition to autistic disorder or classic autism, ASD comprises five categories of pervasive developmental disorder (PDD) described in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association, of which the remaining four are Asperger's disorder; disintegrative disorder; PDD not otherwise specified, or atypical autism; and Rett's disorder, a genetic disorder of postnatal brain development caused by a defect in a single gene.²

ASD is characterized by impairments in three behavioral domains. The first is social interaction, often marked by deficits in reciprocal social interaction, a developmentally delayed or absent ability to communicate verbally, and difficulty with non-verbal cues such as facial expression, body posture, and eye-to-eye contact. The second is communication. Deficits are also typically present in communication, imaginative play, and the normal range of childhood interests and activities. The third is that individuals with ASD often exhibit repetitive, stereotyped behavior, have restricted areas of interest, exhibit repetitive motor mannerisms, and require strict routines or rituals in order to accord with appropriate social standards and have their needs met.

Prevalence

According to data for 2000–2002 published by the Autism and Developmental Disabilities Monitoring Network of the Centers for Disease Control and Prevention (CDC), about 1 in 150 8-year-old children in several areas of the United States have ASD.³ The CDC data demonstrated some geographic variation, with a significantly lower prevalence in Alabama, of 3.3 per 1000 8-year olds, and a higher prevalence in New Jersey, of 10.6 per 1000 8-year olds.³ These figures stand out against the estimated prevalence for ASD of 1 per 1000 population in the early 1990s. It is estimated that as many as 560,000 American youngsters between birth and age 21 have ASD.⁴ The condition affects males at a 4:1 frequency over its occurrence in females.⁴

Etiology and Pathophysiology

The etiology of ASD is currently unknown, although numerous possibilities, based on pathologic findings made in ASD, are currently under investigation. Medical conditions associated with autism include epilepsy, tuberous sclerosis, blindness, deafness, and neurofibromatosis.

Genetics

Evidence suggests that ASD is highly heritable, with some estimates of its heritability reaching 90%.⁵ However, twin studies and the wide range of its phenotypic expression indicate that environmental influences also play an important role in the occurrence of ASD. Research has shown that monozygotic twins have a concordance of more than 60% for classical autism, without any concordance for dizygotic twins. When this same study included a broader range of cases with diagnoses of PDD, the concordance for monozygotic twins rose to 92% while that for dizygotic twins reached 10%.¹ Studies also show a frequency of 2–8% of autism in siblings of autistic children, which far exceeds the frequency of the condition in the general population.¹

Genetic screening studies suggest that at least 10 genes may be involved in the etiology of autism, with studies now examining numerous genes for this possibility, such as those in the speech and language region of the human genome at 7q31-q33, 15q11-q13, FOXP2, RAY1/ST7, and IMMP2L; RELN genes at 7q22-q33; a subunit of the gene for the γ -amino-butyric acid (GABA)(A) receptor; UBE3A genes on chromosome 15q11-q13; the gene for the serotonin transporter (SERT) at 17q11-q12; and the gene for the oxytocin receptor at 3p25-p26.¹ Chromosome 15 duplications are frequently examined owing to their correlation with variable degrees of language delay, ataxia, epilepsy, mental retardation, and facial abnormalities. Studies also indicate that a low level of melatonin, as the result of a primary deficit in ASMT, the gene that encodes the last enzyme in the metabolic pathway leading to melatonin synthesis, is a risk factor for ASD.⁶

Parental Influences and Perinatal Development

Studies have found a greater frequency of certain traits and characteristics among parents of autistic than of healthy children. Thus, greater maternal and paternal age are independently associated with an increased risk for ASD in offspring.⁷ Additionally, mothers who have allergies and asthma during the second

trimester of pregnancy have a twofold greater than average risk of having a child with ASD. Although this same study found maternal psoriasis to be the only autoimmune disease associated with an increased risk for ASD,⁸ another study found a link between both maternal ulcerative colitis and paternal type-1 diabetes and increased risk for infantile autism.⁹

It has been suggested that in many cases, the cerebral developmental abnormalities in autism occur before 30 weeks' gestation.¹⁰ A study of perinatal risk factors and autism found that daily maternal smoking during early pregnancy, a small birth size for gestational age, maternal birth outside of Europe or North America, congenital malformations, cesarean delivery, and a 5-minute Apgar score below 7 were all associated with an increased risk of autism.¹¹ Another study found a link between autism and parental histories of schizophrenia-like psychosis and affective disorders,¹² while yet another study found a twofold greater risk for autism among children born to mothers with diagnosed psychiatric disorders.¹³ The risk for autism has also been found to increase with an increasingly urban location of birth.¹³

Neurologic Dysfunction

Research indicates a significant generalized increase in cerebral cortical volumes of both white and gray matter in autism. This is accompanied by a normal head circumference at birth followed by an abnormally increased growth rate beginning at 12 months of age.¹⁴ Other studies have found an increased cerebellar volume and bilateral enlargement of the amygdala and hippocampus in children with ASD.¹⁵ Recent work with functional magnetic resonance imaging has demonstrated cortical neural underconnectivity in individuals with autism, as well as a smaller corpus callosum—a structure through which many bilaterally activated cortical areas communicate—in individuals with autism as compared to controls.¹⁶ Although the relevance of this is unknown, another study found greater frequencies of left-handedness and preferential left-eye use in children with autism as compared with normal groups, as well as left nasal dominance in most children with autism.¹⁷

Gastrointestinal Dysfunction

Gastrointestinal (GI) symptoms are common in children with ASD. One study found that 70% had histories of such symptoms, as compared to only 28% of children showing normal development.¹⁸ The most common GI symptom in this study was an abnormal stool pattern.¹⁸ Another study of GI complaints in children with ASD found that the most common complaints were chronic diarrhea, gas, and abdominal discomfort and distension.¹⁹ Reflux esophagitis was evident in over 69% of the children, chronic gastritis in 41%, and chronic duodenitis in 66%. Additionally, 58% of the children had decreased intestinal digestive enzyme activity for carbohydrate, and 75% showed increased pancreaticobiliary fluid output after intravenous

administration of secretin.¹⁹ Abnormalities of the gut flora have also been seen in children with ASD, with one study finding an increased incidence of *Clostridium histolyticum*, a known toxin-producing organism.²⁰

Endocrine and Metabolic Dysfunction

Numerous studies indicate endocrine and metabolic abnormalities in children with ASD. Researchers have shown that some of these children have levels of serum/plasma dehydroepiandrosterone and serum total testosterone that are significantly above age- and gender-appropriate values.²¹ The children with ASD were also found to have significantly subnormal levels of serum follicle-stimulating hormone, plasma-reduced glutathione, plasma cysteine, plasma methionine, and serum cystathionine. The investigators who conducted this study suggested that these findings indicate

that in some children with ASD, there is an interaction between the mechanisms for transsulfuration in the methionine cycle that is important for detoxification and androgen pathways, causing hyperandrogenic behavior and developmental abnormalities.²¹ Another study found significantly lower levels of free and total carnitine and pyruvate and elevated levels of ammonia and alanine in children with ASD, possibly reflecting mild mitochondrial dysfunction.²²

Oxidative Stress

Oxidative stress from oxygen-bearing free radicals may have a causal role in ASD. Individuals with autism have shown increased nitric oxide in their red blood cells and increased activity of the antioxidant enzyme glutathione peroxidase in these individuals' plasma.²³ Other studies have shown increased levels of such antioxidant enzymes as superoxide dismutase and xanthine oxidase in autism.²⁴

Increased lipid peroxidation has also been observed in individuals with autism. The antioxidant enzymes associated with transferrin, an iron-binding protein, and ceruloplasmin, a copper-binding protein, have been found to be significantly decreased in autistic children, a finding that has been linked to a loss of language skills.²⁵ Some children with autism show elevated levels of total homocysteine, a finding strongly correlated with decreased erythrocyte glutathione peroxidase activity and diminished levels of vitamin B12.²⁶

Immunologic Dysfunction

Studies have indicated that children with ASD have numerous abnormalities in immune function. These children's CD4 lymphocyte counts are decreased, indicating impaired cellular immunity and an imbalance of Th1/Th2 cytokines.²⁷ Studies of immunoglobulin (Ig) levels in children with ASD have found a significant increase in total serum protein, and serum IgG, IgG2, and IgG4, and have demonstrated a positive correlation between total serum protein and serum gamma globulin and social prob-

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lems.²⁸ Recent studies have identified serum antibodies specific for prenatally expressed brain antigens in mothers of autistic children, suggesting that these autoantibodies could cross the placental barrier and affect fetal brain development.²⁹ Other immunologic findings are that children with autism have significantly higher levels of antibodies to measles virus than do controls, with these antibodies present in 83% of the autistic children in one study, but not in healthy children or in the siblings of the autistic children.³⁰ Antibodies to mumps and rubella are not elevated.³⁰

Some autistic children exhibit autoantibodies to brain proteins such as myelin basic protein (anti-MBP) and neuron-axon filament protein (anti-NAFP). One study found a correlation between these autoantibodies and antibodies directed against measles virus (measles-IgG) and human herpes virus-6 (HHV-6-IgG). This study found that serum that was positive for measles-IgG and HHV-6-IgG also contained anti-MBP and anti-NAFP antibodies, suggesting virus-induced autoimmunity as a possible etiology for autism.³¹ Congenital rubella infection has also been linked to autism, behavioral disorders, and mental retardation.³²

It is highly controversial whether measles–mumps–rubella (MMR) vaccine is a causal factor in autism, and the vast majority of studies do not support such a link.³³ The possibility is based on the correlation of a type of regressive autism with concomitant GI symptoms soon after administration of the MMR vaccine.³⁴ The finding of measles virus persistent in the intestines of some autistic children, as well as in individuals with Crohn's disease and ulcerative colitis, has been considered as suggesting that Crohn's disease and colitis may be responsible for a similar inflammatory enteritis in both of these populations, and may be associated with an autoimmune component.³⁴

Mercury, Heavy Metals, and Vaccines

Disputed epidemiologic evidence has correlated neurodevelopmental disorders with increasing doses of mercury from the ethylmercury-containing preservative thimerosal in vaccines.³⁵ On the basis of the mercury content of the respective vaccines, children who received diphtheria–tetanus–pertussis vaccine (DTP) and *Haemophilus influenzae* type b (Hib) vaccine at the standard vaccination schedule of 2, 4, 6, and 15–18 months of age may be exposed to 100 µg of mercury more than children given the combined DTP/Hib (DTPH) vaccine. According to the Vaccine Adverse Event Reporting System, this may indicate that children given the DTP and Hib vaccines as separate entities are at significantly greater risk for autism and related disorders than those given the combined vaccine.³⁶

Several studies support the theory that children with autism have an impaired ability to excrete heavy metals.^{37–39} One such study found significantly lower concentrations of arsenic, cadmium, and lead in the hair of such children than in controls, suggesting lower excretion rates for these three metals.³⁷

It has also been found that children with ASD have a 2.1-fold greater than average concentration of mercury in their baby teeth, which is a good measure of cumulative exposure to toxic metals during fetal development and infancy.³⁸ In this study, it was noted that these children had also received significantly more oral antibiotics than average during their first 12 months of life, which may have reduced the children's ability to excrete mercury, since studies with rats have found that antibiotics can almost completely inhibit the excretion of mercury by altering the gut flora.³⁸ A study in which the levels of mercury in first

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childhood haircut samples from children with autism were much lower than those of controls also found that the mothers of the autistic children had had significantly greater exposure to mercury from amalgam fillings and thimerosal-containing Rho D immunoglobulin injections than did a control group.³⁹ A Texas

study found a 43% increase in the frequency of special education services and a 61% increase in the rate of autism for every 1000 lb of environmentally released mercury.⁴⁰

Serotonin

Numerous cursory studies indicate abnormalities in the metabolism of serotonin and measurable levels of this amine in autistic individuals. Among findings in this area are that platelet levels of serotonin are significantly higher in autistic than in control subjects, and that a negative correlation exists between platelet levels of this amine and speech development.⁴¹ Significantly lower plasma levels of serotonin have been found in mothers of autistic children than in mothers of children with normal development.⁴² Another finding has been that that supplementation with 5-hydroxytryptophan (5-HT), a metabolic precursor of serotonin, raised serotonin levels to a significantly greater degree in subjects with autism than in a control group.⁴³ Abnormalities in the genes encoding the serotonin transporter and enzymes required for serotonin synthesis are subjects of current study in connection with autism.

Diagnosis of ASD

The diagnosis of ASD is usually made between the ages of 2 and 3, with tools such as the Checklist for Autism in Toddlers (CHAT), Modified Checklist for Autism in Toddlers (M-CHAT), Pervasive Developmental Disorders Screening Test (PDDST), Screening Tool for Autism in Two-year-olds (STAT), and Checklist for Autism in Toddlers-23 (CHAT-23).

Treatment

The wide range in presentations of ASD has led to numerous treatments for it. These include behavioral and psychosocial interventions; occupational, speech, music, and sensory-integration therapy; immunotherapy; and several alternative and com-

plementary therapies including nutritional therapy, chelation, and vitamin and other nutritional supplementation. The following sections describe a number of treatments investigated for autism, and their effects.

Immunotherapy

A small study of the effect of encapsulated human Ig in males with autism, conducted to test the theory that GI symptoms in the condition may stem from a deficiency in mucosal immunity, found reductions in GI signs and symptoms, as well as improvement in behavioral measures, in half of the treated individuals.⁴⁴

Ascorbic Acid

A 30-week, double-blind, placebo-controlled study demonstrated a reduction in symptom severity in autistic children treated with ascorbic acid, supporting the hypothesis that this vitamin has a dopaminergic mechanism of action correlating with research suggesting a hyperdopaminergic state in autistic individuals.^{45,46} The antioxidant activity of ascorbic acid may also be of benefit in autism.

Carnosine

Carnosine, a dipeptide of alanine and histidine, exhibits antioxidant and antiglycating activity, in addition to binding heavy metals. A controlled study involving children with ASD found that an 8-week trial of L-carnosine at 800 mg/day produced a significant improvement in autistic traits as measured with the Receptive One-Word Picture Vocabulary test and the total score and the Behavior, Socialization, and Communication subscales of the Gilliam Autism Rating Scale.⁴⁷

Vitamin Supplementation

A study has indicated that children with ASD show significant improvement in sleep and reduction of GI symptoms when given nutritional supplementation with a multivitamin/mineral preparation.⁴⁸ The pretreatment baseline finding of vitamin B6 levels that were 75% higher in these children than in a control group supported previous reports of deficient conversion of pyridoxal to the active pyridoxal-5-phosphate by pyridoxal kinase in autistic children, and pointed to an indication for supplementation with vitamin B6 in autism.^{48,49}

Lower red-blood-cell levels of magnesium have also been found in children with PDD than in controls, with nearly 70% of the affected children showing significant improvement, unaccompanied by adverse effects, upon supplementation with magnesium at a dose of 6 mg/kg/day and 0.6 mg/kg/day of vitamin B6.⁵⁰

Other nutrient deficiencies have also been found in children with autism. Hair analyses have found lower concentrations of lithium as well as iodine levels 45% below those of controls, as well as a 38% lower level of chromium in autistic children with pica. A 31% greater level of zinc and a 66% lower level of potassi-

um was found in autistic children with diminished muscle tone, suggesting possible avenues for additional vitamin treatment.⁵¹

Omega-3 Fatty Acids

In a controlled 6-week trial, hyperactivity and stereotypic behavior declined in children with ASD who were given supplemental omega-3 fatty acids at 1.5 g per day.⁵²

Diet

Limited evidence suggests that dietary restriction of gluten and casein may be beneficial in children with autism. A small controlled study found that such children showed significantly better development with a gluten- and casein-restricted diet than did controls.⁵³ Food allergy may play a role in autistic symptomology, as suggested by significantly increased levels of antibodies to casein,

beta-lactoglobulin, and lactalbumin in autistic children than in controls, followed by reductions in behavioral symptoms with an 8-week elimination diet for these three food components.⁵⁴ However, a small, double-blind, placebo-controlled study failed to find any significant changes in autistic children with a gluten- and casein-restricted diet, although the children's parents did report improvements in the children's conditions.⁵⁵

Another study found behavioral improvement after 6 months in 60% of autistic children given a ketogenic diet.⁵⁶

Chelation

A small trial of meso-2, 3-dimercaptosuccinic acid combined with leuprolide acetate was conducted to test the concept that ASD may result from interactions between transsulfuration in the methionine cycle and androgen pathways as noted earlier, and in accord with a previous finding of abnormal detoxification associated with the methionine and transsulfuration pathways in children with autism.⁵⁷ After exposure to mercury, the children had a dramatic reduction in severity of symptoms. The results showed a dramatic reduction in severity of symptoms, from the 70–79th percentile of severity to the 40–49th percentile of severity. Behavior, sociability, and cognitive awareness were notably improved. In another study with autistic children, involving antiandrogen and anti-heavy-metal therapy, urinary levels of heavy metals increased and blood levels of androgens decreased.⁵⁸

Pharmaceutical Treatment

The antipsychotic drug risperidone has been approved by the Food and Drug Administration for treating ASD marked by self-injurious behavior, severe tantrums, and aggression in children ages 5–16. Risperidone has been found to improve social responsiveness and nonverbal communication, and to decrease hyperactivity and aggression in these children.⁵⁹ Treatment with selective serotonin reuptake inhibitors (SSRIs) also modifies some symptoms of ASD, including anxiety and repetitive behavior, and improves global functioning.⁶⁰

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Behavioral Interventions

Intensive interventions provide better outcomes than less-intensive treatments for ASD. Several behavioral interventions have shown benefit. Early applied behavioral therapy given at home for 30 hours a week can produce gains in behavior.⁶¹ A small study of long-term follow-up of preschool children who had undergone intensive behavioral intervention showed long-lasting gains at a mean age of 11.5 years as compared to controls.⁶²

Secretin

Secretin, a peptide that functions in both the GI system and the brain, is being investigated on the basis of anecdotal evidence that this peptide may be effective in easing autistic traits, but most studies have not shown it to be significantly beneficial.⁶³

Conclusion

A vast amount of research is currently focused on identifying the etiology of autism. The large variation in phenotypes of this condition indicates that its etiology is most likely to be multifactorial, with both genetic and environmental components. Complementary and alternative therapies provide treatment options that can support conventional behavioral modification therapies for autism. Like the coal miner's canary, with its sensitivity to silent danger, the dramatic increase in ASD over the past decade warns that something may be amiss in our culture. □

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