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REVIEW ARTICLE

Theoretical aspects of autism: Causes—A review

Helen V. Ratajczak

Abstract
Autism, a member of the pervasive developmental disorders (PDDs), has been increasing dramatically since its description by Leo Kanner in 1943. First estimated to occur in 4 to 5 per 10,000 children, the incidence of autism is now 1 per 110 in the United States, and 1 per 64 in the United Kingdom, with similar incidences throughout the world. Searching information from 1943 to the present in PubMed and Ovid Medline databases, this review summarizes results that correlate the timing of changes in incidence with environmental changes. Autism could result from more than one cause, with different manifestations in different individuals that share common symptoms. Documented causes of autism include genetic mutations and/or deletions, viral infections, and encephalitis following vaccination. Therefore, autism is the result of genetic defects and/or inflammation of the brain. The inflammation could be caused by a defective placenta, immature blood-brain barrier, the immune response of the mother to infection while pregnant, a premature birth, encephalitis in the child after birth, or a toxic environment.

Keywords: *Autism; autism spectrum disorder; pervasive developmental disorder*

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Introduction

Autism is a neuro-developmental disorder characterized by impaired communication and social interaction and repetitive behaviors. Several lines of evidence indicate that genetic, environmental, and immunological factors may play a role in its pathogenesis (Kidd, 2002). Some investigators expand the nature of autism to that of a multisystem metabolic disease, not just a brain disorder (Jepson, 2007a). The term autistic spectrum disorder (ASD) or pervasive developmental disorders (PDDs) represents a group of disorders which includes five diagnostic subtypes including autism, PDD not otherwise specified (PDD-NOS), Rett's disorder, child disintegrative disorder, and Asperger's disorder (Posey et al., 2008). The gender ratio is 3–4 boys:1 girl (Bryson and Smith, 1998). Autism is a lifelong condition for most. Historically, 75% of autistic individuals become either institutionalized as adults or are unable to live independently (Paul, 1987). Studies of adults with autism suggest that the cumulative mortality rate is higher among autistic patients than their non-autistic peers (Schonauer et al., 2001).

The estimated lifetime per capita incremental societal cost of autism is $3.2 million. Lost productivity and adult care are the largest components of the cost (Ganz, 2007). Greater than the monetary cost, the emotional devastation caused by the great difficulties posed by the autistic individual, and the strains on the family, cause long-lasting strife and sometimes physical threats to the autistic individual and to others around them.

This complex behavioral disorder encompasses a wide variety of symptoms, defined by deficits in social interaction, communication, and empathy, accompanied by unusual restricted, repetitive behaviors (Volkmar and Klin, 2005). Since there are no objective diagnostic tests for autism, a clinical diagnosis is based on behavior, using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV, TR*) as the gold standard. Using a list of diagnostic criteria, at least six criteria must be exhibited with onset of conditions prior to age three, including at least two relating to social abnormalities and one each regarding impaired communication and range of interests and activities (Volkmar and Klin, 2005). These criteria are not described in detail, leaving latitude for clinical judgment (Barbaresi et al., 2006). To date, no biological markers have been found to reliably diagnose autism in an individual patient (Posey et al., 2008; Ecker et al., 2010). However, many biomarkers (hormones, peptides, etc.) have been documented to be significantly different in autistic subjects compared to age- and sex-matched controls. In a companion paper, the possibility of using statistics to construct a composite biomarker profile and objective measure of autism with a ranking of severity is explored (Ratajczak, In Press).

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The onset of autism is usually documented in the first 3 years of life (Kolvin, 1971). However, there have been case reports of late-onset autism (DeLong et al., 1981; Gillberg, 1986; Gillberg, 1991) in individuals who were 11, 14, and 31 years of age and who previously had herpes encephalitis. Therefore, autism is not necessarily a developmental disorder.

Incidence and prevalence

It is possible that there are several causes of autism since, to date, aberrant findings have not been present in 100% of the autistic subjects in any study. It is first important to assess the incidence and prevalence data to get timelines that might help determine the major causes of autism.

For decades since first described by Leo Kanner in 1943, autism was believed to occur at a rate of 4–5 per 10,000 children (Kanner, 1943). Perhaps, the cause of autism at that time might have been primarily genetic. From surveys done between 1966 and 1998 in 12 countries (e.g., United States, United Kingdom, Denmark, Japan, Sweden, Ireland, Germany, Canada, France, Indonesia, Norway, and Iceland), the prevalence (i.e., number of existing disease cases in a defined group of people during a specific time period) ranged from 0.7–21.1/10,000, with a median value of 5.2/10,000 (or 1/1923; Fombonne, 1999). For all forms of PDDs, the prevalence was 18.7/10,000 (or 1/535). In the United States, the prevalence (measured in 1970) was 0.7/10,000 (or 1/14,286). In California, when the 1998 prevalence of autism was compared to that in 1987, a 273% increase in autism was noted; with respect to other PDDs, the increase was 1966% (Fombonne, 2001).

As with prevalence, the incidence (i.e., number of new cases of disease in a defined group of people over a specific time) of autism has also increased sharply. A 10-fold increase in incidence in the United States was reported in 2001, with a 1990s rate of 1/250 compared to one of 1/2500 in the 1970s (DeFrancesco, 2001). The Center for Disease Control and Prevention states that the prevalence of autism is increasing at epidemic rates (Rice, 2009). Using the same methods for analyses of data from both years, comparisons of the prevalence in 2002 to that in 2006 were made in the Autism and Developmental Disabilities Monitoring (ADDM) Network sites (e.g., areas of Alabama, Arizona, Colorado, Florida, Georgia, Maryland, Missouri, North Carolina, Pennsylvania, South Carolina, and Wisconsin). The results were 1/150 in 2002 and 1/110 for 2006. Of 10 sites that collected data for both the 2002 and 2006 surveillance years, 9 observed an increase in autism prevalence, with increases among males in all sites and among females in 4/11 sites, and variation among the other subgroups. The overall average increase from 2002 to 2006 was 57%. In a parent survey conducted in 2007 by the U.S. National Survey of Children's Health, the prevalence was 1/91 (Kogan et al., 2009). The most recent official prevalence for the United States is an average of 1/110 (Center for Disease Control and Prevention, 2010).

By comparison, incidence in the United Kingdom is also increasing, with higher rates than in the United States. In 2006, the prevalence of autism in a cohort of children in South Thames was 1/86 (Baird et al., 2006). Three years later, a school-based study in Cambridgeshire reported a prevalence of 1/64 (Baron-Cohen et al., 2009). Although improved ascertainment accounts for some of the prevalence increases documented, a true increase in the risk for children to develop autism symptoms cannot be ruled out (Rice, 2009).

It is difficult to compare the figures concerning incidence and prevalence because autism is defined by subjective measures (Ecker et al., 2010). Some questions remain: Are individuals included only those diagnosed by a doctor? How are individuals who were diagnosed in the past but, on retesting, are no longer considered autistic listed? Is the enumeration of the total group correct? Are there environmental influences in particular locations that might cause an increase in the diagnosis? Do families with autistic members move to certain locations where there are superb physicians, therapists, etc.?

In general, the autism increase is not considered a result of reclassification (Sullivan, 2005). Although autism diagnoses have risen, there are no corresponding decreases in other diagnostic categories. Using data from the U.S. Department of Education Office of Special Education Programs (1992–2001), children were classified into 13 primary disability categories. The researchers calculated the prevalence of autism and other health impairments in children 6–17-years old during each of the years and superimposed the data onto birth cohorts as far back as 1975. There were clear significant increases in the prevalence of autism among younger birth cohorts, especially those born between 1987 and 1992. During those years, autism prevalence per 10,000 rose about 50% every 2 years: 5.3 in 1984, 7.8 in 1986, 11.8 in 1988, and 18.3 in 1990. During that time, there were no changes in prevalence of mental retardation, speech/language impairment, or traumatic brain injury, which suggests that the increase in autism is real. The U.S. Department of Education uses only a single autism classification that includes all students receiving services who have been diagnosed with any one of the autism spectrum disorders.

Changes in rates of autism incidence

The California Department of Developmental Services conducted a study of time trends in the prevalence by age and birth cohort of children with autism who were active clients from January 1, 1995 to March 31, 2007 (Schechter and Grether, 2008). The data did not show any decrease in autism in California, despite the exclusion of more than trace levels of Thimerosal from nearly all childhood vaccines by 2002. However, in 2004, inactivated influenza vaccine frequently containing Thimerosal was newly recommended for all children 6–23-months old in the United States (Schechter and Grether, 2008). In addition, influenza vaccination during all trimesters of pregnancy is now universally recommended in the United States (Ayoub and Yazbak, 2006). Most inactivated

influenza vaccines contain Thimerosal, despite its implication in autism (Ayoub and Yazbak, 2006).

Data from a worldwide composite of studies show that an increase in cumulative incidence began about 1988–1990 (McDonald and Paul, 2010). The new version of the measles, mumps, rubella vaccine (i.e., MMR II) that did not contain Thimerosal was introduced in 1979. By 1983, only the new version was available. Autism in the United States spiked dramatically between 1983 and 1990 from 4–5/10,000 to 1/500. In 1988, two doses of MMR II were recommended to immunize those individuals who did not respond to the first injection. A spike of incidence of autism accompanied the addition of the second dose of MMR II. Also, in 1988, MMR II was used in the United Kingdom, which reported a dramatic increase in prevalence of autism to 1/64 (noted above). Canada, Denmark, and Japan also reported dramatic increases in prevalence of autism. It is important to note that unlike the former MMR, the rubella component of MMR II was propagated in a human cell line derived from embryonic lung tissue (Merck and Co., Inc., 2010). The MMR II vaccine is contaminated with human DNA from the cell line. This human DNA could be the cause of the spikes in incidence. An additional increased spike in incidence of autism occurred in 1995 when the chicken pox vaccine was grown in human fetal tissue (Merck and Co., Inc., 2001; Breuer, 2003). The current incidence of autism in the United States, noted above, is approximately 1/100.

The human DNA from the vaccine can be randomly inserted into the recipient's genes by homologous recombination, a process that occurs spontaneously only within a species. Hot spots for DNA insertion are found on the X chromosome in eight autism-associated genes involved in nerve cell synapse formation, central nervous system development, and mitochondrial function (Deisher, 2010). This could provide some explanation of why autism is predominantly a disease of boys. Taken together, these data support the hypothesis that residual human DNA in some vaccines might cause autism.

Vaccines

The incidence and prevalence data indicate the timing of introduction of vaccines and changes in the type and increasing number of vaccines given at one time implicate vaccines as a cause of autism. The current recommended immunization schedule for persons aged 0–6 years in the United States includes six vaccines at 2 months and nine vaccines at 12–15 months (Advisory Committee on Immunization Practices, 2010). This is an increase over recommendations 6 years before, with five vaccines at 2 months and 8 at 12–15 months (Advisory Committee on Immunization Practices, 2004). The immune system is particularly sensitive at 2 months of age. Although specific immune functions, governed by B- and T-lymphocytes, are competent in the newborn (Solomon, 1971), the polymorphonuclear cells are less in number than the lymphocytes in the peripheral blood (Diem, 1962). Also, the phagocytic cells and complement system of a newborn are decreased in function (Xanthou et al., 1975; Madden et al., 1989). Thus, the immune system of an infant is compromised at 2 months. A challenge by so many vaccines while the immune system is compromised might contribute to an onset of autism.

Vaccine antigens

There are many controversies about vaccines and autism, especially since many parents cite normal development of their children until they receive vaccines at about the age of 18 months (Lewine et al., 1999). The vaccine organism itself could be a culprit. For example, one hypothesis of the cause of autism is that the pertussis toxin in the DPT vaccine causes a separation of the G-alpha protein from retinoid receptors in genetically at-risk children (Farfel et al., 1999; Megson, 2000). The pertussis toxin creates a chronic autoimmune monocytic infiltration of the gut mucosa lamina propia and may disconnect the G-alpha protein pathways, leaving some G-alpha-modulated pathways unopposed. In turn, the non-specific branch of the immune system is turned on and, without retinoid switching, cannot be down regulated.

Another organism of suspect is the live measles virus. When the measles vaccine is given, it depletes the children of their existing supply of Vitamin A, which negatively impacts the retinoid receptors, accounting for the distorted vision in autistic individuals (Megson, 2000; Rosales, 2002). This could account for the fact that autistic subjects' ability to see is not normal, with malfunctioning rods causing distortion of the peripheral vision. When the natural form (cis) of Vitamin A was given to autistic subjects for 2–3 months, followed by urocholine, many autistic children showed immediate improvement in their autistic behaviors, including improved eye contact, ability to socialize, ability to sleep through the night, etc. (Megson, 2000).

Vaccine preservative

There is evidence that Thimerosal (which is 49% ethyl mercury) is indeed harmful. Since the 1930s, Thimerosal has been extensively used as an antibacterial agent in vaccines (Geier et al., 2007). Thimerosal has been implicated as a cause of autism. Not only is every major symptom of autism documented in cases of mercury poisoning but also biological abnormalities in autism are very similar to the side effects of mercury poisoning itself (Bernard et al., 2001): these include psychiatric disturbances (e.g., impairments in sociality, stereotypic behaviors, depression, anxiety disorder, and neuroses), increased incidences of allergies and asthma, increases in the presence of IgG autoantibodies against brain and myelin basic proteins, reductions in natural killer cell function, and increases in neopterin levels (indicative of immune activation). Autistic brains show neurotransmitter irregularities that are virtually identical to those arising from mercury exposure, i.e., changes in serotonin and dopamine concentrations, elevated epinephrine and norepinephrine levels in the plasma and brain, elevated serum glutamate levels, and an acetylcholine deficiency in the hippocampus (Bernard et al., 2001). Due to the extensive parallels between autism and mercury poisoning, the likelihood of a causal relationship is great. More evidence linking autism with mercury

poisoning is the timing of inclusion of Thimerosal in vaccines in the 1930s closely preceding the discovery of autism in 1943 (Kanner, 1943).

Metal metabolism disorder

Supporting this relationship are reports documenting that heavy metals are increased in the blood and urine of autistic subjects (Bernard et al., 2001; Walsh et al., 2001). Walsh et al. (2001) studied blood and urine from 503 patients with autism, Asperger's syndrome, or atypical autism, and compared their results to samples from neurotypical controls. The analyses revealed that 85% of the patients exhibited severely elevated Cu:Zn ratios and 99% showed evidence of a metal-metabolism disorder, suggesting defective metallothionein. Defective metallothionein might be responsible for the greater amount of blood mercury found in autistic children compared to neurotypical controls (Desoto and Hitlan, 2007; Geier et al., 2010). Metallothionein plays an important role in the development and continued function of the immune response, in neuronal development, and in the detoxification of heavy metals. Many classic symptoms of autism may be explained by a metallothionein defect, including gastrointestinal (GI) tract problems, heightened sensitivity to toxic metals, and abnormal behaviors. Porphyrinuria in children with autism is considered a marker of heavy metal toxicity (Geier and Geier, 2006a; Nataf et al., 2006, 2008; Rossignal, 2007; Geier et al., 2009). Individuals with severe autism had increased mercury-intoxication-associated urinary porphyrins (Geier et al., 2009).

Neurotoxicity of mercury

Mercury is known to be neurotoxic and has effects on the immune system as well. Mast cells are involved in allergic reactions, and also in inflammation, and innate and acquired immunity. Autistic individuals have a 10-fold greater number of hyperactive mast cells in most tissues. Mercury stimulates vascular endothelial growth factor and interleukin (IL)-6 release from mast cells. These mediators could disrupt the blood–brain barrier and cause brain inflammation (Kempuraj et al., 2010). The USEPA and FDA recommend 1 ppm as the official reference dose for methyl mercury in the United States. The 1-ppm value is also used with regard to total mercury exposure, according to the Joint Expert Committee on Food Additives (Dufault et al., 2009). Thus, in this review, distinctions between effects of different forms of mercury are not made.

Sources of mercury in the environment

Dufault et al. (2009) has provided data linking the diet and environment with autism. Cumulative mercury exposure results from mercury as a pollutant in air, soil, dust, water, consumer products, dental amalgam and lighting fixtures, foodstuffs, fish, and seafood. Concerning air, for every 1,000 pounds of mercury (all forms), there was a 61% increase in the rate of autism. Mercury is found in many foods, including high-fructose corn syrup. The consumption of high-fructose corn syrup could impact the behavior of children with attention deficit hyperactivity disorder (ADHD), which is associated with autism (Loveland and Tunali-Kotoski, 2005). Also, the consumption of some artificial food color additives has been shown to lead to zinc deficiency. Dietary zinc is essential for maintaining the metabolic processes required for mercury elimination. Dietary deficiencies of iron, zinc, iodine, selenium, copper, manganese, fluoride, chromium, and molybdenum are associated with mild to significant changes in neuronal function that can lead to poor health and adverse effects on behavior and learning.

Toxicity of Thimerosal

There are dangerous effects of Thimerosal on the immune system, particularly on T-lymphocytes. Mercury induces glutathione depletion, increased oxidative stress, and apoptosis in these cells (Makani et al., 2002). In addition, Thimerosal causes toxic effects on brain cells (Baskin et al., 2003), inhibits glutamate transport (Mutkus et al., 2005), affects nerve differentiation (Parran et al., 2005), induces immunoproliferation and formation of autoantibodies to fibrillin proteins (Havarinasab and Hultman, 2005), and depletes glutathione (James et al., 2005).

Although the timing of the introduction of Thimerosal in vaccines in the 1930s coincides with the discovery and rise in prevalence of autism, a review of 10 epidemiologic studies, seven of which were cohort studies, concluded that the data do not unequivocally demonstrate a link between Thimerosal-containing vaccines and autism. This is primarily because the number of diagnosed cases of autism continues to increase despite the fact that most childhood vaccines are free of more than trace levels of Thimerosal since about the year 2000 (Schechter and Grether, 2008). In addition, the pharmacokinetics of ethylmercury (the form of mercury in Thimerosal) makes such an association less likely (Parker et al., 2004). With the increasing incidence of autism, the search for a cause of autism continues (Schechter and Grether, 2008).

Measles Mumps Rubella Vaccine (MMR)

There have been a number of reports denying an association of autism with the MMR vaccine (Halsey et al., 2001; Madsen et al., 2002; Wilson et al., 2003; Parker et al., 2004; DeStefano, 2007). The work of Madsen and colleagues (2002; in reporting on autism in Denmark) has been contradicted because longitudinal trends in prevalence data suggest a temporal association between the introduction of MMR vaccine into Denmark and the rise in autism (Goldman and Yazbak, 2004). Other reports have also used prevalence data that support an association of the MMR vaccine with an increased prevalence of autism. Furthermore, an examination of the continuing increase in prevalence in autism in the context of the dates of spikes in increase in prevalence which point to the MMR II vaccine (which did not contain Thimerosal) suggests that something "new" caused the increase in incidence of autism. Changes in vaccine schedule occurred over the years such as changes in the age at which vaccines were given (Ramsay et al., 1991). These changes could contribute to the increases

in incidence of autism. Another change was how some vaccines were propagated. The "new" component could be the human DNA from the preparation of the rubella component of the MMR II vaccine and the chicken pox vaccine. See "Changes in Rates of Autism Incidence" above. The United States Government and Dr. Geberding, Director of Vaccines at Merck & Co., Inc. say that autistic conditions can result from encephalopathy following vaccination (Child Health Safety, 2010).

Genetics

There is indisputable evidence for a genetic component in autism (Rodier, 2000). With identical (monozygotic) twins, if one is autistic, the likelihood that the other twin will have some form of autism is 90%. In great contrast, for fraternal (dizygotic) twins, the likelihood that the other twin will have a form of autism is only 2–3% (DeFrancesco, 2001). The results fit best with models in which variants of several genes contribute to the outcome. Relatives of people with autism may have some of its symptoms but fail to meet all the criteria for the disorder.

Muhle et al. (2004) confirm DeFrancesco's findings but with different percentages: twin studies reported 60% concordance for classic autism in monozygotic twins vs. 0% in dizygotic twins, the higher monozygotic concordance attesting to genetic inheritance as the predominant causative agent. Reevaluation for a broader autistic phenotype that included communication and social disorders increased concordance remarkably from 60–92% in monozygotic twins and 0–10% in dizygotic pairs. This suggests that interactions between multiple genes cause "idiopathic" autism, but epigenetic factors and exposure to environmental modifiers may contribute to variable expression of autism-related traits. Data from whole-genome screens in multiplex families suggest interactions of at least 10 genes in causation of autism.

HOXA1, of autosomal recessive inheritance (Caglayan, 2010), is only one of many genes involved in the spectrum of autism disorders (Rodier, 2000). In addition, the involvement of the *DbetaH* (DBH) gene with autism was documented in families of autistic children that have a low level of serum dopamine β-hydroxylase, which catalyzes the conversion of dopamine to norepinephrine (Robinson et al., 2001). Although the odds ratios suggested only a moderate relevance for the DBH-allele as a risk allele, the attributable risk was high (42%), indicating this allele is an important factor in determining the risk for having a child with autism. Selected genes for a monogenic heritable form of autism include *NLGN3, NLGN4, NRXN1, MeCP2*, and *HOXA1* (Caglayan, 2010).

Other genes are also involved in autism disorders. The *Fragile X* gene is associated with autism (Farzin et al., 2006). There is also a positive association of the *FMR-1* gene with autism (Vincent et al., 1996). Mutations in the *SHANK2* synaptic scaffolding gene have been documented in autism (Berkel et al., 2010). In addition, the Reelin gene has been associated with autism because the gene is responsible for correct lamination of the brain during the embryonic period and cell signaling and synaptic plasticity in adult life (Fatemi, 2002). Reelin protein and mRNA were reduced in the cerebellum of autistic individuals, with increases in mRNA of the Reelin receptor in frontal and cerebellar cortices. EDab-1 mRNA levels were also reduced in the same brain sites, implying involvement of the Reelin signaling cascade in autistic pathology (Fatemi, 2005; Fatemi et al., 2005). Possibly, the most significant genetic finding relevant to autism is the identification of the gene responsible for Rett syndrome (Amir et al., 1999; Lord et al., 2000) because the Rett syndrome is a neurodevelopmental disorder that is associated with mental retardation, loss of communication skills, and has autistic features that vary in prominence at different developmental stages. The Rett syndrome has been placed within the diagnostic category of PDDs, of which autism is the most outstanding. The Rett syndrome is caused by mutations in the *MECP2* gene. Strikingly different from autism, which affects boys more than girls, Rett syndrome is almost exclusively seen in girls (Van Acker et al., 2005). The most common nonspecific diagnosis for children with Rett syndrome above the age of 1 year is early infantile autism. In fact, some researchers suggest Rett syndrome be considered a subtype of autism or an overlapping diagnostic entity. However, the behavioral patterns, progression, and prognosis of these two conditions differ significantly, with a basic distinction made on the basis of motor behavioral analysis (Van Acker et al., 2005).

The fact that the combination of known genes or genetic diseases associated with autism accounts for only ~1–2% of the cases points to defining autism as a neurodevelopmental syndrome for which there is no single major genetic cause but rather many relatively rare mutations (DeFrancesco, 2001). Another reason to discount an overall genetic cause is that autism is now considered an epidemic and there is no such thing as a genetic epidemic (Jepson, 2007a). To date, there has not been one single gene found to be responsible for autism. Other phenomena may cause mutations in genes or alter gene expression, with the end result being autism.

Co-morbidities

Clinical features often associated with autism, with 35% displaying co-morbidity with a psychiatric disorder or other medical diagnosis, include depression, bipolar affective disorder, schizophrenia, schizoaffective disorder, Tourette syndrome, Pica, epilepsy, hypothyroidism, Down's syndrome, and hypertension (Morgan et al., 2003). Other disorders associated with autism are genetic conditions like Fragile X syndrome or tuberous sclerosis (Mansheim, 1979; Meryash et al., 1982), metabolic disorders such as phenylketonuria (PKU) or histidinemia (Kotsopoulos and Kutty, 1979; Baieli et al., 2003), the Landau-Kleffner and Rett syndromes (Lowe et al., 1980; Johnson, 2000), and a variety of other conditions that affect brain development and function (Ornitz, 1983; Coleman and Betancur, 2005). Autistic patients with a co-existing organic condition or neurological symptoms are not distinct (behaviorally or developmentally) from autistic patients without such features (Knobloch and Pasamanick, 1975; Ornitz et al.,

1977; Garreau et al., 1984). Recent data provide the first anatomical evidence of an abnormal amygdala-fusiform system and its behavioral relevance to face-processing deficits in autism (Dziobek et al., 2010).

Other syndromes associated with autism include Prader-Willi, Angelman, Inv dup(15) or idic(15), Joubert, Neurofibromatosis type 1, macrocephaly and overgrowth, Timothy, Tuberous sclerosis complex, Turner, Williams, Smith-Magenis, Klinefelter, XYY, 22q13.3 deletion, Smith-Lemli-Opitz, Cohen, and Sanfilippo. In addition, adenylosuccinate lyase deficiency, Duchenne muscular dystrophy, and mitochondrial cytopathies are associated with autism (Caglayan, 2010). Some data suggest a link between Type 1 diabetes and autism (Freeman et al., 2005). In addition, autoimmunity is very prevalent in autistic subjects and in their parents and close relatives (Megson, 2000).

Age of parents

There are well-documented effects of aging on human genetic traits, especially those that have their effects in early embryonic life (Strickberger, 1968). There are known changes in the rates of chromosome abnormalities at different maternal ages. For example, rates for Down, Edwards, and Klinefelter syndromes associated with XXY genotype increase exponentially from about age 30 to 49, with less dramatic change below age of 30 (Hook, 1981).

Data vary with respect to the contribution of increasing age of parents to the risk of having an autistic child. A study of singleton children (not twins or multiple births) born in northern California from January 1, 1995 to December 31, 1999 ($n = 139{,}419$) documented advanced maternal and paternal ages to be independently associated with risk of autism-spectrum disorders (Croen et al., 2007). These data contradict those of Reichenberg et al. (2006) who reported only advanced paternal age was responsible for increased risk of having an autistic child. In this study, advancing maternal age showed no association with autism after adjusting for paternal age. More recently, the finding of Croen et al. (2007) was confirmed by a study of singleton children born in the state of California from 1989 to 2002 ($n = 7{,}550{,}026$). A 10-year increase in maternal age was associated with a 38% increase in the odds ratio for autism, and a 10-year increase in paternal age was associated with a 22% increase. Maternal and paternal age effects were of greater magnitude among first-born compared to later-born children (Grether et al., 2009). In another large study ($n = 4{,}947{,}935$) of singleton births in California between 1990 and 1999, advancing maternal age increased risk for autism regardless of paternal age. The father's age conferred an increased risk only when mothers were < 30 years old. The trend toward delaying childbearing contributed about a 4.6% increase of autism over the decade (Shelton et al., 2010). Age-related biological mechanisms through which increasing age of the parents could affect the fetus include, for women, hormonal factors which change the *in utero* environment, greater risk of infertility and exposure to assisted reproductive technologies, nucleotide repeat instability, and an increase in cumulative toxic exposure. For men, the most likely biologic explanation is increased *de novo* mutations in sperm occurring more often in older fathers, perhaps affected by cumulative toxic exposure (Grether et al., 2009).

Mitochondrial disease and dysfunction

Classical mitochondrial diseases occur in a subset of autism cases and are usually caused by genetic or mitochondrial respiratory pathway abnormalities (Pons et al., 2004; Rossignol and Bradstreet, 2008). But there is increasing evidence of mitochondrial dysfunction in autistic individuals without the classic features associated with mitochondrial disease. Mitochondrial dysfunction is thought to be caused by environmental toxins and could contribute to the altered energy metabolism in the brains of children with autism (Chugani et al., 1999). Some patients with autistic phenotypes clearly have genetic-based primary mitochondrial disease (Haas, 2010). The lowered cellular energetics and deficient reserve mitochondrial energy capacity could lead to cognitive impairment and language deficits, both common in autistic individuals. It has been determined that autism can be caused by an underlying predisposition to mitochondrial dysfunction (Child Health Safety, 2010).

These data support Jepson's assessment that autism is a multiorgan metabolic disease caused by the environment or a virus in individuals who are genetically prone to the disorder. Whatever its cause(s), autism affects critical parts of metabolism, with symptoms in the immunological, gastrointestinal, toxicological, and neurological systems (Jepson, 2007b). Therefore, other causes of autism must be considered, such as viral, bacterial, and/or environmental.

Conditions

Pregnancy

Immunosuppression induced by pregnancy renders a woman more susceptible to infections (Brabin, 1985; Koga and Mor, 2010). In addition, there are critical windows of time during which the fetus is more vulnerable immunologically (Meyer et al., 2006; Dietert and Dietert, 2008). Data reveal that maternal viral infection in the first trimester and bacterial infection in the second trimester are associated with diagnosis of autism in the offspring (Atladóttir et al., 2010).

The placenta, the first fetal organ that becomes functional during pregnancy, plays an essential role in fetal development (Pasca and Penn, 2010). Many nutrients such as glucose, amino acids, free fatty acids, cholesterol, and phospholipids are moved from maternal to fetal circulation through the placenta. The placenta is a major endocrine organ with endocrine, paracrine, and autocrine effects. The placenta makes progesterone that maintains the pregnancy, relaxing the gravid uterus and inhibiting fetal rejection by suppression of maternal lymphocyte activity. In addition, placental progestins enter the maternal and fetal circulation, crossing the blood-brain barrier to promote both maternal and fetal neurogenesis. The placenta produces inflammatory (i.e., IL-6) and anti-inflammatory (i.e., IL-10) cytokines that would influence both the fetus and the mother. Evidence

from animal and human studies suggests transfer of oxytocin from the placenta to the fetus across the immature blood-brain barrier. The oxytocin could shift γ-amino-butyric acid (GABA) signaling from excitatory to inhibitory. Oxytocin concentrations have been linked to social behavior, and oxytocin pathway signaling may be impaired in autism. It is suggested that autism can be "programmed" by placental signals that fundamentally and permanently change the way the fetus is wired (Pasca and Penn, 2010).

Other investigators report that a defective blood-brain barrier is common in autistic patients (Clifford et al., 2007). Maternal immune activation due to prenatal viral exposure can lead to an increase in maternal IL-6 levels and altered gene expression, which potentially could precipitate autistic behavior and neuropathology in the fetus later in time or after birth (Parker-Athill and Tan, 2010). A dysfunctional chronic pro-inflammatory state has been shown to exist in the brain and cerebral spinal fluid in subsets of autistic patients (Chez and Guido-Estrada, 2010). It is theorized that preexisting autoreactive T-lymphocytes may migrate across the blood-brain barrier and induce activation of local antigen-presenting cells, such as microglia and astrocytes. Production of IL-2, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α may result in oligodendrocyte damage and demyelination, thereby playing a role in the pathogenesis of autism. As such, a mother's immune response(s) to infection includes the formation/release of antibodies and cytokines that could cross the immature blood-brain barrier of the fetus and which, over time, could cause autism (Vojdani et al., 2002; Atladóttir et al., 2010).

Infections

Infections/infectious agents that appear to be causally related to the development of autistic behavior include encephalitis caused by measles, congenital rubella, herpes simplex virus, mumps, varicella, cytomegalovirus, and Stealth virus (Chess, 1971; DeLong et al., 1981; Libbey et al., 2005). Rubella virus was the first known cause of autism (Chess, 1971; Ziring, 2001). In addition, measles and mumps viruses can cause encephalitis that can result in autism later in time (Chess, 1977; Ziring, 1997). The viral infections that cause encephalitis that result in autism often occur *in utero*. However, encephalitis caused by herpes viruses has been documented to cause autism in older individuals (mentioned above). Taken together, these data show that some viruses can cause autism.

Intracellular pathogens

The measles virus, cytomegalovirus, human herpesvirus 6, and the bacterium *Yersinia enterocolitica* have been documented to live inside monocytes in autistic individuals (Binstock, 2001). Effects of these intracellular pathogens manifest as lowered hematopoiesis, lowered peripheral immunity, and altered blood-brain barrier function often accompanied by demyelination. The viruses may induce an immune response, resulting in neuroinflammation, autoimmune reactions, and brain injury. Because the reactivity of the immune system is shifted from a balance of cell- and antibody-mediated activities to favor the latter, pathogens are more capable of hiding inside cells for long periods and then intermittently inducing an immune response during replication cycles, resulting in a chronic pattern of inflammatory disease (Jepson, 2007c).

Imbalance in neural systems

Based on the fact that seizures are associated with autism and that abnormal evoked potentials have been observed in autistic subjects in response to tasks that require attention, several have proposed that autism might be caused by an imbalance between excitation and inhibition in key neural systems including the cortex (Polleux and Lauder, 2004). Three main types of defects have been revealed in autism: the brainstem and cerebellum, the limbic system (amygdala and hippocampus), and the cortex (Bauman and Kemper, 1994, 2005; Courchesne, 1997). Abnormal regulation of brain growth in autism results in early overgrowth followed by abnormally slowed growth (Courchesne et al., 2001). The strongest evidence implicates the glutamatergic and GABAergic and serotonergic systems, with weaker evidence for catechol-aminergic, peptidergic, and cholinergic systems (Polleux and Lauder, 2004). The serotonergic system may be dysregulated in autism; serotonin levels are initially lower than normal but gradually increase to a greater extent than adult levels by 2–15 years of age.

Autoimmune reactions versus brain

There is a serological association of measles virus and human herpesvirus-6 with brain autoantibodies in autism (Singh et al., 1993, 1998, 2002). For example, measles-IgG-positive autistic sera were also positive for brain antigens, i.e., 90% were positive for anti-myelin basic protein and 73% for anti-neuron-axon filament protein. Human herpesvirus-6 antibody in autistic sera was similarly positive for brain antigens, i.e., 84% were positive for anti-myelin basic protein and 72% for anti-neuron-axon filament protein.

In addition, in children with autism, neuron-specific antigens may cross-react with encephalitogenic proteins from milk, *Chlamydia pneumoniae* and *Streptococcus* group A. The antibodies may have been synthesized as a result of an alteration in the blood-brain barrier, allowing preexisting T-lymphocytes and central nervous system antigens access to immunocompetent cells, which may start a vicious cycle (Vojdani et al., 2002).

Environment

A relatively new theory regarding the etiology of autism suggests it may be a disease of very early fetal development (approximately day 20–24 of gestation), with environmental exposures during pregnancy causing or contributing to autism based on the neurobiology of developmental genes (London and Etzel, 2000).

Fetal testosterone levels

An extreme-male-brain theory of autism has been proposed (Baron-Cohen and Hammer, 1997), with subsequent evidence

presented in various manners, including psychometric ways (Baron-Cohen, 1999), social development and attentional focus (Knickmeyer et al., 2005), and sexual dimorphism in human behavior (Knickmeyer and Baron-Cohen, 2006). Autistic traits were documented to be increased following prenatal exposure to abnormally high levels of testosterone caused by congenital adrenal hyperplasia (KnickMeyer et al., 2006). Confirming these studies is the work that links autistic traits with fetal testosterone levels measured in amniotic fluid during routine amniocentesis (Auyeung et al., 2009). Exposure to fetal testosterone was positively correlated with lack of social development and attentional focus.

Other data supporting the influence of fetal testosterone on the development of autism is the negative correlation of prenatal testosterone to the ratio of the length of the 2nd and 4th digits (i.e., 2D:4D) in the left and right hands (Manning et al., 2001). Children with autism had lower than expected 2D:4D ratios and children with Asperger's syndrome had higher than expected 2D:4D ratio in relation to their fathers'. The 2D:4D ratio may be a possible marker for autism that could implicate prenatal testosterone in its etiology.

Medications

Medications may also be implicated in autism. In 1994, the use of thalidomide by the mother provided an environmental contributor to autism (Strömland et al., 1994). Most of the thalidomide victims with autism had anomalies in the external part of their ears but no malformations of the arms or legs. This pattern indicated that the subjects had been injured very early in gestation, 20–24 days after conception (Landrigan, 2010). Because motor neurons develop at the same time as the external ears, one might predict that the thalidomide victims with autism would also suffer from dysfunctions of the cranial nerves. The Strömland study confirmed this prediction. All subjects with autism had abnormalities of eye movement or facial expression, or both. It is probable that the nerve dysfunctions in people with autism reflect an early brain injury that not only affects the cranial nerves but also has secondary effects on later brain development. Many cases of autism are initiated very early in gestation.

Other medications used in early pregnancy are associated with autism (Landrigan, 2010). For example, Misoprostol, a prostaglandin analogue used for prevention of gastric ulcers and in some countries as an abortifacient, was associated with autism following unsuccessful abortion attempts. The mean exposure was in the sixth week post conception. Prenatal exposure (3–4 weeks after conception) to valproic acid, an anti-convulsant, resulted in autism. In addition, maternal rubella infection, with greatest risk in the first 8 weeks after conception, resulted in autism in the child after birth.

Acetaminophen has also been suggested to cause autism (Schultz et al., 2008; Schultz, 2010). Children given acetaminophen after the MMR II vaccine were significantly more likely to become autistic than children given ibuprofen. Aspirin was not involved because it was not considered safe for infants and young children after being implicated in Reye's syndrome (liver and brain damage after viral infection) in the 1980s (Good, 2009) [However, others offered compelling arguments that aspirin was not the cause of Reye's syndrome (Orlowski et al., 2002)]. During pregnancy, mothers of autistic children commonly suffer more bacterial and viral infections (Rodier, 2000) and fevers (Torres, 2003), which could affect the fetus to predispose the child for autism (Meyer et al., 2006). These mothers often take acetaminophen to treat the infections. Acetaminophen overdose depletes the liver's supplies of sulfate and glutathione, impairing its ability to detoxify and excrete harmful substances (Kidd, 2002). Therefore, the fetus could be impaired by the mothers consuming acetaminophen. After birth, if acetaminophen were given to the child, and used repeatedly, the drug could cause depletion of sulfate and glutathione, and the child could regress into autism.

Xenobiotic exposure

Porphyrins, derivatives of the heme synthesis pathway and used as measures of xenobiotic exposure, have been documented to be increased in the urine of autistic individuals (Geier and Geier, 2006a; Nataf et al., 2006). The quantitation of porphyrins allows the identification of environmental exposure that can be correlated with autistic symptoms. Glutathione (GSH) is the most important antioxidant for detoxification and elimination of environmental toxins (Chauhan and Chauhan, 2006). GSH is decreased in the plasma of autistic subjects (Geier and Geier, 2006b; Geier et al., 2009). In addition, GSH plays a major role in methylation and is intimately involved in detoxification processes.

Phthalates

Other environmental agents that have been implicated in autism include the phthalates. Phthalates are a class of high production-volume synthetic chemicals with widespread human exposure because of their use in plastics and other consumer products. Phthalates leach into the environment and expose humans through ingestion, inhalation, and dermal routes. When the concentration of phthalates in the urine of autistic subjects was calculated, there was a significant relationship between the concentration and the degree of autism calculated by teacher-rated ADHD scores (Kim et al., 2009). Polychlorinated biphenyls (PCBs) might also be suspected as causes of autism since prenatal exposures to PCBs have been known to affect cognitive function in infancy through the pre-school years (Jacobson et al., 1992). Prenatal PCB exposure displayed an interaction with the size of the splenium of the corpus callosum (Stewart et al., 2003). In general, the smaller the splenium, the larger was the association between PCBs and errors of commission. In addition, environmental contaminants, including PCBs, herbicides, perchlorates, mercury, and coal derivatives (such as resorcinol, phthalates, and anthracenes) interfere with thyroid function (Román, 2007). The environmental contaminants alone, or in addition to insufficient dietary iodine intake, can affect maternal thyroid function during pregnancy. These outcomes can result in low triiodothyronine (T3) levels in the fetal brain during the period

of neuronal cell migration (i.e., weeks 8–12 of pregnancy) and may produce morphological brain changes leading to autism (Roman, 2007).

Organophosphate pesticides

Organophosphate pesticides, at levels common among the United States children, may contribute to ADHD prevalence (Bouchard et al., 2010). Cross-sectional data from the National Health and Nutrition Examination Survey (2002–2004) were available from 1139 children between 8–15 years of age. Exposure to the pesticides could be prenatal, direct, or from food, drinking water or residential pesticide use. The data prove an association between urinary dimethylalkylphosphate (DMAP) metabolic concentrations (indicative of exposure to dimethyl-containing organophosphate pesticides) and increased odds of ADHD. A primary action of organophosphates is inhibition of acetyl cholinesterase (Sultatos, 1994). Disruptions in cholinergic signaling are thought to occur in ADHD (Nedic et al., 2010). In addition, Chlorpyrifos, an organophosphate insecticide widely used until a few years ago to control insects in schools and homes and still used extensively in agriculture, is a developmental neurotoxicant (Landrigan, 2010).

Other environmental causes

Perhaps, additional environmental causes could be responsible for documented unusual brain growth patterns in early life in autism (Courchesne et al., 2001). The data suggest that autism involves abnormal regulation of brain growth during early life, with an unusual developmental neuroanatomic phenotype characterized by hyperplasia of cerebellar white matter and neocortical gray matter at the youngest ages with slowed growth afterward, slowed growth in the cerebellar hemispheres, and a smaller vermis at all ages examined (i.e., 2 to 16 years). There is evidence of a reduced head size at birth and a sudden and excessive increase in head size between 1–2 and 6–14 months, with brain overgrowth in the first year of life in autistic individuals (Courchesne et al., 2003). Other investigators reported brain volumes were significantly larger for children with autism 12 years old and younger, but those older than 12 (including adults) had brain volumes similar to those of controls. The head circumference was increased in both younger and older groups of autistic individuals, suggesting that those subjects greater than age 12 had increased brain volumes as children. Brain volumes in autistic adolescents and adults were normal, perhaps, due to a slight decrease in brain volume for the autistic subjects at the same time that normal individuals are experiencing a slight increase (Aylward et al., 2002).

There may also be an interaction of genes with the environment. Epidemiology studies have documented the presence of cluster sites of incidence of autism. The number of identified superfund sites correlates with the rate of autism/1000 residents in 49 of the 50 states in the United States ($P = 0.015$, excluding the state of Oregon; Ming et al., 2008). Another report documents that in the location with the highest rate of autism, the rate is higher in schools near EPA Superfund sites ($P = 0.001$; DeSoto, 2009). A cluster site of autism is Brick Township, New Jersey, a rural township close to several Superfund sites (London and Etzel, 2000). Specifically, Brick Township was documented to have four times more prevalence of autism than that of the entire country. Although no causal agents were known, some suspected agents were three contaminants in the drinking water of Brick Township, e.g., tetrachloroethylene, trichloroethylene, and trihalomethanes. The trihalomethanes were associated with a two-fold increase in neural tube defects in the same township. This finding supports research suggesting that autism may be caused by a neural tube defect (Rodier, 2000).

Summary

Autism has increased to epidemic proportions, affecting four times as many males and females. With a prevalence of 1/110 in the United States, 1/64 in the United Kingdom, and similar ratios in many other countries, a very significant threat to future generations is evident. This review cites documentation of causes of autism, including genetic mutations/deletions, viral infections (i.e., rubella and herpes), and encephalopathy following vaccination.

It is possible that autism results from more than one cause, with different manifestations in different individuals that share common symptoms. Integrating the data presented here, a hypothesis is that autism is the result of genetic defects, with the contributory effect of advancing age of the parents, and/or inflammation of the brain. The inflammation could be caused by a defective placenta, an immature blood-brain barrier, the immune response of the mother to a viral or bacterial infection, a premature birth, encephalitis in the child after birth, or a toxic environment. Also, intracellular pathogens could induce an immune response, resulting in neuro-inflammation, autoimmune reactions, brain injury, and autism.

Conclusion

Autism has been documented to be caused by genetic defects and/or inflammation of the brain. The inflammation could be caused by a wide variety of environmental toxicants, infections, and co-morbidities in individuals genetically prone to the developmental disorder.

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Declaration of interest

The author reports no conflicts of interest. The author is alone responsible for the content and writing of the paper.

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