Preventable cases of autism: relationship between chronic infectious diseases and neurological outcome

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There is evidence that chronic infections and the immune reactions associated with them may contribute to causing autism spectrum disorders. These infections include *Babesia*, *Bartonella*, *Borrelia burgdorferi*, *Ehrlichia*, *Human herpesvirus-6*, *Chlamydia pneumoniae* and *Mycoplasma* (in particular *Mycoplasma fermentans*). Maternal immune reactions to infections appear to adversely affect fetal brain development and possible pathophysiological mechanisms include both inflammatory cytokines, such as IL-6, and maternal autoantibodies to fetal neural tissue of the same kilodalton mass as those seen with *B. burgdorferi* and some other chronic infections. The timing of the infection and immune response is critical in determining the pathophysiology. It is advisable to evaluate women who are pregnant or planning on becoming pregnant for chronic infections, especially if they demonstrate symptoms of an infection or a systemic illness with persistent inflammatory symptoms. The mother and the newborn should be treated when indicated.

Family case report

This article includes brief clinical summaries and single photon emission tomography (SPECT) scans of a mother and her three children who have all been diagnosed with autism spectrum disorders (ASDs). The 48-year-old mother had previously been diagnosed with chronic fatigue syndrome, possible multiple sclerosis and depression (Figure 1). Three of her four children had ASD. Subsequently, she and the three children were diagnosed with a number of chronic infections and were treated with different degrees of effectiveness. The presence of *Borrelia burgdorferi* was confirmed by testing from IGeneX Labs, CA, USA, and the presence of the viral infections were confirmed at Medical Diagnostic Laboratories, NJ, USA. The 23-year-old daughter was treated extensively with antibiotics, subsequently became pregnant and gave birth to a normal healthy infant with an Apgar score of 10 and normal developmental milestones (Figure 2). Retrospectively, the maternal grandmother had cognitive impairments and Asperger's traits. She was positive for *B. burgdorferi* (the causative agent of Lyme disease) by ELISA and western blot. There was *B. burgdorferi* present in her heart tissue upon autopsy confirmed by microscopy and polymerase chain reactivity and she died from multiple myeloma, which was considered to have had a possible infectious etiology. This case raises the question of whether ASD could have been prevented by effective antimicrobial treatment for the maternal grandmother or the mother before or during pregnancy or by treating the children at an early point in development (Figures 2–4).

The mother had a diagnosis of chronic fatigue syndrome, multiple sclerosis, depression and possible congenital Lyme disease. She had an acute episode of mononucleosis while pregnant with the son. The SPECT scan demonstrates an extensive hypoperfusion pattern, predominantly in the cerebral cortices and much of the frontal lobes, with a lesser degree in the temporal lobes and a small degree of hypoperfusion in the cerebellum. The hypoperfusion is moderately extensive and is likely associated with toxic, inflammatory and infectious processes. There is hyperperfusion of the basal ganglia, which is associated with anxiety and mood dysregulation (Figure 1). Laboratory testing was positive for *B. burgdorferi*, *Babesia duncani*, *Bartonella henselae*, *Mycoplasma fermentans*, *Human herpesvirus* (HHV)-6, Epstein–Barr virus (EBV), high antistreptolysin-O titer and gamma streptococci in stool.

The 26-year-old son is low functioning with autism since 2 years of age and has also been diagnosed with grand mal seizures, movement disorder, ataxia, hypotonia, megacolon, possible mitochondrial disorder, mild hypergammaglobulenmia and syncope. There are some motion artifacts; however, significant hypoperfusion pattern is both focal as well as generalized. The SPECT scan demonstrates

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Keywords

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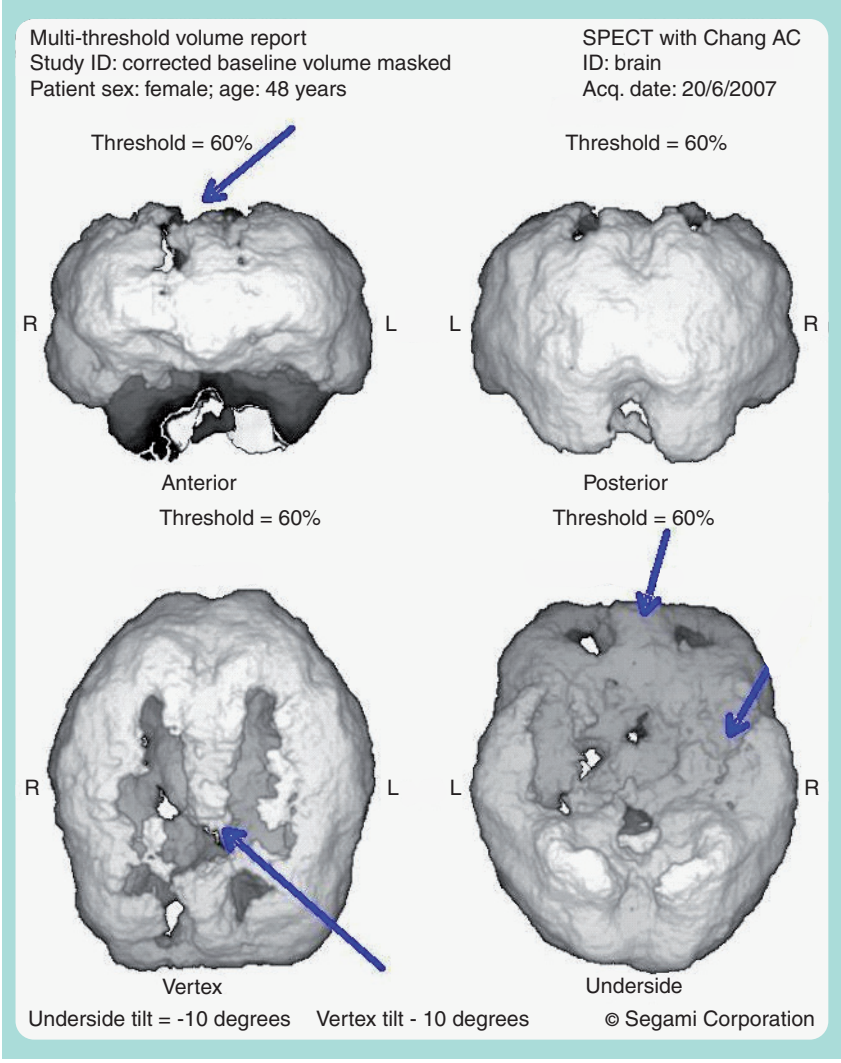

Figure 1. 48-year-old mother diagnosed with chronic fatigue syndrome and multiple chronic infections.
Acq.: Acquisition; Chang AC: Chang's single iteration method for attenuation compensation; SPECT: Single photon emission computed tomography.

a focal pattern throughout the cerebral cortex bilaterally and the cerebellar hemispheres, which demonstrate atrophy on MRI. There is mild hyperperfusion of the basal ganglia and a focally intense hypeperfusion area in the deep white matter of the temporal lobe. There is a hyperperfusion pattern involving the temporal lobes and cerebellar hemispheres. The focal decrease is more suggestive of etiologies that would include hypoxic, neuroimmune, traumatic factors, infectious and inflammatory processes. There is a hyperperfusion pattern of the basal ganglia, which may be associated with an element of anxiety, whereas the focal intense areas can be associated with present interictal seizure focus and are clinically significant as the present dose of anticonvulsant is not controlling this area. Laboratory testing was positive for *B. burgdorferi*, *B. duncani*, *B. henselae*, *M. fermentans*, HHV-6, EBV and high-streptococcal titers; the stool was positive for *Citrobacter freundii*, *Klebsiella pneumoniae* and gamma streptococci (Figure 3).

The 23-year-old daughter was diagnosed with Asperger's syndrome, obsessive compulsive disorder, generalized anxiety, social anxiety disorder, depression, post-traumatic stress disorder from an autoaccident, possible narcolepsy, tremors, cardiac disease, myocardial infarction, osteopenia and arthritis with psuedo rhematoid nodules since 5 years of age. The SPECT scan demonstrates an extensive hyperperfusion pattern in the cerebral cortices, temporal lobes and cerebellum and hypoperufsion of the frontal lobes and is likely associated with toxic, inflammatory and infectious processes. Laboratory testing was positive for *B. burgdorferi*, *Anaplasma phagocytophilum*, *M. fermentans*, *Haemophilus*, HHV-6, EBV, elevated streptococcal titers; stool was positive for toxoplasmosis, cornybacteria and gamma streptococci (Figure 2).

The 20-year-old daughter was diagnosed with ASD since 14 months, petit mal seizure disorder, hypotonia, perceptual impairments and anxiety. The SPECT scan demonstrates a seizure focus with hyperperfusion in the right cerebellar hemisphere. There is extensive hypoperfusion in the frontal lobes, temporal lobes and to a lesser degree to the occipital lobes and slightly to the cerebellum. There is hyperperfusion in the right cerebellar hemisphere. The hypoperfusion is likely associated with neuroinflammatory, neuroimmunological, infectious and toxic substance exposure. Laboratory testing was positive for *B. burgdorferi*, *B. henselae*, *M. fermentans*, HHV-6; the stool was positive for *Parvovirus B-19*, *K. pneumoniae*, *C. freundii* and gamma streptococci (Figure 4).

Defining autism & autism spectrum disorders

Autism is a group of disorders with proposed differing causes but common symptoms, which include impaired social interaction, impaired communication, stereotyped or repetitive interests or behaviors that may involve developmental arrest, slowing or even regression, most commonly apparent by 14–24 months of age [1,2]. ASD is a broader term that includes autism disorder, Asperger's disorder, Rett's disorder, childhood disintegrative disorder and pervasive developmental disorder not otherwise specified [1]. ASD may frequently be comorbid with seizure disorders, mental retardation

(30% mild-to-moderate; 40% serious-to-profound), attention-deficit hyperactivity disorder (ADHD), gastrointestinal disorders, immune dysregulation, sleep disorders and hearing and visual impairments, and may be comorbid with any psychiatric diagnosis.

Increased reporting of autism spectrum disorders

There have been increased reports and an increased concern in the media regarding ASD. For example, in 1992 only 15,580 children in the US school system were classified with ASD, in 2002 this increased to 407,578 and currently, 560,000 in the USA have ASD [3,201,202]. In the UK, researchers at Cambridge University's Autism Research Centre have estimated that one in 58 children suffer from some form of the disorder, compared with previous estimates of approximately one in 100 [203]. In 2000, a survey of eight states identified regional patterns with one in 150 children in the USA with ASD, with the highest rate in New Jersey at 9.9 in 1000 and the lowest rate in West Virginia at 5.1 in 1000 [204]. Studies in the past 15 years have suggested the prevalence of autism is rising and media coverage has indicated the presence of an autism epidemic; however, some have questioned whether such an epidemic is fact or artifact [3–5]. Regardless of whether there is an increased prevalence or just an increase awareness, it can cost approximately US $3.2 million to care for one autistic person in his or her lifetime and the prevention of ASD is a high priority when considering the total financial burden, including lost productivity and the human cost to families and caregivers [6].

Known causes of autistic spectrum disorders

Unlike many other neurological impairments, symptoms of ASD are often not apparent at birth, which increases the difficulty in determining the cause–effect relationships. The known and mostly rare causes of ASD include fragile X syndrome, tuberous sclerosis, cerebral palsy, phenylketonuria, neurofibromatosis, Rett's syndrome, Rasmussen's encephalitis, Lennox–Gastaut syndrome, pyruvate dehydrogenase deficiency, impaired purine metabolism (whereby uric acid is increased), brain structural anomalies (e.g., cyst), phenylketonuria, Angelman's syndrome, Landau–Kleffner syndrome, Prader–Willi syndrome, Williams syndrome and multiple other genetic impairments. In one study, ASD has also been associated with older paternal age. Some research attention has been focused upon vaccines, toxins, nutrition and other environmental triggers. Although the cause of some cases of ASD is known, the cause of the majority of ASDs is still unexplained. Congenital rubella, syphilis and toxoplasmosis have long been associated with causing ASD and other neurological impairments. However, these infections can still explain only a very limited number of preventable cases of ASD and research into other possible infectious contributors has been limited.

Can autism be associated with chronic infections?

Historically, acute rubella infections have been a pathophysiological model for acute infections contributing to the cause of autism and other neurological impairments. A study conducted after the 1964 rubella outbreak in

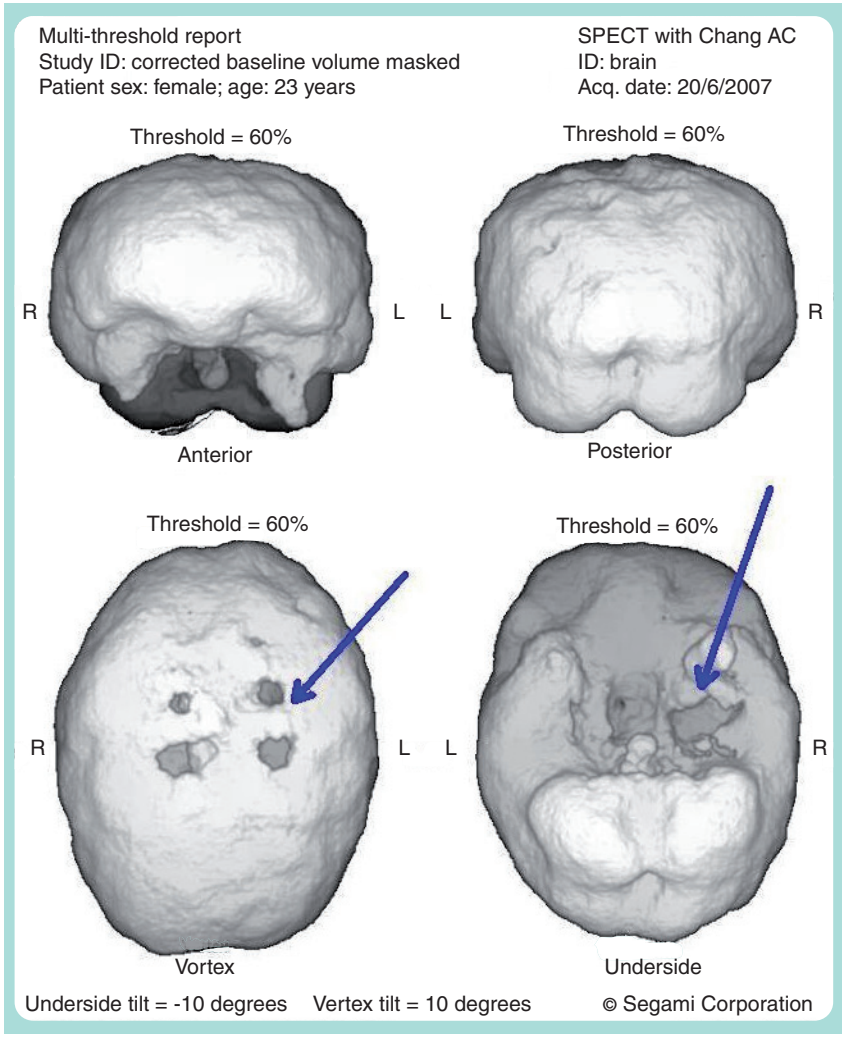

Figure 2. 23-year-old daughter with autism spectrum disorder and multiple chronic infections.
Acq.: Acquisition; Chang AC: Chang's single iteration method for attenuation compensation; SPECT: Single photon emission computed tomography.

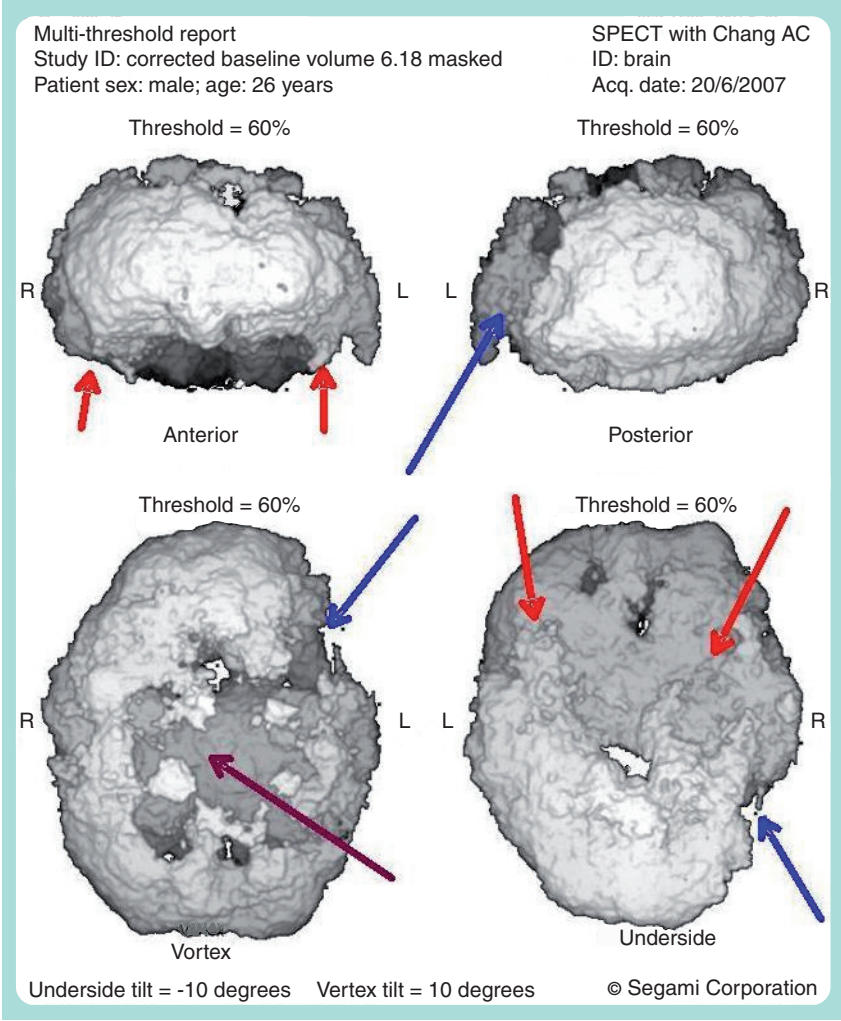

Figure 3. 26-year-old son diagnosed with autism and multiple chronic infections.
Acq.: Acquisition; Chang AC: Chang's single iteration method for attenuation compensation; SPECT: Single photon emission computed tomography.

New York City, NY, USA found autism rates much higher than normal in children born to pregnant women infected with rubella [7]. A subclinical rubella infection in a vaccinated woman has also been reported [8]. Syphilis has long been a pathophysiological model for chronic infections contributing to the cause of neuropsychiatric illnesses including autism. More recently, the role of other chronic, low-grade, relapsing infections has been considered as well. These infections may present with more subtle symptoms and clinical findings and are more difficult to detect. Since most cases of autism are still unexplained, and in view of the very high human and economic cost of autism, insight into every possible contributor or cause of autism may assist towards the development of possible preventative strategies. This article investigates the evidence that chronic infections in the mother or newborn child may contribute towards causing autism, ASD and other neurological impairments, and we discuss the possible preventative options.

What is the pathophysiology of autistic spectrum disorders?

Since monozygotic twins are 70–90% concordant, there are significant genetic predisposing factors [9]. Data suggest that autism results from multiple etiologies with both genetic and environmental contributions, which may explain the spectrum of behaviors displayed in this disorder [10]. Environmental insults contributing to ASD may include a complex interaction with infections, heavy metals, biotoxins, allergens, nutritional excesses/deficits and, possibly, vaccines. In addition, physiological and psychological changes associated with chronic unremitting stress contribute to chronic psychiatric symptoms and a chronic immunocompromised and inflammatory state [11]. Neurological disease precipitated by an interaction of these environmental insults and susceptibility factors often results in a pathogenic interaction that includes inflammation, oxidative stress, mitochondrial dysfunction and excitotoxicity resulting in neuronal dysfunction [12]. In the developing brain, these processes can adversely affect cell proliferation, migration, differentiation, synaptogenesis, myelination and apoptosis, which can contribute to the development of autism [13].

Theoretical issues: genes & infections

Mendel stated that human traits are determined by individual genes that function independently of other genes and of environmental influences, while Koch stated that many human diseases are caused by microbes, which exert their effect independently of other microbes, environmental factors and genes. These theories, which advanced science at one point in history, can prevent further progress if they are not revised with currently expanding knowledge. Just as the theories of Newton were revised by Einstein, those of Mendel and Koch also need revision. Yolken revised these theories by stating, "most common human diseases are caused by the interaction of environmental insults and susceptibility genes. Many of the susceptibility genes are diverse determinants of human response to environmental factors to infection and prevention or treatment of the infections may result in the effective treatment of complex disorders" (Figure 5) [14].

A complex disease model that incorporates multiple variables is needed to explain the causes, pathophysiology and multiple presentations of ASD.

What are the genes?

A significant number of the genes associated with ASD are genes related to the immune system. For example, a group of genes with known links to natural killer cells, the first to attack viruses, bacteria and malignancies, are expressed at high levels in the blood of children with autism when compared with children without the disorder [15]. Genes alone do not tell the whole story. Recent increases in chronic diseases such as diabetes, childhood asthma, obesity or autism cannot be due to major shifts in the human genome. They must be due to changes in our environment [205].

What are the environmental contributors?

The geographical patterns seen with ASD also suggest environmental contributors and many possible environmental explanations have been proposed. We are witnessing a rapidly changing environment that includes globalization and increased exposure to various toxins in the environment. Globalization has resulted in the spread of parasites throughout the world to populations that may have had limited or no exposure or resistance to these organisms and may be quite susceptible to their pathogenic effects. In addition, biotoxins, inorganic toxins and heavy metals can be both toxic and conducive to the proliferation of parasites in the environment. Mercury toxicity is one of the toxins proposed to contribute to the development of ASD. Although controversy surrounds this issue, recent evidence has been more supportive of this association [16]. Epidemiological studies have reported mixed results. Higher prevalence of autism has been associated with geographical regions with higher environmental mercury release, higher precipitation rates and higher prevalence of Lyme disease [17–19].

Infections causing psychiatric illness

The original model for infections causing mental illness was syphilis, an infection with *Treponema pallidum pallidum*. After the introduction of the polio vaccine, penicillin and other antibiotics, it was felt the war against infectious diseases had been won and infectious causes of chronic illnesses were often not considered.

Although psychiatric conditions are well categorized and defined according to symptoms with the American Psychiatric Association Diagnostic and Statistical Manuals, the cause of most psychiatric illness is unknown [1]. Since mental illness often begins early and persists throughout life, degenerative disease cannot explain the cause of most psychiatric illness. There is a large body of research documenting that infectious disease can cause mental illness.

The same syndrome may be caused by different infections in different individuals, but the same infection can cause different syndromes in different individuals. For example, obsessive compulsive disorder has been caused by *Streptococcus*, Lyme disease, Hong Kong and other flu strains, *Coxsackievirus*, toxoplasmosis, *Mycoplasma* and the pandemic flu of 1918 [20]. However, many of these infections have been documented to cause other psychiatric and somatic symptoms. For example, Hajek

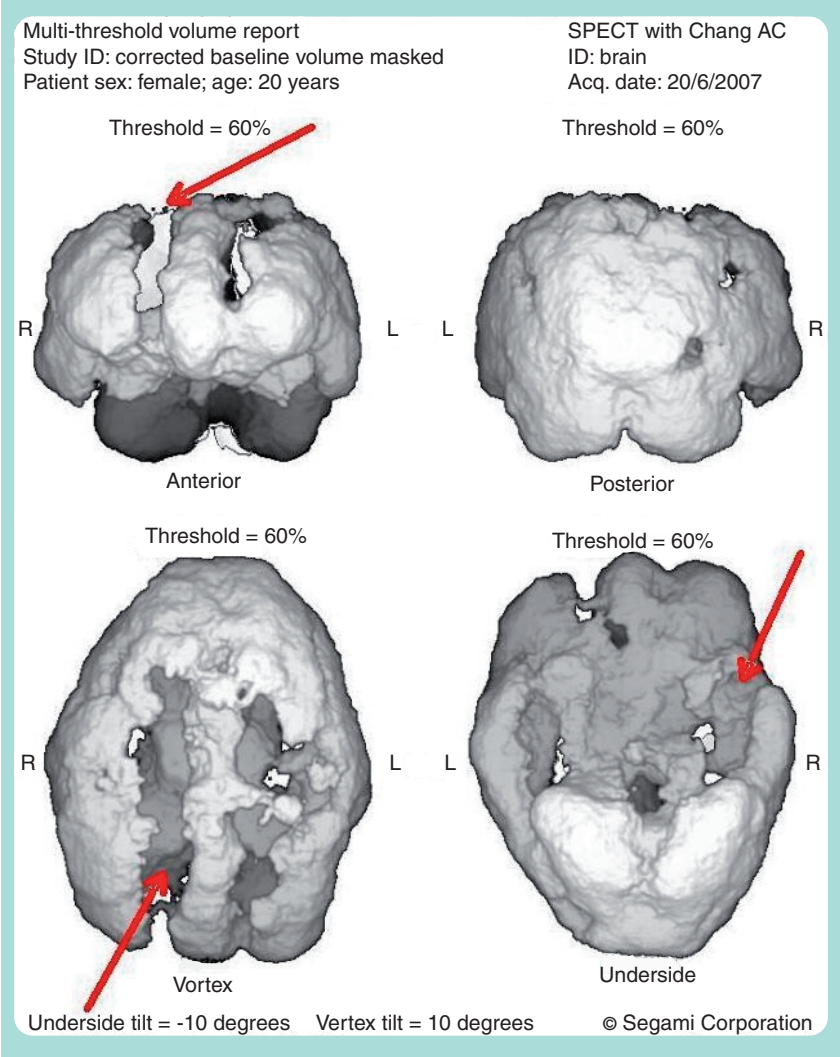

Figure 4. 20-year-old daughter diagnosed with autism spectrum disorder and multiple chronic infections.
Acq.: Acquisition; Chang AC: Chang's single iteration method for attenuation compensation; SPECT: Single photon emission computed tomography.

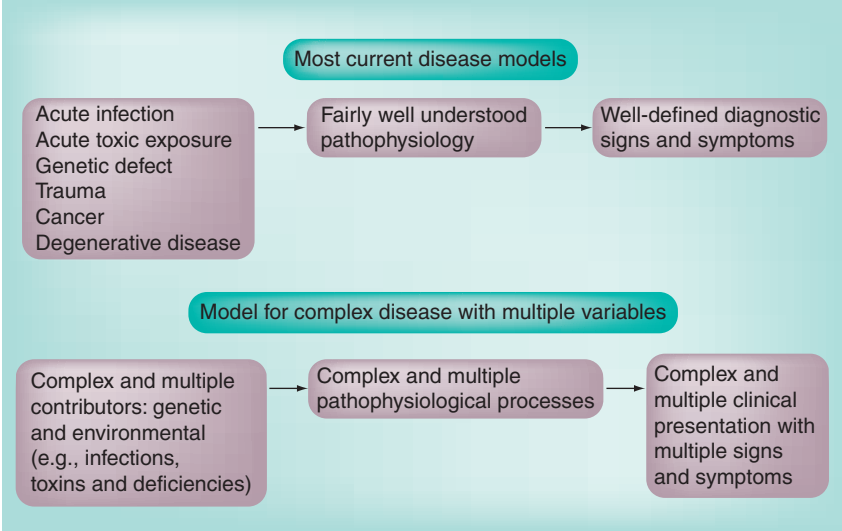

Figure 5. Disease models.

demonstrated the same infection, *B. burgdorferi*, can be associated with many different psychiatric diagnoses [21]. Some infections result in residual injury and are no longer present, while others may persist in a chronic relapsing and remitting state. Chronic persistent infections are more commonly viral, venereal and zoonotic vector-borne. The WHO defines zoonotic diseases as infections that are naturally transmitted between vertebrate animals and man (Box 1).

Infections & the developing fetus

Infections associated with pregnancy may be transplacental, perinatal or postpartum. In addition, infections in the mother may indirectly affect the developing fetus through immune-mediated effects even when the fetus is not actually infected. Adverse effects from infections upon the fetus include fetal death, prematurity, intrauterine growth retardation, congenital disease and also developmental abnormalities that may not be apparent at birth. It has been recently recognized that prenatal exposed to maternal cystitis, pyelonephritis, diarrhea, coughs and/or vaginal yeast infections resulted in an increased risk for epilepsy in childhood [22].

In evaluating the association between infections and schizophrenia, a review of over 250 studies in different geographical regions have demonstrated that the incidence of schizophrenia of people born in the winter or spring is 5–8% higher than average. It was initially hypothesized that viruses, which are more prevalent during the fall, may be causative [23]. Polio and several flu epidemics have been associated with an increased incidence of schizophrenia [24]. Since the 1950s, more than a dozen epidemiological studies have suggested that a pregnant woman's exposure to influenza directly increases her child's risk of developing schizophrenia [206]. Infants born to mothers exposed to the flu only during the first trimester had a sevenfold greater risk of developing schizophrenia [25]. More recent studies have also demonstrated an association between schizophrenia and antibodies to *Toxoplasma gondii* [26], Chlamydophila [27] and *Herpes simplex virus 2* [28].

Prenatal exposures to certain infections are immunogenic. Inflammatory cytokines can play a key role in the link between prenatal exposure to infection and the risk for schizophrenia by significantly reducing dendrite development and complexity of developing cortical neurons [29]. In addition, it appears prenatal exposure to certain infections can also induce maternal autoantibodies that cross-react with proteins in the developing fetal brain, resulting in aberrant fetal neurodevelopment [30].

Infectious link with autism spectrum disorder

As aforementioned, *T. pallidum pallidum* (syphilis), rubella and *Toxoplasma gondii* have been recognized for causing congenital neurological symptoms. Although rubella and syphilis are well-understood models for causing ASD, these two infections are relatively uncommon now and the significant incidence of ASD cannot be explained. An association between infections during fetal development and in infancy with autism, ASD and autistic symptoms in children has been noted by a multiple clinicians and parents and in the medical literature. A closer review of more recent research has expanded the list of infections associated with causing ASD. A number of infections have been associated with causing symptoms of ASD or Klüver–Bucy syndrome, which is associated with ASD, including rubella [10,31], *Herpes simplex virus* [32,33], Herpes virus family [10], *Borna* (animal models) [10,34], varicella [25], *Cytomegalovirus* [35–37], *Mycoplasma pneumoniae* [38], *M. fermentans, Mycoplasma genetalium, Mycoplasma hominis,* HHV-6, *Chlamydia pneumoniae* [39–41], *Shigella* [42], syphilis [25], neurocysticercosis [43], malaria [44], toxoplasmosis [36,45], *Blastocystis* [46,47], *Rubeola* [48,49], *B. burgdorferi* and other tick-borne diseases [19], unknown [50] and yet unrecognized infections (Box 2) [51].

Acute versus chronic infections

Infections adversely impacting the developing nervous system may be either acute or chronic and persistent and may cause neurological impairments through a number of pathophysiological

processes. The acute infections are more readily recognized and are treated more aggressively, while chronic persistent infections are more easily overlooked and less effectively treated. The chronic infections may be associated with biofilms that are created by multiple organisms interacting in a manner that perpetuates their survival in the host, and stealth pathogens that have adaptive mechanisms to evade elimination by the immune system [52]. Physicians are trained to recognize and treat the acute symptoms of acute infectious diseases; however chronic infections associated with chronic symptoms may be more significant in causing persistent immune reactions and psychiatric symptoms. Most commonly, these infections may have an

Box 1. Some microbes associated with mental symptoms & mental illness.

Spirochetes

- *Borrelia afzelii* (Lyme disease in the UK and the rest of Europe)
- *Borrelia burgdorferi sensu stricto* (Lyme disease in the USA, UK and rest of Europe)
- *Borrelia garinii* (Lyme disease in the UK and rest of Europe)
- *Borrelia hermsii* (relapsing fever)
- *Borrelia turicatae* (relapsing fever)
- *Leptospira* (Leptospirosis)
- *Treponema pallidum pallidum* (syphilis)

Bacteria

- *Anaplasmas phagocytophilum* (human granulocytic ehrlichiosis)
- *Bartonella henselae* (cat scratch fever)
- *Bartonella quintana* (trench fever)
- *Bartonella rochalimae* (bartonellosis)
- *Chlamydophilia pneumoniae* (chlamydia)
- *Chlamydophila psittaci* (chlamydia)
- *Coxiella burnetti* (Q-fever and post-Q fever fatigue syndrome)
- *Ehrlichia chaffeensis* (human monocytic ehrlichiosis)
- *Francisella tularensis* (rabit fever or tularemia)
- *Haemophilus influenzae* (haemophilus)
- *Listeria*
- *Meningococcus* (meningococcal meningitis)
- *Mycoplasma fermentans*
- *Mycoplasma pneumoniae*
- *Mycobacterium tuberculosis* (tuberculosis)
- *Rickettsia akari* (rickettsialpox)
- *Rickettsia rickettsii* (rocky mountain spotted fever)
- *Rickettsia* species (eastern tick-borne rickettsiosis)
- *Shigella* (shigellosis)
- *Streptococcus pneumoniae* or pneumococcus (pneumonia)
- *Streptococcus* (pediatric autoimmune diseases associated with *Streptococcus*, Sydenham's chorea and St Vitus dance)

Yeast

- *Candida albicans* (candidiasis)
- *Candida dubliniensis*

Box 1. Some microbes associated with mental symptoms & mental illness (cont.).

Prion

- Variant Creutzfeldt–Jakob

Viruses

- Borna virus
- *Coltivirus* (Colorado tick fever)
- *Coxsackievirus*
- *Cytomegalovirus*
- *Enterovirus*
- *Flaviviridae* virus (Japanese B encephalitis)
- Hepatitis C virus
- Herpes virus family
- Human endogenous retroviruses
- *Human herpesvirus 4* or Epstein–Barr virus
- HIV
- Influenza A virus subtype H3N2 (Hong Kong flu)
- Influenza virus
- Pandemic influenza of 1918
- *Papopavirus*
- *Paramyxovirus* (measles virus)
- *Parvo B19*
- *Poliovirus*
- Rabies virus
- Rubella
- Toga virus
- Varicella zoster virus (chicken pox)
- Viral meningitis
- West Nile virus

Protozoa

- *Plasmodium* (malaria)
- *Babesia microti* (babesiosis)
- *Babesia duncani* (babesiosis)
- Other *Babesia* species (babesiosis)
- *Toxoplasma gondii* (toxoplasmosis)

Parasites

- *Blastocystis* (blastocystosis)
- *Taenia solium* (neurocysticercosis or cysticercosis)

Fungal

- *Cryptococcoccus*
- Coccidiomycosis
- Histomycosis

Box 2. Infections associated with autism spectrum disorders or Klüver-Bucy syndrome.

- *Babesia*
- *Bartonella*
- *Blastocystis*
- *Bornavirus* (animal model)
- *Borrelia burgdorferi* and other tick-borne diseases
- *Chlamydia pneunomiae*
- *Cytomegalovirus*
- *Ehrlichia*
- *Herpes simplex virus*
- Human herpesvirus-6
- Herpes virus family
- *Mycoplasma fermentans*
- *Mycoplasma genitalium*
- *Mycoplasma hominis*
- *Mycoplasma pneumoniae*
- *Plasmodium* (malaria)
- Rubella
- Rubeola
- *Shigella*
- *Taenia solium* (neurocysticercosis)
- *Toxoplasma gondii* (toxoplasmosis)
- *Treponema pallidum pallidum* (syphilis)
- Varicella
- Unknown viral and other infectious

adverse effect upon the fetus by causing an aberrant immune reaction that has an adverse effect upon the developing fetus.

Infections & neuroanatomy

One hypothesis to explain autism is the amygdala theory of autism, which states there is a network of neural regions that comprise the social brain and this includes the amygdalae. Since the childhood psychiatric condition of autism involves deficits in perceiving and responding to social cues, it is hypothesized that autism may be caused by an amygdala abnormality and the Klüver–Bucy syndrome is an experimental model that partially replicates autism [53,54]. Klüver and Bucy removed the temporal lobes bilaterally in rhesus monkeys, which resulted in them developing visual agnosia (inability to recognize objects or faces), emotional changes, hypermetamorphosis (a desire to explore everything), oral tendencies, hypersexualism and flattened emotions (placidity). The monkeys became emotionally dulled with less expressive facial expressions. They were also less fearful of things that would have instinctively evoked fear. For example, they would approach a snake, even after being attacked by it (placidity). Patients with trauma to the temporal lobes may demonstrate some features of this syndrome, including other temporal lobe symptoms, such as memory disorders, flattened emotions, bulimia, communication impairments and visual agnosia.

Other major anatomical structures associated with autism include the cerebral cortex, hippocampus, basal ganglion, corpus callosum, brain stem and cerebellum. On a microscopic level, loss of Purkinje cells in the cerebellum are also involved in cases of ASD.

Infection or immune reaction to infection?

The placenta is considered to prevent most viruses, bacteria and parasites from entering the developing fetus. There are known exceptions such as rubella, syphilis and *B. burgdorferi*. Many infections, such as influenza, are localized to the nasal passages and airways and do not appear to cross the placenta. Therefore, these infections most likely affect the fetus by evoking a reaction in the mother's immune system or possibly the fetus's or infant's immune system.

Inflammatory signals are propagated across the intact or ruptured blood–brain barrier to the CNS by proinflammatory cytokines, prostaglandins or lipopolysaccharides. These changes can then trigger microglia to release cytokines, oxygen free radicals and trophic factors, which can adversely influence dendritic length and spine density, dopaminergic cells, neurogenesis, glial proliferation, white matter functioning, emotional stability and cognition [55]. Infections that cause immunological events in early fetal life can adversely affect these brain developmental processes and predispose the developing nervous system to undergo additional failures in subsequent cell migration, target selection, and synapse maturation and pruning that may eventually lead to multiple brain and behavioral abnormalities that become apparent later in life [56].

Animal models of maternal immune reactions

Maternal immune reactions in pregnant rodents result in offspring with gene expression, histology and behavioral abnormalities with similarities to schizophrenia and autism. One study demonstrated that IL-6 mediated these effects. A maternal injection of this cytokine in early pregnancy resulted in deficits

in the adult offspring. By contrast, coadministration with an anti-IL-6 antibody normalized gene expression and behavior in the adult offspring [57].

In a mouse model, respiratory infection with influenza virus leads to behavioral abnormalities in the adult offspring. These behaviors are consistent with abnormalities seen in schizophrenia and autism, including deficits in social interaction. The adult offspring display neuropathology in the cortex and hippocampus similar to that found in schizophrenia and a localized deficit in Purkinje cells that resembles that in autism. The cause of these abnormalities was the maternal response to viral infection, since treatment of uninfected, pregnant mice with the double-stranded ribonucleic acid polyinosinic-polycytidylic acid (which evoked an antiviral-like immune response) also caused the same deficits and Purkinje cell changes in the offspring. Similar Purkinje cells losses have been observed in post-mortem brains of people with autism [58].

The timing of infection is crucial for some infections. When pregnant mice are injected with flu virus on embryonic day 9, there are significant changes in more than 200 genes of the cerebellum [59]. By contrast, injecting the mice on embryonic day 18 generates significant alterations in gene expression in the frontal, hippocampal and cerebellar cortices of the fetal brain [60]. When mice are injected on embryonic day 16, it affects the expression of genes involved in the production of myelin and these associated genes may be more significant with autism [61,206]. Brain developmental processes (i.e., cell proliferation, migration, differentiation, synaptogenesis, myelination and apoptosis) occur at vulnerable periods during development of the nervous system and are sensitive to environmental insults, and changes in these processes can contribute to autism [61].

Could maternal antibodies to infections cause autism spectrum disorders?

Rhesus monkeys gestationally exposed to IgG class antibodies from mothers of children with ASD consistently demonstrated increased whole-body stereotypes and were also hyperactive compared with controls [62]. Another study demonstrated that the sera of mothers of autistic children exposed to prenatal rat brain proteins presented specific patterns of reactivity in immunoblotting when compared with controls [63]. Three studies analyzed IgG antibodies associated with autism. One study demonstrated as association with autism and 37 and 73 kDa maternal antibodies on western blot testing of the serum of mothers of autistic children [64]. A second study demonstrated an association with 36, 39 and 61 kDa maternal antibodies on western blot testing of serum from mothers with autistic children [65]. A third study of serum from mothers who subsequently gave birth to autistic children measured maternal autoantibody reactivity by western blot to fetal brain tissue. Reactivity to a band at 39 kDa was more common among mothers of children with autism (7%) compared with the control mothers and control subjects and simultaneous reactivity to bands at 39 and 73 kDa was found only in mothers of children with early onset autism [66]. Therefore, the 36, 37, 39, 61 and/or 73 kDa bands on western blot testing may be associated with something that provokes am immune reaction and contributes to causing autism. In addition, reactivity of the 37 kDa band is associated with three species of *Mycoplasma* [67–69]. The 73 kDa band is associated with *C. pneumonia*, *Streptococcus pneumoniae* and *Mycoplasma* [70–72]. Both the 37 and the 73 kDa bands are associated with *B. henselae* and *Bartonella quintana* [73]. The 36 and 37 kDa bands may represent the same antibody and is a marker for Lyme neuroborreliosis [74]. The 37 and 39 kDa antibodies are highly specific for *B. burgdorferi* infections. A 60 or 62 kDa antibody is found in Lyme borreliosis and 73 kDa proteins of *B. burgdorferi* are dominant immunogens and expressed in all strains of *B. burgdorferi* [75].

Other pathophysiological findings

Most neurological diseases are associated with a gene–environment interaction. Parasites may adversely affect the host by a number of mechanisms, including cell penetration, toxin release and incorporation of parasite genes into the host genome. The host response may then contribute to the pathophysiology by a number of processes that may include cytokine release, antibodies, inflammation and other cellular responses. This, in turn, results in pathological cascade that includes oxidative stress, inflammation, excitotoxicity and mitochondrial dysfunction resulting in neural dysfunction [76]. Chronic intracellular infections (e.g., *Mycoplasma*, *Borrelia* and *Chlamydia*) cause increased oxidative stress by their release of reactive oxygen species and stimulation of reactive oxygen species in mitochondria. This causes increased oxidation of mitochondrial

lipid membranes and proteins and loss of mitochondrial function. The same process is seen in adults who acquire these chronic infections; however, the consequences are different upon a fully developed brain [40].

Altered tryptophan metabolism is seen with chronic infections that adversely affect the CNS. Inflammation and proinflammatory cytokines result in increased indoleamine 2,3-dioxygenase, which increases the levels of neurotoxins, quinolinic acid and 3-hydroxykynurenine and decreases the levels of serotonin and kynurenic acid, which is neuroprotective [77–79].

Changes in lymphocytes are noted in both ASD and chronic infections. Changes in populations of natural killer cells are noted in the blood of autistic children when compared with children without the disorder and these changes are noted in changes in gene expression associated with these cells [80]. Invasion and cytopathic killing of human lymphocytes and reduced natural killer cells subsets have been noted in chronic infectious diseases [81,82].

A number of metabolic changes are noted in both autism and chronic infections. These include disorders of the oxidoreductive system in cerebrospinal fluid and serum, increases of superoxide dismutase, increased glutathione peroxidase activity, decreased glutathione levels, increased concentration of serum malondialdehyde, alterations in homocysteine or methionine metabolism, and impaired methylation and sulfation (Figure 6) [83–87].

Box 3. Chronic infections associated with autism spectrum disorder.

- *Babesia*
- *Bartonella*
- *Blastocystis*
- *Borrelia burgdorferi*
- *Chlamydia pneumoniae*
- *Cytomegalovirus*
- *Ehrlichia*
- *Herpes simplex virus*
- Herpes virus family
- *Human herpesvirus-6*
- *Mycoplasma fermentans*
- *Mycoplasma genetalium*
- *Mycoplasma hominis*
- *Mycoplasma pneumoniae*
- *Plasmodium*
- *Taenia solium*
- *Toxoplasma gondii*
- *Treponema pallidum pallidum*

Chronic infections associated with autism spectrum disorder

A number of chronic infections have been associated with ASD (Box 3). However, what infections may be the most significant at this point in time? The author and colleagues previously described an association between ASD and Lyme disease and other tick-borne diseases including *Mycoplasma*, *Bartonella*, *Ehrlichia* and *Babesia*. Nicholson has demonstrated an association between ASD and *M. fermentans, M. genetalium, M. hominis,* HHV-6 and *C. pneumoniae.* He also noted an association between Gulf war syndrome and ASD in the children of these veterans associated with mycoplasma infections [40]. The association between ASD and *M. fermentans* appears to be particularly significant. There are a number of reports and citations of maternal transmission of Lyme disease and associated adverse events [88–95]. Gardner reviewed 263 cases of congenital and gestational Lyme borreliosis in the literature. A total of 66 of the 263 were associated with adverse outcomes and 15% of the 263 cases had neurological malformations [96]. Jones *et al.* performed a comprehensive case history review on the charts of 102 gestational cases of *B. burgdorferi* and other tick-borne disease infections. Of these cases, 9% had been diagnosed with autism and 56% with ADHD. Psychiatric symptoms included irritability or mood swings (54%), anger or rage (23%), anxiety (21%), depression (13%), emotional (13%), obsessive compulsive disorder (11%) and suicidal thoughts (7%). Neurological symptoms included headache (50%), vertigo (30%), developmental delays (18%), tic disorders (14%), seizure disorders (11%), involuntary athetoid movements (9%) and hypotonia (7%). Sensory sensitivity symptoms included photophobia (43%), hyperacuity (36%), motion sickness (9%) and other (tactile, taste or smell; 23%). Cognitive symptoms included poor memory (39%), cognitive impairments (27%), speech delays (21%), reading/writing (19%), articulation (17%), auditory/visual processing (13%), word selectivity (12%) and dyslexia (18%). GI symptoms were common and included gastroesophageal reflux disease (27%), abdominal pain (29%), diarrhea or constipation (32%) and nausea (23%) [19,97]. Four independent studies demonstrated significant reactivity of ASD patients for Lyme disease on western blot testing, another study demonstrated a high incidence of autism and hyperactivity in over 300 gestational Lyme disease patients with the mothers reporting difficult pregnancies and frequent miscarriages, and similarities were

noted between ASD and Lyme disease patients in regard to clinical symptoms, epidemiological findings, biochemical findings, brain imaging studies and pathophysiology [19].

Although Lyme disease is considered to be caused by *B. burgdorferi*, evidence is slowly accumulating that Lyme disease is a far more complex condition than borreliosis alone. This hypothesis suggests that it may be more appropriate to regard Lyme disease as a tick-borne disease complex. Over the recent years, numerous different microbes have been found in ticks, which are known to be zoonotic and can co-infect the human host. The hypothesis suggests that multiple co-infections are invariably present in the clinical syndromes associated with Lyme disease and it is suggested that these act synergistically in complex ways. It may be that patterns of co-infection and host factors are the main determinants of the variable clinical features of Lyme disease rather than borrelia types [98,99].

Review of research findings

In summary, it is challenging to draw conclusions when so many variables exist. The pathophysiology through which infections can contribute to causing ASD is not well understood. Since many different types of infections have been described in the literature as being associated with contributing to ASD, it appears the immune response to the infection rather than the infection itself is the more critical process. Different research has proposed a number of possible mechanisms. It also appears that multiple mechanisms may be involved in contributing to the cause of ASD. Although rubella and malaria are well-documented causes of ASD, a significant number of cases of ASD cannot be explained. More common or overlooked infections need to be considered as possible contributors. For example, piroplasms other than malaria, such as *Babesia microti* and *B. duncani*, are more prevalent in some geographical areas and need to be considered as more likely contributors in those locations. Syphilis is another well established model for congenital disease, but cannot account for a significant number of current cases of ASD; however *B. burgdorferi* is a more prevalent spirochete and may be a significant contributor to causing ASD.

Patient evaluation

Since information in this area is still evolving, rigid guidelines cannot be established regarding assessment and treatment. In view of the current findings, it is advisable to evaluate women who are planning to become pregnant for chronic low-grade, relapsing infections, especially if they appear symptomatic with signs of a systemic illness with persistent inflammatory symptoms. Regional patterns of infectious diseases should be considered. A comprehensive general history, previous exposure to infectious diseases and a thorough review of systems are indicated when screening for a possible acute or chronic infectious process. Testing for the microbes discussed in this article is a consideration, especially when indicated by history, signs and symptoms. Since controversy exists regarding the reliability of some testing methods, such as the 56% sensitivity of the CDC two-tier epidemiology criteria for Lyme disease, clinical judgment is critical in making a proper assessment [100]. In higher-risk cases, the evaluation of the placenta, cord blood and newborn babies for infections are recommended.

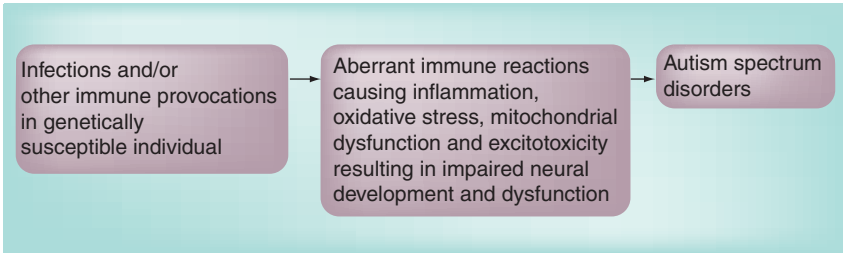

Figure 6. Model for infections contributing to autism spectrum disorder.

Treatment

When signs, symptoms and clinical findings indicating the presence of chronic infections associated with causing ASD are present, antimicrobial treatments targeted towards the chronic infections are an option with women intending to become pregnant, women who are pregnant and newborn children. However, doxycycline should be avoided in pregnant or lactating women and newborn babies. Treatment of children with ASD with antibiotics is an area of potential benefit if there is a clinical impression that active infection is contributory. In one study, the short-term benefit from oral vancomycin treatment of regressive-onset autism was noted, although this benefit was mostly lost after the antibiotic was discontinued [101].

Since Lyme disease and syphilis are both spirochetal diseases with many similarities, some suggest that treating pregnant women suffering from Lyme borreliosis with the same strategy that is used in treating pregnant women with syphilis [96]. Jones studied 66 mothers with Lyme disease who were treated with antibiotics prior to conception and during the entire

pregnancy and found that all gave birth to normal healthy infants. However, eight pregnancies resulted in positive reactivity to *B. burgdorferi* and/or *B. henselae* in placentas, umbilical cords and/or foreskin remnants. Those who were PCR-positive were treated successfully with oral antibiotics [19,97]. In a study by Maraspin *et al.*, 105 pregnant women with Lyme disease were treated with antibiotics, of these, 88.6% demonstrated normal pregnancies with healthy infants with normal developmental milestones [102]. There are guidelines for the treatment of Lyme and tick-borne diseases [207].

Since there is evidence that immune reactions may contribute to the pathophysiological process, it appears advisable for pregnant women to avoid vaccines, toxins, allergens or other substances known to provoke inflammatory reactions.

Further research

Research is needed to better identify chronic persistent infections that result in pathological symptoms; to better clarify the genetic and environmental contributors and their interaction; to better define the pathophysiology; to develop screening and evaluation protocols for women who are planning to conceive, pregnant women and newborns and to develop effective treatment strategies. The work at the University of California at Davis, CA, USA has been opening up new areas of research and further work needs to be undertaken to explain the etiology of the maternal autoantibodies against fetal neural tissue. Treatment can be antimicrobial and/or directed towards modifying the immune response by reducing the inflammatory cytokines with antibodies against the inflammatory cytokines, plasmaphoresis of the mother to

Executive summary

- A family with multiple cases of autism spectrum disorders (ASD) associated with chronic infections was described.
- There is a significant prevalence of ASD and there are geographical patterns.
- Autism spectrum disorders result from multiple etiologies with both genetic and environmental contributions.
- Rubella has been associated with causing ASD and now attention has been also focused upon chronic persistent infections.
- Infections associated with ASD include *Babesia, Bartonella, Blastocystis*, *Borna* virus (animal model), *Borrelia burgdorferi* and other tick-borne diseases, *Chlamydia pneumoniae, Cytomegalovirus, Ehrlichia, Herpes simplex virus, Human herpesvirus-6,* Herpes virus family, *Mycoplasma fermentans, Mycoplasma genetalium, Mycoplasma hominis, Mycoplasma pneumoniae, Plasmodium* (malaria), rubella, *Rubeola, Shigella*, *Taenia solium* (neurocysticercosis), *Toxoplasma gondii* (toxoplasmosis), *Treponema pallidum pallidum* (syphilis), varicella and other unknown viral and infectious agents.
- Chronic infections may be more significant in causing persistent immune reactions and may be associated with biofilms and stealth pathogens.
- Autism is associated with the Klüver–Bucy syndrome.
- Maternal immune reactions to infections adversely affect fetal brain development.
- The timing of the immune response is critical in determining the pathophysiology.
- IL-6 is associated with causing ASD.
- Based upon three different studies, antibodies that react to the 36, 37, 39, 61 and/or 73 kDa bands on western blot testing are associated with provoking an immune reaction and contribute to causing autism. Reactivity to these bands is also associated with *Borrelia burgdorferi* and, to a lesser degree, *Bartonella henselae*, *Bartonella quintana*, *Mycoplasma*, *C. pneumonia* and *Streptococcus pneumoniae.*
- Chronic infections associated with causing ASD include *Babesia*, *Bartonella*, *Blastocystis*, *Borrelia burgdorferi*, *Chlamydia pneumoniae*, *Cytomegalovirus*, *Ehrlichia*, *Human herpesvirus-6* and *Mycoplasma* (in particular *M. fermentans*), *Plasmodium*, *T. solium*, *T. gondaii and T. pallidum pallidum.* Coinfections of *B. burgdorferi* and *M. fermentans* associated with ASD are frequently observed in clinical settings.
- It is advisable to evaluate women who are planning on becoming pregnant for chronic, low-grade, relapsing infections, especially if they appear symptomatic with signs of a systemic infection or illness with persistent inflammatory symptoms.
- When chronic infections associated with causing ASD are present, antimicrobial treatments targeted towards the chronic infections are an option with women intending to become pregnant, women who are currently pregnant and newborn babies.
- Research is needed to better identify chronic persistent infections; to better clarify the genetic and environmental contributors; to better define the pathophysiology; to develop screening and evaluation protocols for women who are planning to conceive, pregnant women and newborns; and to develop treatment protocols.
- Microarrays and other newer diagnostic techniques and effective treatments with antimicrobials and possibly plasmaphoresis may help to further clarify the association between chronic persistent infections and the immune reactions to them that may contribute to these developmental disorders.
- This is an opportunity to prevent some cases of ASD that previously could not be prevented.

eliminate maternal autoantibodies against neural tissue and plasmaphoresis of the child to eliminate antibodies against neural tissue. This treatment could be similar to how it is used successfully for pediatric autoimmune diseases associated with streptococcal infections (PANDAS).

Since this is a complex issue, it is necessary for clinicians and researchers from different backgrounds to effectively work together as a team. The greatest challenge may be to coordinate the efforts of those who have something to contribute in an effective manner.

Conclusion

In the presence of genetic susceptible factors there is evidence that chronic infections and associated immune reactions contribute to causing autism spectrum disorders. These infections include *Babesia, Bartonella, B. burgdorferi*, *Ehrlichia,* HHV-6, *C. pneumoniae* and *Mycoplasma* (in particular *M. fermentans*). Maternal immune reactions to infections adversely affect fetal brain development and possible pathophysiological mechanisms appear to be mediated by both cytokines and antibodies. Increased levels of the cytokine IL-6 are associated with causing ASD. There have also been some recent identifying maternal antibodies associated with contributing to causing ASD. These antibodies are of the same molecular weight as those seen with *B. burgdorferi* (Lyme disease) and also *B. henselae*, *Bartonella quintana*, *C. pneumoniae*, *S. pneumoniae* and *Mycoplasma.* It appears a combination of inflammatory and autoimmune processes may be involved in the pathophysiology of ASD. The timing of the infection and the immune response is critical in determining the pathophysiological process. It is advisable to evaluate women who are planning on becoming pregnant for chronic, low-grade, relapsing infections, especially if they appear symptomatic with a systemic illness or infection or with persistent inflammatory symptoms, and to treat when indicated. Adequate evaluations and treatments could help to prevent some cases of ASD and their associated human and financial costs.

Future perspective

This is a complex issue that advances a new paradigm and future progress requires successful coordination from clinicians and researchers from many different fields. Persistent immune reactions caused by a hit-and-run infection is a more established concept, however, chronic and persistent infections triggering a persistent autoimmune reaction must also be considered. Since the cause of most cases of ASD is unknown, every possible explanation must be considered and explored. Microarrays and other newer diagnostic techniques may be quite useful in identifying known and still unknown infections, genes, gene expressions and the immune reactions to them that are contributing to these developmental disorders. We are living in a global community with increasing exposure to toxins and infections. Adequate attention to these issues may help to prevent the catastrophic human and economic impact of ASD.

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