

Pathophysiology of autism spectrum disorders: Revisiting gastrointestinal involvement and immune imbalance

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Abstract

Autism spectrum disorders (ASD) comprise a group of neurodevelopmental abnormalities that begin in early childhood and are characterized by impairment of social communication and behavioral problems including restricted interests and repetitive behaviors. Several genes have been implicated in the pathogenesis of ASD, most of them are involved in neuronal synaptogenesis. A number of environmental factors and associated conditions such as gastrointestinal (GI) abnormalities and immune imbalance have been linked to the pathophysiology of ASD. According to the March 2012 report released by United States Centers for Disease Control and Prevention, the prevalence of ASD has sharply increased during the recent years and one out of 88 children suffers now from ASD symptoms. Although there is a strong genetic base for the disease, several associated factors could have a direct link to the pathogenesis of ASD or act as modifiers of the genes thus aggravating the initial problem. Many children suffering from ASD have GI problems such as abdominal pain, chronic diarrhea, constipation, vomiting, gastroesophageal reflux, and intestinal infections.

A number of studies focusing on the intestinal mucosa, its permeability, abnormal gut development, leaky gut, and other GI problem raised many questions but studies were somehow inconclusive and an expert panel of American Academy of Pediatrics has strongly recommended further investigation in these areas. GI tract has a direct connection with the immune system and an imbalanced immune response is usually seen in ASD children. Maternal infection or autoimmune diseases have been suspected. Activation of the immune system during early development may have deleterious effect on various organs including the nervous system. In this review we revisited briefly the GI and immune system abnormalities and neuropeptide imbalance and their role in the pathophysiology of ASD and discussed some future research directions.

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Key words: Autism spectrum disorders; Gastrointestinal abnormalities; Immune activation; Crohn's disease; Neuropeptides; Brain-derived neurotrophic factor; *Mycobacterium paratuberculosis*

Core tip: According to the March 2012 report released by United States Centers for Disease Control and Prevention there was a 78% increase in the prevalence of autism spectrum disorders (ASD) during 2002-2008 in the United States. Although several genes causing ASD have been discovered, genetic cause of ASD is about 25% of cases. There was not a significant research focus on environmental factors and ASD-associated comorbidities in the last two decades. We revisited the gastrointestinal (GI) involvement, GI infection, immune imbalance, maternal infection and immunity, and intestinal microflora in ASD. Some neuropeptides, neurotrophins, their effects, and side effects have also been discussed.

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INTRODUCTION

Autism spectrum disorders (ASD) comprise a group of neurodevelopmental abnormalities that begin in early childhood although the first diagnosis may sometimes occur later in life and are characterized by problems in communication and social behavior. According to the 5th edition of the diagnostic and statistical manual of mental disorders (DSM-5) diagnostic criteria that has recently been released, major ASD manifestations include impairment in social communication and behavioral problems such as fixated (restricted) interests and repetitive behaviors; delay in language and age of onset are not emphasized in DSM-5 diagnostic criteria^[1,2].

According to a report by Centers for Disease Control and Prevention that was released in March 30th 2012, referring to 2008 surveillance year, the prevalence of ASD among 8 years old children in 14 Autism and Developmental Disabilities Monitoring (ADDM) sites in the United States is more than 1% (11.3 per 1000 or one per 88 children) and that male/female ratio is approximately 4/1 (ASD is more seen among boys, 18.4 per 1000, that is one in 54 boys while in girls the prevalence was 4.0 per 1000, that is one per 252 girls). The report found differences among race and ethnicity as well, although, the latter findings were recommended to be interpreted by caution^[3] (<http://www.cdc.gov/mmwr/pdf/ss/ss6103.pdf>). Nevertheless, the study shows a 23% increase in the prevalence of ASD from 2006 to 2008 and an overall 78% increase during 2002-2008 among children aged 8 years^[3]. The focus of that study by Centers for Disease Control and Prevention on 8 years old children is due to the baseline study by CDC demonstrating this age as identified peak prevalence of the disease. Moreover, ASD evaluation in that report was according to the DSM-IV-Text Revision diagnostic criteria that included the Autistic disorder, Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS, that includes the Atypical Autism), or Asperger Disorder. Although DSM-V criteria that was introduced in 2013 has modified the ASD diagnostic criteria^[2] and the ASD prevalence estimates will probably be lower under the DSM-V criteria^[4], the numbers in the statistics given are high and indicate that more research and effort is needed to investigate the pathomechanism of ASD, its treatment, and patient care under new criteria while continue to support the ASD patients who were identified under previous diagnostic criteria.

PATHOMECHANISM OF ASD

Genetic causes

The exact pathomechanism of ASD is not known so far

while several factors have been implicated in its pathogenesis of autistic disorders. Among these, the genetic cause has long been implicated to be a strong evidence-based etiology^[5,6] in cases of some co-occurring or associated conditions with ASD such as tuberous sclerosis, fragile X syndrome, Rett syndrome^[7] and some other. Siblings of autistic offspring have a higher incidence of autism than general population^[8] and twin studies have also indicated strong role for inheritance^[9]. There is wide range of phenotype but more genetically homogeneous ASD patients present with less phenotypic heterogeneity^[10]. In addition, human genetic investigations and animal models^[11] of ASD detected de novo copy number mutations^[12-14], and rare variant mutations resulting in abnormal alleles in the person or close ancestry that influence neuroanatomical and behavioral traits^[15]. These studies have shown dysregulations in genes involved in synapse function^[16]. A comprehensive and informative review of several genetic studies by Banerjee *et al*^[17] show abnormal assembly or structure of several transmembrane and scaffolding proteins involved in synaptogenesis and its maintenance, as well as dysregulation of genes involved in the signal transduction mechanism of synapse formation are among the major genetic abnormalities of ASD. Nevertheless, with the discovery of several genes as well as interactions of multiple genes in one individual, epigenetic factors, and effects of environmental modifiers on these genes in ASD, genetic causes including the diagnosable medical conditions, single-gene defect, and cytogenetic problems comprise 25% of the ASD patients so far^[18-20]. Therefore, a number of clinical phenotypes and associated co-morbidities have become the characteristic features of ASD^[21]. Although some studies indicated a role for mitochondrial DNA mutation in ASD that may possibly lead to impairment of mitochondrial energy metabolism, more research is needed for definitive answers^[22]. Mitochondrial dysfunction has been implicated in several neurological disorders^[23,24] and it may have a role in ASD. Mitochondria has antibacterial immunity^[25] and would be important in case of infections especially that of the GI tract in ASD children.

Male to female ratio in ASD

The reason for 4/1 male to female ratio in ASD is not very well understood but it is very important. Recent studies implicate some epigenetic phenomena such as sex-specific effects of Y-linked genes, balanced, as well as skewed X-inactivation, escaping X-inactivation, and parent-of-origin allelic gene among others in the etiology of ASD^[26] and heterogeneity in gene regulation at allelic level as well as total gene expression^[27]. These sex differences may be due to genetic and hormonal differences that could be initiated during early times of development due to differences in responses to and interactions with various environmental factors such as diet, stress, infection, and drugs. Due to the involvement of many X-linked genes involved in placenta formation and placenta-specific epigenetic processes, placenta plays an important

role in sex-specific responses to environmental factors and disease states later in life^[28]. Internal and external environmental factors have long been implicated in the etiology of ASD. Early maternal immune activation may cause prenatal stress, affecting boys more severely due to a vulnerable genotype^[26].

NEUROPATHOLOGICAL CHANGES OF ASD

Both postmortem and neuroimaging studies and animal models of ASD show abnormalities in different brain regions such as the frontal cortex, cerebellum, hippocampus, and the amygdaloid nucleus and cerebello-thalamo-cortical pathways^[29]. One of the neuropathological findings in ASD includes the presence of focal cortical dysplasias due to possibly the heterochronic division of germinal cells leading to abnormal migration of daughter cells to their target regions^[30,31]. Abnormal neuronal migration leads to circumscribed foci of thin cortical areas in ASD human brain especially in frontal lobe containing smaller pyramidal neurons and interneurons. These pathological findings have been attributed to the sensory and motor deficits as well as the epileptic seizures seen in ASD^[30]. Autism-epilepsy phenotype has recently been shown to be associated with macrocephaly, a pathologic condition due to accelerating brain growth in early development leading to ASD^[32]. There are evidences that the overall size of the brain is increased in some cases of ASD^[29].

NON-GENETIC FACTORS IMPLICATED IN ASD

Several other conditions such as GI abnormalities, inflammation, environmental factors, infection, toxins, diet, and drugs have been associated with ASD^[8,28].

GASTROINTESTINAL ABNORMALITIES IN ASD

Several studies have indicated a higher prevalence of gastrointestinal problems such as abdominal pain, constipation, chronic diarrhea, vomiting, and gastroesophageal reflux disease in ASD patients^[8], but a nested-case control study using United Kingdom database indicated that there was not a considerable association between GI abnormalities and ASD^[33].

A number of other conditions such as GI immune/inflammation-mediated pathology in ASD or a leaky gut referring to increased intestinal permeability have not been established due to limitations and speculations in those studies^[34]. Similarly, studies referring to leaky intestinal epithelium and damaged tight junctions and passage of dietary gluten or casein or digestion product through intestinal barrier into the blood stream causing immunogenic responses in the brain were not conclusive^[8,35-38].

Other studies that indicated more frequent diarrhea and other GI symptoms in autistic children reported inconclusive results^[39] and that intravenous secretin administration to autistic patients with GI symptoms didn't improve their language problem in contrast to other reports^[40]. Therefore experts suggested the needs for properly powered investigations^[34] in these issues.

GI abnormalities are often seen to correlate with the severity of the ASD behavioral problems and current literature favors a gut-brain interaction where GI abnormalities may be involved in the pathogenesis or severity of ASD^[41].

There is high degree of disability when these patients grow up and studies show only 15% of ASD children may have a favorable life in adulthood while a great majority of them will have poor or very poor outcomes when becoming adult^[42,43].

Gut mucosa, absorption, barrier function, permeability, immune response and oral tolerance

One of the well-established functions of the GI tract is to break down the structure of the food particles by digestion and converting them to the smallest molecules. This digested material will be absorbed by the luminal surface of intestinal epithelium through various types of transport mechanisms, and transported into the blood or lymph capillaries on the other side of the intestinal mucosal cells^[44].

GI tract works very closely with the immune system to maintain homeostasis and protects our body against microorganisms and foreign antigens.

Intestinal mucosa is continuously challenged by huge amount of foreign antigens and microorganisms from environment. The organized regulation of the intestinal barrier maintains the mucosal immune function and prevents inflammation^[45]. In spite of the microorganisms of the gut flora, various antigens from digested food, and pathogenic microorganisms, the response of the mucosal immune system is a controlled physiologic inflammation that regulates the population of T helper (Th)2 *vs* Th1 responses^[46]. Intestinal epithelial mucosal cells express classical and non-classical MHC molecules and activate specific regulatory T cells (Tregs) and therefore, serve as non-professional antigen-presenting cells^[46]. Different elements of our intestinal barrier include the epithelial cell integrity, mucus production, epithelial paracellular permeability, and innate immune response. Abnormal changes in these components may lead to inflammatory diseases of the intestine^[45].

There are other cells in the intestinal mucosa, the microfold (M) cells that are able to engulf bigger molecules^[47]. These cells belong to a group of cells forming the gut associated lymphoid tissue (GALT, which comprise the intestinal lymphoid follicles, the Peyer's patches as well) in the mucosa. M cells can pass their engulfed material to the antigen presenting cells such as macrophages and dendritic cells in the subepithelial tissue that are in cross talk with lymphocytes, the B cells, for antibody pro-

duction (*i.e.*, intestinal IgA) and are also responsible for oral tolerance towards the ingested material through other classes of immunoglobulins and cytokines^[44].

Although larger molecules may get into the circulatory system^[48], the amount of material that M cells take in under normal conditions seems to be small compared to the epithelial lining of the intestine. Nevertheless, when single unites of lipids are being absorbed by the intestinal cells they can reassemble and bound to lipoproteins, forming large molecules such as chylomicrons that leave the intestinal cells through vesicular transport to the extracellular space into the lymph capillaries (due to having larger fenestration) in the subepithelial tissue to larger lymphatic vessels and finally into circulation^[44,49]. A similar path for other larger molecule is possible.

We have shown that small proteins such as green fluorescent protein (GFP) bound to cholera toxin-B (CTB) subunit is able to get into intestinal epithelial cells in large amounts “by binding to ganglioside M1 (GM1) receptor^[50]” and find its way into the blood stream and be found in the liver and the spleen^[51]. In a series of studies we aimed to introduce large amount of bigger peptides (such as proinsulin) to induce oral tolerance towards the protein and treat autoimmune diseases such as diabetes, by converting the Th1 response to Th2 response with its associated cytokines^[52].

The cholera toxin-A subunit which is the toxic part attaches to the intestinal cells by means of its CTB subunit, increasing the permeability of the intestinal mucosa that eventually disrupts the Cl⁻ transport and other ionic and water transport disturbances leading to diarrhea^[53]. Several reports indicate GI infection in ASD patients. GI infections can increase intestinal permeability.

E. coli bacteria is able to enter the intestinal cells, change the actin dynamics, modulate the immune response and disrupt the tight junctions, leading to a compromised barrier and increased intestinal permeability resulting in diarrhea^[54]. Interferon-beta (INF β) has been shown to protect the intestinal barrier while tumor necrosis factor-alpha (TNF- α) disrupts such barrier through inhibition of INF β by another molecule^[54]. Other inflammatory conditions such as Crohn's disease are also able to increase intestinal permeability^[55] but also the increased baseline permeability in some at risk individuals and exaggeration to environmental stimuli may increase the chance of Crohn's disease^[56]. Frequent intestinal infections in ASD patients have been reported.

Several factors have been implicated in the pathogenesis of Crohn's disease. *Micobacterium paratuberculosis* (MAP) has been found in the milk, blood and surgical tissue samples of individuals suffering from Crohn's disease^[57-59]. MAP due to having a molecular mimicry to heat shock proteins has been postulated to be involved in the pathogenesis of ASD by stimulating antibodies that may cross react with the nervous system myelin basic protein^[60].

Sutterella species have recently been found in the ileum of ASD patients with GI abnormalities while no

control patients with GI disturbances had the bacteria^[61]. *Clostridium bolteae*, a bacterium that was shown to be immunogenic in rabbits, is often found in the intestine of the ASD children and was proposed to possibly be aggravating the GI symptoms in ASD patient^[62]. The first reported case of enterovirus encephalitis linked to or possibly causing ASD in a 32-mo-old child has been recently published^[63].

As mentioned earlier, there are several reports about the increased permeability or leaky intestine in ASD patients but more research and convincing data is needed therefore, we think this area of research deserves more work due to various GI symptoms in ASD patients. However, it is well known that infections can lead to increased permeability and GI symptoms and beyond. Since ASD children are often reported to have GI infection and diarrhea and that the immune system is imbalanced in ASD patients due to a direct relation of the GI mucosa with the immune system (see the following section) it is necessary to do more research to better understand the GI mucosal environment and barrier activity, subepithelial tissue, susceptibility to infection, causative agents, and the immune response in ASD patients in order to treat them more effectively.

IMMUNE SYSTEM IMBALANCE IN ASD

Other co-morbid conditions in ASD such as inflammation, inflammatory response, and immune activation have long been implicated in the pathogenesis of ASD but studies so far were not conclusive^[21,64,65]. A number of studies reveal abnormalities of the peripheral immune system supporting the ides of immune involvement in ASD however, immune abnormalities such as activation of microglial cells and innate neuroimmune system are also found in the brain and cerebrospinal fluid (CSF) of ASD patient, the neuroinflammation^[66].

Neuroimmune abnormalities have been recently reviewed elsewhere^[43]. Blood brain barrier (BBB) is an important regulator of the brain homeostasis^[67]. There are evidences that the BBB function is altered in ASD children due to neurological inflammation, immune dysregulation and increased inflammatory cytokines in the brain^[68]. Immune response abnormalities are seen in the GI tract and other tissues, the peripheral blood, and in the central nervous system (CNS) of the ASD patients. On the other hand, maternal infection or inflammation, and autoimmune diseases of the family of ASD children have also been shown to cause immune problems in the offspring. We discuss that briefly as maternal immune activation in the following section.

Significantly lower subpopulation of CD4⁺ and CD8⁺ lymphocyte as well as imbalance between Th1 and Th2-like cytokines have been observed in autism^[69]. Several interleukins (ILs) and IFN-gamma imbalance has been reported in the peripheral blood of ASD children with increased activation of both Th1 and Th2 pathways leaning more towards Th2 arm^[70]. The immunoglobulins are

also reported to be imbalanced in the serum of ASD children. Total serum protein was significantly increased in autistic patients referring to increased albumin and gamma globulin, as well as increased serum IgG, IgG2 and IgG4 that was attributed to possibly an underlying autoimmune disorder and/or increased vulnerability to infections^[71]. A number of other immune abnormalities have also been reported in ASD^[24]. The immune system is activated in many neurological and psychiatric disorders including those with genetic abnormalities and growing evidence shows that these neurological disorders are aggravated by the immune system activation leading to worsening of the initial disease^[72,73] although immune cells have beneficial effects as well^[74].

Immune system has several beneficial effects protecting us from microorganisms and helps destroying the tumor cells or disrupting their growth. Immunotherapy has been an effective approach that uses molecules of the body's own immune system to interfere with the growth of cancer cells and is being used in the treatment of brain tumors such as metastatic melanomas^[67,75]. Nevertheless, what we see in case of neurological and psychiatric disorders is mostly the deleterious effect of the immune activation against brain tissue and its related structures.

Since the Th2 pathway produces more immunosuppressory cytokines compared to Th1 arm that favors more the pro-inflammatory cytokines, and both arms are reportedly activated with a predominant Th2 arm in ASD patients, it might help the body tolerate and not to react towards many antigens (possibly penetrated through GI tract), but these antigens can have deleterious effect on other tissues such as brain. More research is needed to understand the role of immune system in ASD.

MATERNAL IMMUNE ACTIVATION AND ASD

Many studies show alteration of immune system and an imbalance of various cytokines in ASD children^[76,77]. A number of studies show a link between ASD and a family history of autoimmune diseases or those families with altered inflammatory cytokines or other immune problems^[76,78]. The autoimmune hypothesis and development of the mental disorders has long existed^[79].

When antibodies developed in immune-mediated disorders were introduced to pregnant monkeys, the offspring showed behavioral changes and CNS pathology^[80]. Perinatal exposure to infection has been implicated in the pathogenesis of ASD and schizophrenia^[81]. Activation of the immune system in pregnant mice leads to the activation of macrophages in the offspring^[82].

A recent study investigating the role of maternal autoimmune disease, asthma, and allergy on developmental disorders looked at 560 ASD patients and 168 cases of developmental delay without autism (DD) has found a significant modest increase in both the ASD and DD combined (the ASD alone data was not significant) in the children of sick mothers during pregnancy^[83]. Anti-

phospholipid antibodies have been linked with psychological problems such as cognitive malfunction, repetitive behavior and anxiety. Increased levels of anti-cardiolipin, b2-glycoprotein 1, and anti-phospholipid antibodies were found in the blood plasma of the ASD children compared to their age matched typically developing children and the DD children^[84].

Results of the animal studies indicate that the behavioral and maternal immune activation are different among different mice species referring to the possibility that a subpopulation of human might be more vulnerable to particular environmental agents^[85].

Maternal immune activation due to infections, inflammatory diseases and autoimmune diseases can have a deleterious effect on the fetus by affecting fetal tissue and its consequences during postnatal period. This area deserves more focus. Animal models of ASD especially the infection models can be very informative.

MICROBIOTA IN ASD

Microbiota is an emerging topic that has attracted several researchers to look for the possible connection between the GI microflora and behavioral abnormalities. Earlier report of deficient disaccharidase enzymatic activity in ASD children and GI symptom^[86] prompted investigations looking for intestinal mucosal microbiota involved in carbohydrate metabolism. Abnormal carbohydrate digestion and transport and mucosal dysbiosis (imbalance in the intestinal microbial ecosystem) was reported in the ASD children^[87].

Gut dysbiosis was proposed to be involved in the pathogenesis of several diseases^[88]. Reduced level of fermenters has been found in the intestinal microflora of the ASD patients^[89]. The microbiota-gut-brain axis refers to the ability of gut microbiota to communicate with brain and regulate behavior^[90]. Fecal microbiota transplantation has been used in treating several GI disorders but increase knowledge and control trials are needed before it can be used broadly in clinic^[91].

Nevertheless, other studies didn't find a difference in GI microbiota of ASD children with and without GI disturbances^[92]. Imbalance in gut microbiota population may render the intestinal mucosa susceptible to injuries, infections, inflammation, abnormal digestion, immune imbalance, immune reaction and cross reaction in other tissues including the brain. More research is emerging in this area.

VASOACTIVE INTESTINAL PEPTIDE AND OTHER NEUROPEPTIDES IN ASD

Elevated levels of several neuropeptide including vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), brain-derived neurotrophic factor (BDNF) and neurotrophin 4/5 (NT4/5) in the blood of 60 neonates who were just born compared to 56 age-matched control group^[93] opened many lines of investigation.

Those 60 neonates developed ASD or mental retardation later in life. Nelson and colleagues looked at their blood in the archived neonatal blood samples that are usually drawn at birth.

VIP and pituitary adenylate cyclase-activating peptide (PACAP) are members of the VIP-glucagon-secretin family of peptides^[94]. VIP has several functions in the digestive tract, cardiovascular system, lungs, kidney, and endocrine system^[95] and is involved in cerebral growth and neurogenesis and astrocytogenesis^[8]. VIP is a parasympathetic neurotransmitter and neuromodulator that has been implicated in the pathogenesis of cluster headaches^[96].

VIP is involved in activation of brainstem reflexes, and its infusion was shown to decrease the blood velocity in the middle cerebral artery. VIP/PACAP have been implicated in homeostasis of the immune system and are believed to have anti-inflammatory effect on innate and adaptive immunity, promote Th2 responses and decrease the proinflammatory Th1 response^[97,98]. Several properties of VIP including those mentioned above and its function on intestinal tight junctions and permeability, as well as therapeutic use have been recently reviewed^[99].

BDNF is a well-known neurotrophic factor of the nerve growth factor family together with other neurotrophins that acts mainly on high affinity tyrosine kinase (TrkB) receptor but also like all other family members acts on the low affinity neurotrophin receptor, the p75 receptor.

Low concentration of BDNF is able to excite neurons in cerebral cortex, cerebellum, and the hippocampus^[100]. BDNF and NT4/5 were able to depolarize brain neurons as rapidly as glutamate (one of the strongest excitatory neurotransmitters) at 1000-fold lower concentrations^[100]. BDNF deficiency has been implicated in a number of psychiatric disorders and ASD including their animal models^[101,102].

Although neurotrophic factors are important for neuronal survival, they can have adverse effects as well. It is not known why BDNF is increased in the blood of infants in Nelson's study. Although the trophic effects of the neurotrophic factors is very well known and low levels of BDNF has been reported in some psychiatric diseases and ASD^[103,104] a recent study on mice overexpressing BDNF shows that the animals found abnormal behavior by age^[105]. As mentioned above, if BDNF is 1000 fold stronger than glutamic acid in exciting neurons^[100] the adverse effect of overexpression might be due to excitotoxicity and possible neuronal degeneration; those mice suffered from epilepsy^[105].

BDNF acting on p75 receptor causes axonal degeneration^[106] which is used during normal development when some sprout should be eliminated. Another study shows that BDNF has increased the spasticity in spinal cord injured mice^[107]. BDNF has been reported to activate glutamate receptors^[108] and this might cause excitotoxicity^[109]. Moreover, BDNF mediates nociceptive plasticity^[110] and was found to initiate and maintain a chronic pain state^[111]

and that BDNF enhances the excitability of small diameter trigeminal ganglion neurons^[112].

Neurotrophic factors may not be stable at normal body temperature, are expensive as recombinant proteins and therefore several animal studies have introduced neurotrophic factor genes through injection of viral vectors into animal tissue which make the amount of gene product (protein) thus the dosage difficult to predict, while immunity of the host against the virus is a major problem usually in gene therapy.

CGRP is a neuromodulator/neurotransmitter peptide that is found in tissues including the nervous tissue. It is a sensory neuropeptide that coexists usually with glutamate and substance P and neurokinin A (NKA) in sensory neurons^[113]. It is a vasodilator peptide and causes hyperemia in some pathological conditions and has been implicated in the pathogenesis of migraine^[114]. Its receptors are found on blood vessels and axons and neurons in several tissues including the central nervous system.

CGRP has been found elevated in the peripheral blood of migraine patients^[115]. CGRP receptor antagonists are the gepant family of drugs such as Olcegepant and Telcagepant, and B144370TA, are some of the newest antimigraine drugs that lack vasoconstrictive activity and were thought to overcome some of the adverse effect of the Triptan family of drugs (serotonin 1B/D receptor agonists), but elevated liver enzymes and other side effects have been observed and drugs are still in clinical trials phase II and III^[114,116,117]. CGRP potently enhanced BDNF release from trigeminal ganglion neuronal culture indicating that BDNF might be a mediator of nociceptive plasticity^[98,110].

It is not known precisely why neuropeptide levels are increased in newborn children that later develop ASD. Elevated neuropeptide levels might be due to inflammation, or compensation and restoration of neuronal or other tissues homeostasis in ASD infants. This merits a thorough investigation to see their role in ASD.

CONCLUSION

Although ASD has a strong genetic base, GI abnormalities and immune imbalance as part of the environmental factors have been implicated in the pathogenesis of ASD. A number of GI abnormalities such as abdominal pain, diarrhea, constipation, gastroesophageal reflux, and GI infections have been reported in ASD patient but a clear and convincing link of these symptoms to ASD has not yet been found.

An expert panel of American Academy of Pediatrics^[34] has strongly recommended further investigation in the role of GI abnormalities in the pathophysiology of ASD. As we discussed, the GI disturbances are directly related to the immune system. Immune imbalances are common in ASD patients. GI infections can also activate the immune system in ASD patients. Maternal autoimmune disease and infections can also cause damage to the embryonic/fetal tissues and aggravate a genetic problem

in ASD if not causing the damage to the nervous system. The significant increase in the prevalence of ASD (at least 78% from 2002-2008) in the United States reported by the Center for Disease Control and Prevention in 2012 is a strong indication for revisiting critically every possible factor and look for possible clues in order to slow down or prevent this sharp increase in the prevalence of ASD in our young population and find more therapeutic opportunities to treat ASD more efficiently.

Increased VIP and other neuropeptides in ASD newborns were discussed briefly but this area certainly deserves more exploration and conclusive studies on how to proceed with the findings. Decreased BDNF has been shown later in life in ASD and other mental disorder patients, but its administration although may have positive effects, may also have adverse effects and neurotoxicity on the already compromised nervous tissue in ASD and other diseases that should be taken into consideration. We have not discussed several other factors that have been linked to ASD such as impairment in gut development^[8] or autonomic dysfunction^[43] or other factors.

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