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Deciphering the Risk Factors of Autism: Are We There Yet?

Rasheeba Nizam, Suad Al Fadhli*

Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, Kuwait University, Kuwait City, Kuwait
Email: *s.alfadhli@hsc.edu.kw, *suadq8@yahoo.com

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Abstract

Background: Autism represents a group of developmental disorder that pose a major challenge to world-wide societies and healthcare providers with limited diagnostics and medical cure. It is widely been considered as a mental disorder characterized by speech deficit and repetitive behavior. The presumed etiology of autism involves genetic, immunologic, intestinal and synaptic irregularities, aside from environmental toxicities. Yet, the prospective factor that triggers or predominates autism remains barely understood. **Objective:** Herein we aim to review the literature to identify the risk factors associated with the development of autism and the need to investigate the underlying pathological events. **Results:** Genetic factors have been widely investigated in autism for its role in inflammation, neuronal function, metabolism and detoxification. It's assumed to be negatively impacted by heavy metals, allergens, infectious agents and environmental pollutants. Considering the fact that, these elements individually does not make up autism, one would expect a complex interplay of neuro inflammatory and gastrointestinal system in the pathophysiology of the disease. Gut-brain axis may serve as a potential pathological link representing the plethora of mechanistic events involved in the development of autism. Abnormal activation of mast and neuro glial cells may lead to deregulated expression of cytokines and neuroactive compounds, which may disrupt the blood brain barrier permeability leading to inflammation. Alternatively it may also interfere with intestinal permeability, gut physiology, microbial composition and related metabolites. **Conclusion:** A glance through the literature indicates the likelihood of genetic variations and environmental factors in triggering a cascade of inflammatory events leading to the development of autism. Though relatively little information is known regarding the factors that initiate the onset and the progression of the disease; the rising prevalence of autism across the globe alarms us towards a better know-how of the disease and the shortfalls in disease treatment and management.

Keywords

Autism, Risk, Gut-Brain Axis

1. Introduction

Autism spectrum disorder (ASD [MIM 209850]) includes a group of complex developmental disorders characterized by difficulties in social interaction, verbal and non-verbal communication and repetitive behaviors. It affects 1% world population with wide range of behavioral and clinical heterogeneity that leads to substantial challenges in their diagnosis [1] [2]. Autism is found to be four times more common in males than females [3] [4]. Its outpacing prevalence across different geographical locations alarms us towards a better know-how of disease. The exact cause/triggers of autism remains unknown with multiple genetic, immunological and environmental factors contributing to the disease (**Figure 1**).

2. Genetics of Autism

Increasingly, genetic predisposition and immune reactions are presumed to be the key

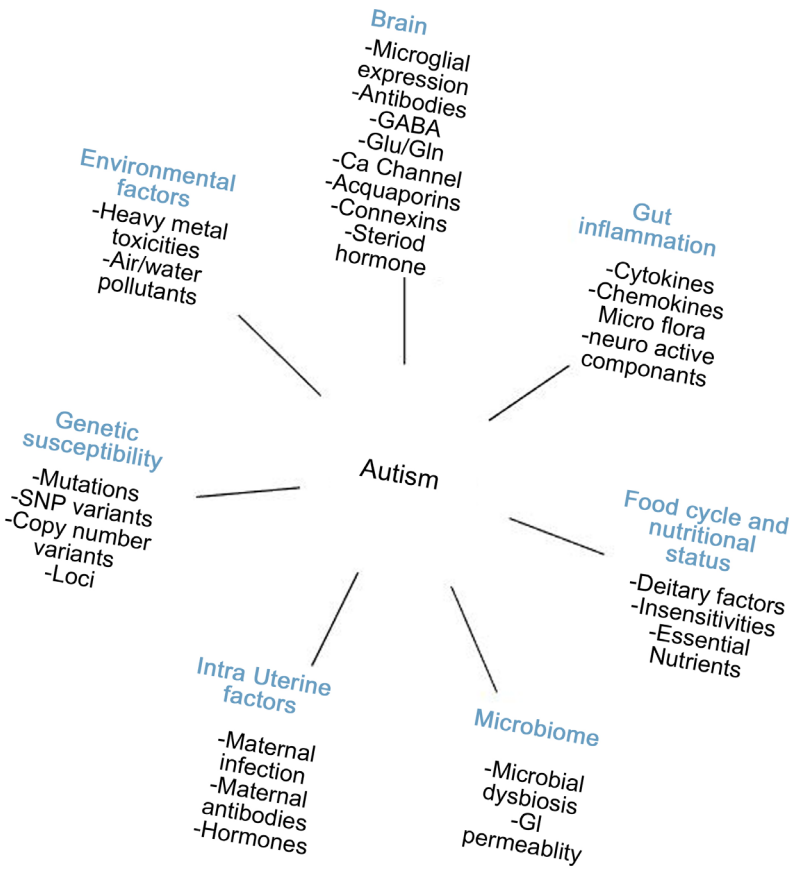

Figure 1. Represents core elements that tend to influence the onset of Autism.

players of autism. Twin studies and family studies have shown a strong genetic contribution to their etiology with 82% - 92% concordance in monozygotic twins and 1% - 10% in dizygotic twins [3] [4]. Genome wide linkage, association, sequencing and copy-number variant studies have led to the identification of multiple variant's that can predispose to autism, presented in **Figure 2** [5]-[10]. Multiple loci have been identified to be responsible for autism and these include chromosome 1q31.1, 1p13.2, 2q31, 3q, 5p13, 7q (22, 34), 8q24, 13q, 16p, 17q, 15q, 19p and Xq [11] [12]. A broad variety of mutations responsible for autism have been discovered in recent years, including the mutant forms of *NRXN*1, *CNTN*4, *NLGNs* and *SHANK*3 [5]. Vastly, these mutations are presumed to be involved in neuronal development, synaptic functions, ion channel and transmembrane activity. Literature data indicates that majority of these genes are inter-related and may influence the function of each other indicating a complex network of deregulated genes in autism (**Figure 2**). However, increasing incidence of autism (1in 68, Centers for Disease Control, 2014) and their heterogeneous behavioral and clinical spectrum direct towards the role of additional factors in the pathogenesis of disease. The theory of rare variants and common complex diseases also gains attention in autism due to larger effect size and associated clinical heterogeneity. Understanding the exact model of genetic architecture entails further intensive research.

3. Gut-Brain Axis: An Inflammatory Dialoguein Autism

Gut-brain inflammation has been regarded as one of the most intriguing causes of autism. The enteric nervous system (ENS), recently been considered as the second brain, is embedded in the gastrointestinal system with multiple neurons organized into two layers of gut tissues known as myenteric and submucosal plexus; comprising ofimmune cells and neurotransmitters such as serotonin, dopamine, glutamate, norepinephrine and nitric oxide, aside from glial cells, neuropeptides and psychoactive compounds. Apart from its evident role in persuading emotional outcomes such as stress, fear or excitement; ENStends tobe involved inmast cell mediated allergic and/or host immune response.

An imbalance in Th1 and Th2 like cytokines and an increase in circulating autoantibodies to neuron-axon filament protein and glial fibrillary acidic protein indicates a series of selective immune regulatory events in the development of autism [13] [14]. One of the hypothesis of autism development postulates that hyper-activation of mast cells results in increased secretion of inflammatory cytokines and histamine [15] leading to leaky gut and apparently brain inflammation. Supportively, increased levels of IL-6 and TNF have been reported in brain and cerebro spinal fluid of autistic patients respectively [16] [17]. Reduced plasma levels of TGF-b in ASD [18], probably accounts for increased mast cell activation and reduced T-cell regulatory functions. High histamine levels are often observed in males as is the prevalence of autism. As a neurotransmitter, increased production of histamines tends to have deleterious effect on brain causing mood swings, hyper activity, compulsive behavior, anxiety, lack of appetite, loss of memory and frequent crying, which are predominantly observed in autistic children.

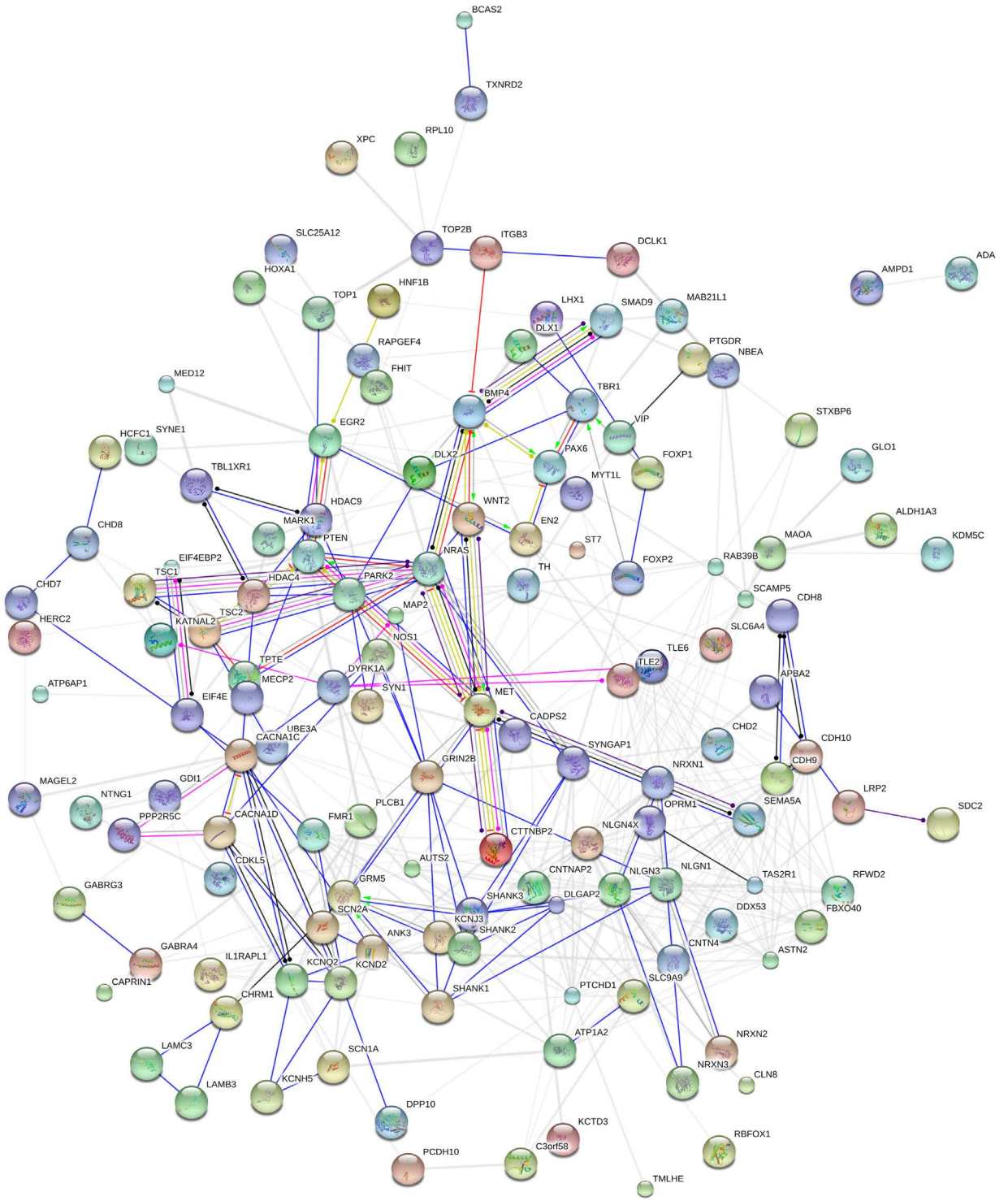

Figure 2. Protein network of the predicted genes from the literature presumed to be associated with autism development. The network nodes are proteins and the edges represent the predicted functional associations. Differently colored lines, represent their mode of action. A blue line indicates-Binding; a violet line-Catalysis; a pink line-Post translational modification; and a yellow line-Expression. Arrow at the end of the edge next indicates the directionality of the action. Red bar indicates down-regulation and green arrow indicates up-regulation. The circle indicates that the directionality of the interaction is known, but the end result is unknown.

One of the consequences of perinatal mast cell activation includes gut-blood brain barrier (BBB) disruption permitting the neurotoxic molecules to enter brain causing inflammation. BBB permeability tends to be tightly regulated by the contribution of cerebral endothelial cells, pericytes and glial cells [19]. Among the endothelial cells, tight junctions are most important components of BBB; significantly altered expression of MMP9 in autistic subject's [20] possibly directs towards MMP2/MMP9 mediated disruption of tight junctions [21]. MCP1 is a chemoattractant for mast cells that has shown to be elevated in cerebro spinal fluid and microglia of autism patients [22], and may further contribute to vasodilation. Neurotensin is yet another protein that tend to stimulate the mast cells and exert neuro-modulatory functions [23]. Microglial neurotensin stimulates glial cell proliferation; abnormal microglial growth and activation have been reported to be central inautism development [24] [25]. It also tends to facilitate seizures through activation of glutamate receptors [26]. Glutamate is the most abundant aminoacid present in the CNS and gut. Recently increased plasma levels of glutamate and decreased levels of glutamine has been reported in high-functioning autistic children compared to controls [26]. Post mortem studies have also implicated abnormalities in the expression of glutamate receptors and transporter system in the brain tissues of autistic subjects [27]. Relative changes in the measure of glutamate and/or GABA have been proposed to affect the excitation/inhibition equilibrium of cortical networks, interfering with neural communication, memory formation and learning [28]. Dysregulation of other neuropeptides such as oxytocin and vasopressin also gains attention in autismdue to its influential role in behavior and social interaction [29]. The impact of environmental, nutritional and microbial flora may further depict the inflammatory role of gut-brain axis in the development of autism.

4. Environmental Causes of Autism

Existing data also suggests the significance of dietary and environmental exposure to heavy metals in autsim development [19]. Marked up increase in the level of mercury, lead and aluminum in the autistic children, radically indicates its impact on neural functions [30]. These heavy metals are likely to disturb calcium channel activity and may negatively impact endothelial cells and astrocytes [31]. Calcium essentiallyplays a key role in the expression of aquaporin's and connexins that tend to regulate cerebral blood flow. Remarkably, deregulated expression of aquaporin's and connexins have been implicated in autism [32]. Genes involved in heavy metal detoxification such as *PON*1 and *GST* have also been linked to autism development [33] [34]. Safety of vaccines has also been much on debate with an unsubstantiated link between MMR and autism development. It has been speculated that toxicological contribution of vaccine components and simultaneous administration of multiple vaccines devastates/weakens the immune system and creates an interaction with the nervous system triggering autism in genetically susceptible individual. Living in areas with higher levels of styrene and chromium and exposure to dioxins during pregnancy have also been associated with the risk of autism [35].

5. Food Cycle and Nutritional Status in Autism

Dietary factors can cause varying degree of inflammation influencing the disease risk and severity. Increased sugar uptake, processed food and low nutrient diet are some of the factors contributing to the inflammation cycle. Food allergies are more prevalent in children with autism than those without, including the picky eating habits and food aversions [36]. Food that contain or tend to release histamine upon ingestion includes fermented food products, wheat, milk, soy etc. There are reported cases of children with autism who showed notable decline in symptoms when placed on gluten-free and/or casein-free diets, though not scientifically proven yet. The decreased absorption/deficiency of essential nutrients such as omega-3 fats, vitamin A, B1, B6, B12, C, D, zinc and magnesium, through the intestinal tract could also lead to inflammation. Deficiency of essential amino acids such as tyrosine and tryptophan have also been raised as a concern, given their role as neurotransmitter [37]. Low Vitamin D status has been recently associated with autism [38] suggesting deficit in brain and gut function. There are multiple reports indicating improvement in core symptoms of autism on Vitamin D supplementation [38]. Similarly, low vitamin B12 status has also been speculated with autism onset for its role in myelin sheath formation.

6. Microbiome and Autism

Selective animal model and human studies also indicate that disturbances in intestinal microflora may have an over-riding influence on the bidirectional communication between the gut-brain axis, instigating gastrointestinal and neurobehavioral issues [39]. Variations in gut microbiome have been linked to autism with clostridia growth rate being a key risk factor. It has been speculated that the relative balances between the inflammatory microbes such as clostridia and desulfovibrio, and the anti-inflammatory microbe bifidobacteria may become destabilized prior to autism development [40] [41]. Certain enteric metabolite such as p-cresol, enteric short-chain fatty acids such as propionic acid derived from clostridia species have been reported to be elevated in autistic children [42]. The overload of these components could also be of environmental origin due to its role as disinfectant and preservative agents [43] [44]. Bacterial over load, dietary factors and accumulative environmental toxins may collectively contribute to the gastrointestinal (GI) permeability associated with autism.

7. Intra Uterine Factors

Maternal viral infection in the first semester and bacterial infection in the second semester have been associated with the risk of autism development in the offspring [45]. Hormonal imbalance during pregnancy could also contribute to the development of autism. Increased steroid hormones such as progesterone, 17α-hydroxy-progesterone, androstenedione and testosterone in autistic subjects stipulates the influence of steroidogenic activity on early fetal brain development [46]. High level of testosterone coupled with reduced expression of estrogen receptor beta, estrogen co-activators and aromatase; an enzyme that converts testosterone to estrogen [46] [47], possibly clues

the gender bias observed in autism. Given its critical role in the development of cholinergic and dopaminergic neurons, deficiency of thyroid hormones could also contribute to the behavioral and cognitive deficits observed in autism.

8. Conclusion

Autism in a nutshell signifies beyond a mere state of communication deficit. It indicates a complex series of neuro inflammatory-gastrointestinal events subsequent of immune dysfunction. Genetic predisposition is considered to be a key factor contributing to the disease; a comprehensive understanding of gene-gene network and gene-environment interactions may provide valuable tool to explain the clinical outcomes and severity of disease. Given the complex interaction between genetic, environmental, neuronal, immunologic, nutritional, microbial and intra uterine factors, the root cause that initiates/triggers the disease remains largely unknown. Gut-brain axis could be a potential target to unravel the root cause of the disease. An intensive research with respect to specific risk factors would enable early interventions, increasing the momentum of hope to cure the disease.

9. Looking Forward

The rising autism rates and the lack of well-defined medical treatment regime represents a major challenge to the medical sector. Despite the remarkable increase in the number of causative factors associated with autism, the need for the assessment of underlying medical comorbidities appears to be largely overlooked by the current system. Though intense speech /language/ occupational therapy would improve the associated behavioral and social issues; the underlying pathological condition requires a more intense treatment plan. There is an intimidate need for laboratory/clinical profiling for the efficient management of the disease, if not the diagnosis. A general screening for the deficiency of essential nutrients, food hypersensitivity, urine and stool comprehensive analysis for the presence of bacteria/fungal overload, aminogram for inborn errors of metabolism, heavy metal screening and hormonal imbalance, may to some extent address the related complications and comorbidities. A professionally supported integrative holistic approach involvingclinical and psychological interventions, alongside life style modifications such as customized diet plan, nutritional & probiotic supplementation and regular detoxification protocols mayenormously benefit the disease treatment and management policy.

Conflict of Interest

None declared.

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Abbreviations

ASD: Autism development disorder,
BBB: Blood brain barrier,
EEG: Electroencephalogram,
GABA: Gamma aminobutyric acid,
GST: Glutathione S-transferase,
IL: Interleukin,
MMP: Matrix metalloprotein,
MCP: Monocyte chemoattractant protein,
MMR: Measles, mumps, and rubella,
PON1: Paraoxonase 1,
Th: T-helper,
TGF-b: Transforming growth factor beta,
TNF: Tumor necrosis factor.

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