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Brain Fires in Autism Spectrum Disorders

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Abstract

Autism spectrum disorders (ASD) is characterized by social and communicative deficits, severe anxiety, and stereotypic movements. Despite affecting as many as 1 in 45 US children in the USA, the pathogenesis of ASD is still unknown. Recent epidemiological studies indicated a strong statistical correlation between risk for maternal / infant atopic diseases and ASD suggesting the possible involvement and activation of mast cells (MC). These unique immune cells are located close to blood vessels in all tissues, including the thalamus and hypothalamus in the brain, which regulate emotions known to be dysfunctional in ASD. Moreover, MCs are stimulated by two brain peptides, corticotropin-releasing hormone (CRH) and neurotensin (NT), which we showed to be high in the blood of children with ASD. Stimulated MCs then secrete inflammatory molecules that activate brain microglia, which proliferate and "choke off" nerve communication. These inflammatory molecules are increased in the brain and serum of patients with ASD and also lead to disruption of the protective blood-brain barrier (BBB), which is regulated by MCs, permitting the entry of circulating white blood cells and toxins contributing to brain. We further reported that the elevated blood levels of two inflammatory molecules, IL-6 and TNF, identify a subgroup of children with ASD, who benefit most from a promising treatment with the natural flavonoid luteolin that combats brain inflammation. Extinguishing inflammation ("Brain fires") may be the best hope for curing ASD.

List of abbreviations

ABC: Aberrant behavior checklist; ADHD: Attention-deficit hyperactivity disorder; ASD: Autism spectrum disorders; BBB: Blood-brain barrier; BDNF: Brain-derived neurotrophic factor; CRH: Corticotropin-releasing hormone; DAMPs: Damage-associated molecular patterns; MC: Mast cells; MCP-1: Monocyte chemoattractant protein; Mt: Mitochondrial; NAC: N-acetylcysteine; NT: Neurotensin; NTs: Neurotensin receptor; SSRIs: Selective serotonin re-uptake inhibitors; SP: Substance P; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor

Introduction

Affecting more than 1 in 45 children in the US, Autism Spectrum Disorders (ASD) are pervasive neurodevelopmental disorders characterized by deficits in communication and social interactions, as well as the presence of increased anxiety and stereotypic behaviors [1-3]. Current ASD diagnosis depends on the recognition of presenting behaviors suggestive of ASD (Table 1) and is corroborated by meeting the cut off scores on both the DSM-IV-TR symptom list [4] and the Autism Diagnostic Observation Schedule (ADOS) algorithm [5].

Despite its inclusion in the DSM-IV-TR and increased awareness, ASD remains mysterious making its treatment exceedingly difficult and costly. While past research has helped uncover a number of gene mutations linked to ASD, still no specific pattern or direct link has been uncovered [6,7]. Current ASD research using mouse "models", where genetically based mice with phenotypes resembling autism are studied [8,9], does not adequately reflect the extent of ASD, and other inflammatory diseases in humans [10].

With a lack of adequate scientific understanding about ASD, child and adolescent outpatient mental health services in the USA have increased considerably [11] to an estimated annual economic burden of $268 billion in 2015 and will continue to increase to a projected annual burden of $416 billion in 2025 [12]. As a result, the community is in scientific and economic urgent need of appropriate scientific research, including more relevant animal "models" of ASD in order to better understand ASD in humans [13].

Ultimately, the lack of reliable biomarkers, [14] lack of specific pathogenesis, and the existence of many subgroups (Table 2), makes a unified treatment approach difficult [15-17]. Therefore, the path to developing effective ASD treatments should focus on identifying the ASD subgroups listed in Table 2 through the use of a series of useful diagnostic tests (Table 3).

Discovering the pathogenesis of and a cure for ASD requires a concerted effort, as was demonstrated in the European Autism Interventions-A Multi Centre Study for Developing New Medications (EU-AIMS) Initiative [18]. This review will also present evidence that activation of mast cells (MCs), tissue immune cells involved in allergic reactions [19] can be triggered by many stimuli and both disrupt the blood-brain-barrier (BBB) and activate microglia leading to focal inflammation of the brain.

Prematurity and low birth weight is linked to obesity in the mother and increases the risk of inflammation in the brain and ASD

S.No	Autism spectrum disorders (ASD)
1.	Lack of response when name is called
2.	Isolation
3.	No group play
4.	Loss of vocabulary
5.	Adherence to rigid routines
6.	Lack of imaginative play
7.	Inability to follow directions
8.	Anxiety
9.	Intolerance to stress
10.	Repetitive non-purposeful movements
11.	Hyperactivity
12.	Tantrums
13.	Tip-toeing
14.	Hand flapping
15.	Intolerance to sensory overload
16.	Strange food habits

Table 1: Presenting Behavior Indicative of ASD.

S.No	Subgroups
1.	ADHD
2.	Allergies
3.	Food intolerance
4.	Fragile X syndrome
5.	Gastrointestinal symptoms
6.	Hyperactivity
7.	Methylation deficiency
8.	Mitochondrial dysfunction
9.	PANDAS*
10.	Phenol intolerance
11.	PTEN* mutations, macrocephaly
12.	Rett syndrome
13.	Seizures
14.	Tuberous sclerosis

*Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infections

* Phosphatase and tensin homolog

Table 2: ASD Subgroups.

There are a number of perinatal, allergic, genetic, environmental, immune and infectious factors that may increase the risk of or contribute to the pathogenesis of ASD [20-22] (Table 4). A major risk factor that contributes to the development of ASD is infantile prematurity and low birth weight, characterizing about 15% of all infants delivered at 32-36 weeks in the USA [23]. Preterm labor and premature birth was associated with in utero inflammation or infection [24-26], factors that are now implicated in ASD (see later sections).

Premature and low birth weight infants are at risk for neurologic injury [27-30], cerebellar hemorrhagic injury that can lead to neurodevelopmental disabilities [31] including reduced attention, increased anxiety, as well as difficulties in social interaction and learning [32,33]. A number of studies reported that ASD children less than 33 weeks gestation are associated with higher risk of ASD [34-37]. Neonatal jaundice was also associated with ASD [38]. Increased risk for ASD was strangely associated with the use of Cesarean section only through general and not spinal anesthesia [39].

Prematurity has been linked to obesity in the mother during pregnancy and large weight gain during pregnancy increased the risk for ASD in the offspring [40]. This finding may be linked to the hormone leptin, which is increased in obese individuals [41,42] and elevated plasma levels of leptin during pregnancy indicate placental dysfunction [43]. In fact, leptin is increased in children with regressive autism [44], autistic disorder (n=35) [45] or Rett syndrome (n=16) [45]. This is interesting in view of the fact that obesity has been considered an inflammatory state involving release of adipocytokines [46,47]. Moreover, MCs have been linked to obesity [48,49] and also express leptin and leptin receptors, a finding implicating paracrine or autocrine immunomodulatory effects [50].

Blood Test	Condition	Test Code	CPT code(s)
Anti-IgE receptor antibody	Autoimmune urticaria	18877	83520
C3a desArg Fragment	Angioedema	17689X	83520
Total IgE	Allergies	7320	82785
Allergy profile (RAST to Food and environmental antigens)	Allergies	10659X	82785,86003(X15)
Catecholamines, Fractionated Plasma [314X]	Anxiety/irritability	14566	82384

Interleukin-6, Highly Sensitive ELISA [34473X]	Inflammation	7259	83520
Tumor Necrosis Factor-Alpha, Highly Sensitive ELISA	Inflammation	34485	83520
Lactate/Pyruvate *	Oxidative stress and chronic fatigue	11296X	83605, 84210
Glutathione	Oxidative stress	90379X	82978
Histamine	Urticaria	16838	86343
Serotonin	Flushing	29851	84260
Heavy Metals Comprehensive Panel	Neurologic complaints	14573	82175, 82570,83655, 83825, 83018 (x2)
Food intolerance panel			
*Preferably obtained from an arm after 1 min exercise with a squeeze ball or spring			

Table 3: Useful Diagnostic Tests for ASD.

S.No	Perinatal Conditions
1.	Identical twin of sibling with autism
2.	Allergies
3.	Asthma
4.	Presence of brain autoantibodies
5.	Caesarean section with general anaesthesia
6.	Environmental toxin exposure
7.	Exposure to heavy metals
8.	Exposure to mold
9.	Haemorrhage
10.	High fever
11.	Infection
12.	Low birth weight
13.	Low APGAR score
14.	Obesity
15.	Oxytocin, prolonged use for labor induction
16.	Preeclampsia
17.	Prematurity
18.	Psoriasis
19.	Psychotropic medication use
20.	Sexual abuse
21.	Stress

Table 4: Perinatal Conditions Increasing the Risk of ASD.

Mother's health during pregnancy is linked to increased risk for ASD

Prenatal stress in mothers has been linked to increased risk of ASD in offspring [21,51,52]. Stress, through activation of receptors [53] for the neuropeptide corticotropin-releasing hormone (CRH), secreted from the hypothalamus, can activate MCs to secrete vascular endothelial growth factor (VEGF) [53] leading to increased BBB permeability [54,55]. MCs are located around blood vessels especially in the thalamus and hypothalamus, adjacent to CRH-positive neurons [56], where they contain most of the brain histamine [57,58]. We reported that CRH and another brain hormone, neurotensin (NT), were increased in the serum of young children with ASD compared to normal controls [59]. CRH and NT synergistically stimulate MCs [60]. The highest expression of NT receptors in the human brain is in the hypothalamus and band of Broca [61], as well as the amygdala [62], which regulates emotions and language known to be dysfunctional in ASD. NT is neurotoxic [63]. We recently reported that NT stimulates activation and proliferation of human microglia [64], which are for the first time considered to play a major role in the pathogenesis of ASD [65-67].

Children born to mothers with mastocytosis, characterized by the presence of many activated MCs [19], had a 10-fold higher risk of developing ASD, [68] implying the role of MC activation in ASD [69,70]. Mastocytosis patients have increased serum IL-6 that correlates with disease activity [71-73]. Interestingly, the mouse model of autism induced by maternal immune activation (MIA) is due to increased blood IL-6 [74,75]. We had reported that acute stress significantly increases serum IL-6 in mice that was entirely dependent on MCs, as it was absent in MC-deficient W/Wv mice [76]. Recent studies have shown strong associations between the presence of allergies and autoimmune diseases, especially psoriasis, and increased risk of ASD in the offspring [77-79]. Such findings suggest the involvement of environmental triggers [20,22,80-83]. There was a strong association between higher ASD prevalence and proximity to industrial facilities emitting air pollutants [84]. Moreover, chemical intolerant mothers were three times more likely to have a child more prone to allergies and sensitivities and to develop ASD [85]. Exposure to mold was linked to decreased cognitive function in children [86]

and volatile mycotoxins have been reported to induce neuropsychiatric symptoms [87]. Different species of mold can trigger MCs [88-91].

MCs can be further stimulated by aluminum, Bis-phenol A (BPA), organophosphate insecticides and mercury [92-96]. In fact, chemical exposure to mercury [97] and aluminum [98,99] has been associated with symptom severity in children with ASDs. While Aluminum has replaced mercury as an adjuvant in vaccines, its health effects are not negligible [100]. For instance, aluminum oxide can triggers a series of allergic reactions, including the invasion of the brain and inducing of microglia TNF release [101].

Atopic diseases are linked to inflammation of the brain and are strongly associated with increased risk of ASD

Atopic diseases (including allergies, asthma, eczema and rhinitis) [102] and auto-immune diseases [103,104] have been increasing at a rate similar to that of ASD. Atopic diseases in preschoolers were strongly associated with psychological and behavioral problems, [105] including attention-deficit hyperactivity disorder (ADHD) [106]. Two large epidemiological studies based on 92,642 children [107] and the other on 14,812 children [108] showed that eczema in the former and allergies in the second were strongly associated with ASD and ADHD. Early reports had indicated more frequent allergies in ASD children [109,110] with food allergies being the most prevalent complaint [111-114]. Recent studies have confirmed strong associations between allergies, asthma and ASD [77-79,115].

Atopic diseases develop due to activation of MCs, which derive from bone marrow progenitors and mature in tissues depending on microenvironmental conditions [116]. Stimulated MCs secrete over 50 molecules with important pathophysiological actions, of which histamine is the best known; others include the proteolytic enzyme tryptase, the chemoattractant chemokines IL-8 and MCP-1, the inflammatory cytokines (IL-1, IL-6, TNF, as well as vascular endothelial growth factor (VEGF) [19]. New evidence indicates that brain histamine is involved in the pathogenesis of neuropsychiatric diseases [117] and in the disruption of the BBB [118], which is regulated through MCs [54,119]. We reported that stimulation of human MCs also leads to fission and translocation to the cell surface of mitochondrial [120], typically known for producing energy for the cell, accompanied by the secretion of mitochondrial DNA extracellularly without cell death [121]. These mitochondrial components could augment allergic responses [122] and act as "innate pathogens" triggering inflammation and potentially contributing to ASD [123]. We further showed that serum mtDNA was significantly in children with ASD as compared to the reported serum mtDNA in controls [124]. The pathological significance of the presence of extracellular mtDNA could be particularly important in the subgroup of ASD patients with mitochondrial dysfunction [125]. MCs are now considered critical for the development of allergic reactions [19], also immunity [126], autoimmunity [127] and inflammation [128]. As a result, we proposed that patients with ASD may suffer from "allergies in the brain" [129] and "focal brain inflammation" [130].

Inflammation of the brain may cause ASD

Increasing evidence indicates that perinatal brain inflammation [21,131] is important in the pathogenesis of neuropsychiatric disorders [131-134]. In fact, ASD pathogenesis may also involve some immune [20,135-139], autoimmune [123,140] and inflammatory [21,141] component. For example, based on experiments performed on mice,

gestational immune activation was reported to alter social behaviors in genetically vulnerable mice [142]. In humans, auto-antibodies directed against fetal brain proteins have been reported in the blood of mothers with children with ASD [137,143] and in about ASD patients [144-147]. The presence of these auto-brain antibodies in humans significantly correlated with allergic symptoms [148].

The markers of inflammation shown to be increased in the brain of many ASD patients [149-152] include IL-6, and TNF [153], molecules secreted from MCs, as well as IL-8 and MCP-1, which are chemotactic for MCs [128]. In particular, plasma levels of IL-1β, IL-6 and IL-8 were increased in children with ASD and correlated with regression, as well as impaired communication and aberrant behavior [154]. Increased levels of MCP-1 in amniotic fluid [155] and in archived neonatal blood specimens [156] were strongly correlated with increased risk for infantile autism. IL-6 and TNF could disrupt the BBB and cause "focal encephalitis" in specific brain areas, thus contributing to the pathogenesis of ASD [157]. Moreover, MC-derived IL-6 and TGF-β induce maturation of T-17 cells [158] and MCs can secrete IL-17 themselves [159]. In fact, TGF-β has been reported to be increased in the brain of ASD patients [65], while IL-17 [160] has been increased in the serum of children with ASDs as well as in the MIA mouse model [161]. MC-derived histamine [162] and tryptase [163] can activate microglia, and MC-microglial interactions are important in neuroinflammatory diseases [164]. Microglia, the innate brain immune cells, is increasingly implicated in neuropsychiatric [165-167] and neuro-inflammatory diseases [164,168,169]. Microglia is important during healthy brain development [116,170] because they demonstrate neuroprotective qualities as they may "prune" neural circuits [171]. However, abnormal microglia activation and proliferation could lead to focal inflammation and "choking" of normal synaptic traffic [169]. Neuroglial activation and neuroinflammation has been reported in brains of patients with ASD [65-67,172] and are now considered an important component of the pathogenesis of ASD [173,174] and Rett syndrome [175].

Treatment Approaches

While the severity of symptoms might differ, it is essential that most symptoms be addressed as soon as possible. Some of the most important behavioral and social treatment approaches for ASD are listed in Table 5. Moreover, potentially effective drugs, vitamins and supplements used most often for treatment of ASD are listed in Table 6.

Psychotropic medications

Most children with ASD are often prescribed psychotropic medications, [176] primarily risperidone and aripiprazole [177], because these drugs have been known to reduce general disruptive and aggressive behaviors. However, these drugs have shown no effect on the core symptoms of ASD [178-180] and often have frequent adverse effects, such as weight gain, sedation, tremor, movement disorders and drooling [181] and increase the risk for unwanted drug interactions [182]. A recent review also concluded that the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) are not effective in ASD and frequently lead to hyperactivation [183]; in fact, one such drug, citalopram, was deemed to be detrimental [184]. Moreover, recent papers reported higher risk for delivering children with ASD in mothers who used antidepressants during pregnancy [185,186].

S.No	Treatment
1.	Treat any comorbid conditions, especially allergies
2.	Eliminate food triggers, especially casein and gluten
3.	Minimize phenol containing substances, especially chocolate and acetaminophen
4.	Tolerate food idiosyncrasies and advance slowly
5.	Address gastrointestinal symptoms, especially constipation
6.	Limit sensory overload
7.	Respect child's routines
8.	Be firm, but not abusive
9.	Participate in child's world
10.	Initiate speech therapy
11.	Initiate work therapy
12.	Initiate play therapy

Table 5: Useful Treatment Approached for ASD.

Drugs for OCD and Disruptive Behavior
Aripiprazole
Risperidone
Drugs for Hyperactivity
Hydroxyzine
Propranolol
Risperidone
Supplements for Anxiety
N-acetyl cysteine (NAC)
S-adenosyl methionine (SAMe)
Valerian/Paciflora extract
Supplements for Oxidative Stress
Broccoli extract
Fish oil
Glutathione
Supplements for Inflammation
Luteolin/berberin (BrainGain)
Luteolin/quercetin (NeuroProtek)
Supplements for Neuroprotection
Methyl B12
Biotin, hydroxytyrosol, selenium (BrainGain)

Table 6: Drugs and Supplements Used for ASD.

Antioxidant compounds

A recent double-blind, placebo-controlled, study using the broccoli-derived anti-oxidant sulforaphane for 18 weeks showed significant improvement (34%) in social interaction and communication using the Aberrant Behavior Checklist (ABC) scale of adult patients with ASD specifically selected for their history of reduced symptoms during febrile episodes [187]. Another antioxidant, N-acetylcysteine (NAC), used either at 900 mg/day x 4 weeks, then 900 mg twice/daily x 4 weeks and finally 900 mg three times/daily x 4 weeks) found no difference on the total ABC, but significant improvement on the irritability subscale [188]. In another also randomized, placebo-controlled, study (n=40), a high dose of NAC added to a stable dose of risperidone, again had no effect on total ABC, but decreased the irritability subscale [189].

Anti-inflammatory compounds

Immunomodulatory treatments have been considered for ASD [136], but few studies have been published. Unfortunately, there are no clinically approved anti-inflammatory drugs other than cortisone, which is unlikely to be used in children as it prevents growth, in addition to many other unwanted effects. Luteolin (5, 7, 3', 4'-tetrahydroxyflavone) is a naturally occurring flavonoid, found in green plants, herbs and seeds, with potent antioxidant, anti-inflammatory properties [190] (Table 7). Luteolin is structurally related to 7, 8-dihydroxyflavone, which was shown to mimic brain-derived neurotrophic factor (BDNF) [191], which reduced symptoms in a mouse model of Rett syndrome [192]. Moreover, luteolin improved memory in a rat amnesia model [193] and inhibited autism-like behavior in a mouse "model" of autism [194], while its structurally related flavonol quercetin (5, 7, 11, 3', 4'-pentahydroxyflavonol) improved cognition in a mouse "model" of Alzheimer's disease [195] and reversed acute stress-induced autistic-like behavior in mice [196]. Luteolin inhibit MC [122,197-200] and microglial activation and proliferation [201,202]. These flavonoids are generally considered safe [203,204].

S.No	Properties
1.	Antioxidant
2.	Anti-inflammatory
3.	Mast cell inhibitor
4.	Microglia inhibitor
5.	BDNF* analogue
6.	Acetylcholinesterase inhibitor
7.	Glutamate release inhibitor
8.	GABA receptor agonist
9.	Demethylase inhibitor
*Brain-derived neurotrophic factor	

Table 7: Useful Properties of Luteolin Relevant to ASD.

A formulation containing the natural flavonoids luteolin and quercetin (administered as one capsule/10 kg weight/day for 6 months) resulted in significant (p<0.005) improvement in attention and behavior (34% in total ABC and 8.43 months in age-equivalent scores

in the VABS communications domain) in children with ASD [205]. We recently reported that patients from that study who showed most improvement (65%) were the ones who had the highest serum TNF and IL-6 levels at the beginning of the study and decreased significantly at its conclusion [151]. These results indicate that objective inflammation markers may identify a subgroup of children with ASD, who are most amenable to treatment with luteolin/ quercetin. We recently showed that methoxyluteolin (5, 7, 3', 4'-tetramethoxyflavone) is a more potent inhibitor of human cultured MCs than luteolin [206] and has better bioavailability [207]. It could, therefore, be developed for treatment of ASD.

Antipurines

Suramin, an old antiparacytic drug which also has antipurinergic properties, was reported to inhibit autism-like behavior in mice [208,209]. However, suramin has serious adverse effects in humans [210].

Conclusion

With the ever growing prevalence of ASD and autoimmune disorders, their management is becoming of increased concern. Important steps step in the fight against ASD is to avoid known risk factors and provide supportive help (such as speech, music and exercise interventions) as early as possible. However, addressing allergic symptoms and reducing inflammation, as with the use of luteolin/quercetin, may target the core pathology. For these reasons, flavonoids are now being increasingly discussed for the treatment of neuropsychiatric [211] and neurodegenerative [212] diseases, including "brain fog," characterized by reduced attention span, memory and learning [213].

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Disclosures

TCT has been awarded US Patents No 8,268,365; 9,050,275 and 9,176,146 covering treatment of brain inflammation and of ASD. TCT has also developed the Trademarked dietary supplements BrainGain, NeuroProtek, NeuroProtek-Low Phenol and is the Scientific Director of Algonot, LLC.

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