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BRIEF REPORT

Brief Report: "Allergic Symptoms" in Children with Autism Spectrum Disorders. More than Meets the Eye?

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Abstract Many children with Autism Spectrum Disorders (ASD) have either family and/or personal history of "allergic symptomatology", often in the absence of positive skin or RAST tests. These symptoms may suggest mast cell activation by non-allergic triggers. Moreover, children with mastocytosis or mast cell activation syndrome (MCAS), a spectrum of rare diseases characterized by increased number of activated mast cells in many organs, appear to have ASD at a rate tenfold higher (1/10 children) than that of the general population (1/100 children). Mast cell activation by allergic, infectious, environmental and stress-related triggers, especially perinatally, would release pro-inflammatory and neurotoxic molecules. We speculate these could disrupt the gut–blood–brain barriers, thus contributing to brain inflammation and ASD pathogenesis. Increased mast cell responsiveness may define at least a subgroup of ASD subjects, who could benefit from inhibition of mast cell activation.

Keywords Allergy · Autism · Brain · Food intolerance · Inflammation · Mast cells

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Autism Spectrum Disorders

Over the last 20 years, there has been an impressive rise in Autism Spectrum Disorders (ASD) to a current prevalence of about 1/100 children (Fombonne 2009; Kogan et al. 2009; Blaxill 2004). ASD are pervasive developmental disorders that comprise of autistic disorder, Asperger's Disorder and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) (Johnson and Myers 2007). ASD are characterized by variable deficits in cognitive, language and social skills, as well as stereotypic behaviors. ASD manifest during childhood and at least 30% present with sudden clinical regression of development, characterized by loss of skills that had been previously acquired (Matson and Kozlowski 2010; Stefanatos 2008; Zappella 2010). In the majority of cases, the cause of ASD is unknown (Levy et al. 2009), although some autism susceptibility genes may be involved (Weiss et al. 2009). However, such genes do not explain more than about 5% of ASD inviting the suggestion that gene interactions with environmental factors may be involved (Herbert 2010).

Table 1 Diseases involving mast cell activation

1. Primary
(a) Mastocytosis
(b) Monoclonal mast cell activation disorder (MMAS)
2. Secondary
(a) Allergies
(b) Mast cell activation in inflammation or cancer
(c) Physical urticarias
(d) Chronic autoimmune urticaria
3. Idiopathic
(a) Anaphylaxis
(b) Angioedema
(c) Urticaria
(d) Mast cell activation syndrome (MCAS)

Adopted from (Akin et al. 2010)

Table 2 Diseases in which mast cells participate

Asthma
Atopic dermatitis
Food intolerance
Inflammatory bowel disease
Interstitial cystitis
Irritable bowel syndrome
Migraines
Multiple sclerosis
Rhinitis, allergic/perennial

In view of the fact that an "epidemic" of atopic diseases has been developing over the last decade (Holgate and Polosa 2008), we reviewed available evidence about allergies and "allergic-like" symptoms in patients with ASD. It should be noted, however, that there are different diseases with such symptoms that do not qualify as "allergic" but are officially classified as involving mast cell activation (Table 1) (Akin et al. 2010) and those should also be taken into consideration. Moreover, there are additional diseases in which mast cells are involved, but are not necessarily classified as "mast cell diseases", such as asthma and rhinitis (Table 2). Most publications discussed are case–control studies inherently subject to possible reporting bias of parents. Moreover, ASD endophenotypes were often not defined, possibly leading to misinterpretations in data analysis. Nevertheless, there are some interesting associations that call for further investigation.

Seasonal Changes and "Allergic Symptoms" in Children with ASD

There is some evidence that there are significant changes in behavioral problems among young adults with autism (n = 23) with worsening of their symptoms occurring in mid-April (Boso et al. 2010). This observation is consistent with anecdotal information that ASD symptoms worsen when allergy season peaks or "allergic symptoms" worsen. Additional findings have prompted the suggestion that ASD may have a "neuroimmune" component (Theoharides et al. 2009), as well as dysfunctional immune system (Ashwood et al. 2006; Goines and Van de Water 2010), as also implied in a recent observational study of ASD and allergies in children (Jyonouchi 2010).

A case–control study (420 ASD cases vs. 2,100 controls), nested within a cohort of infants born in California between 1995 and 1999, used health records to examine the association of 44 "immune-related conditions" with ASD; it reported that high prevalence of maternal psoriasis, asthma, hay fever and atopic dermatitis during the second trimester of pregnancy correlated with a greater than two-fold elevated risk of ASD in their children (Croen et al. 2005). A more recent study of Asperger patients (n = 15) reported that immune allergic responses (represented by the frequency of atopic dermatitis, asthma and rhinitis, as well as high serum IgE, number of eosinophils and positive skin tests) were observed in 86.6% of patients, compared to 7% of age-matched healthy controls (Magalhaes et al. 2009). In a National Survey of Children's Health, parents of autistic children (n = 483) reported more symptoms of allergies (also anxiety/depression) than those of healthy control children (n = 84,789), with food allergies being the most prevalent complaint (Gurney et al. 2006). It should be noted, however, that parents often confuse food allergies with food intolerance or sensitivities. In another study of autistic children (n = 50, 30 with mild to moderate autism and 20 with severe autism) 52% had allergic manifestations (bronchial asthma, atopic dermatitis, and allergic rhinitis) as compared to 10% in the control group (n = 50) ($p = 0.001$); moreover, there was a significant positive correlation between symptom severity and allergic manifestations (Mostafa et al. 2008). Children with ASD (n = 245) were evaluated in a recent paper of autism endophenotypes and a strong association was detected between autism and a history of allergies (Sacco et al. 2010). In a study of environmental factors and children with ASD (n = 72) in Sweden, there was a statistically significant association of polyvinyl chloride (PVC) exposure, wheezing and asthma with the development of ASD 5 years later (Larsson et al. 2009).

There is also evidence of non-IgE-mediated "allergic symptoms". In a hospital-based case–control study, 30% of autistic children (n = 30, 1–4 years old) compared to 2.5% of age-matched "neurologic controls" (n = 39) had a family history of allergic features ($p < 0.005$), based on

questionnaires completed by the parents and scored blindly by an allergist. Even though ASD children (47.8%) were positive for at least one of skin prick tests to 12 common antigens, there was no difference from controls with regards to allergic symptoms (Bakkaloglu et al. 2008). However, the limitations of this study should be taken into account; for instance skin prick tests were administered only in the ASD group. Interestingly, assessment of 5 children with multiple skin prick testing positivity revealed that the 4 tested negative for antigen-specific IgE. The percentage of positive skin testing in ASD (47.8%) was apparently similar to that seen in the Turkish source pediatric population; however the latter was surprisingly higher than that reported for the 4–5 year-old pediatric population in other countries like Finland (17–19.6%).

Another study investigated the prevalence of atopy, asthma, food allergy in two subsets of children with ASD (n = 26 was the test subgroup with frequent infections and more behavioral problems; n = 107 was the ASD "control" subgroup without frequent infections), compared to non-ASD controls (n = 43). Despite the fact that many ASD children were reported by their parents to have "allergic symptoms", there was no difference from controls. However, non-IgE-mediated food sensitivity was observed at a significantly higher frequency in both ASD subgroups compared to controls (Jyonouchi et al. 2008).

"Allergic-like" skin reactions in some ASD patients may be indicative of idiopathic or autoimmune urticaria, (Kaplan and Greaves 2009; Novembre et al. 2008) instead of allergies (Table 1). Moreover, many patients with "allergic-like" symptoms may qualify for a new diagnostic entity, "mast cell activation syndrome" (MCAS) (Akin et al. 2010). The *Mastocytosis Society* (www.tmsforacure.org) together with the American Academy of Allergy, Asthma and Immunology recently produced a DVD, entitled "*Mast cell activation symptomatology*" (available to physicians) in order to highlight the fact that allergies may be only one aspect of mast cell activation. Preliminary results suggest that the prevalence of ASD and some additional relevant diagnoses other than those commonly accepted as part of the spectrum, is tenfold higher (1/10 children) in patients with mastocytosis or MCAS, than that in the general population (1/100 children) (Theoharides 2009). Mastocytosis is a rare spectrum of disorders with a prevalence of about 1/4,000 children, which involve proliferation and activation of mast cells in the skin (urticaria pigmentosa, UP) and other organs (Castells 2006). Symptoms include skin reactions, food sensitivities, behavioral problems, lack of concentration ("brain fog") and irritability (Akin et al. 2006; Valent et al. 2001).

Functional mast cell-neuron interactions occur in the brain (Roznieckі et al. 1999) and the gastrointestinal (GI) tract (Asadullah et al. 2003). Mast cells are involved in GI pathology, inflammation and increased intestinal permeability (Farhadi et al. 2007), which may also explain the relationship between food intake and GI-related symptoms in ASD patients (Erickson et al. 2005; Jyonouchi 2009; Levy et al. 2007). However, properly-powered prospective studies with appropriate controls are needed to support existing evidence and define the role of abnormal intestinal permeability in ASD pathogenesis (Buie et al. 2010).

Non-immune Mast Cell Triggers

Some of the case–control studies reviewed suggest mast cell activation, even though not necessarily by allergic triggers. Mast cells are critical for allergic reactions during which they are stimulated by IgE binding to high-affinity receptors (FcεRI), aggregation of which leads to degranulation and secretion of numerous pre-stored and newly-synthesized mediators (Blank and Rivera 2004; Kraft and Kinet 2007). Mast cells are also important in both innate and acquired immunity (Galli et al. 2005), as well as in inflammation (Theoharides and Cochrane 2004).

The involvement of mast cells in IgE-mediated or non-IgE "allergic reactions" varies considerably among different tissues and diseases (Jyonouchi 2010), as well as different species (Bischoff 2007), making generalizations difficult. In addition to IgE, many substances originating in the environment, the intestine or the brain can trigger mast cell activation (Theoharides and Kalogeromitros 2006) (Fig. 1).

The apparent presence of "non-IgE allergic-like" symptoms in ASD patients points to mast cell stimulation by non-allergic triggers, possibly involving release of mediators selectively, without degranulation (Theoharides et al. 2007). For instance, bacterial lipopolysaccharide (LPS) activates Toll-like receptor-4 (TLR-4) on mast cells and induces selective release of TNF (Varadaradjalou et al. 2003), while IL-1 induces selective release of IL-6 (Kandere-Grzybowska et al. 2003). In this context it is interesting that TNF was high in the cerebrospinal fluid (CSF) (Chez et al. 2007), and IL-6 gene expression was increased in the brain (Li et al. 2009) of autistic patients. Mast cells also express viral TLR-3, activation of which by viral double-stranded RNA induces release of TNF and IL-6 without degranulation (Kulka et al. 2004). The ability of viruses to trigger mast cell activation is especially relevant, since a number of rotaviruses have been isolated from asymptomatic neonates (Dunn et al. 1993) and could activate mast cells at that age.

Environmental toxins have been implicated in developmental neurotoxicity (Grandjean and Landrigan 2006) and also in mast cell activation: for instance, polychlorinated biphenyl (PCB) (Hertz-Picciotto et al. 2008) and mercury

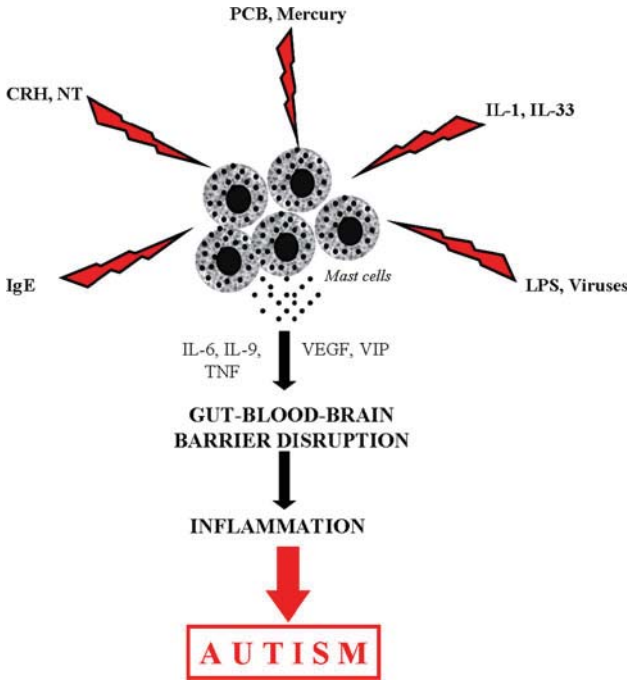

Fig. 1 Schematic representation of the possible involvement of mast cell activation by allergic and non-immune triggers in the pathogenesis of autism. *CRH* corticotropin-releasing hormone, *IL* interleukin, *LPS* lipopolysaccharide, *NT* neurotensin, *PCB* polychlorinated biphenyl, *TNF* tumor necrosis factor, *VEGF* vascular endothelial growth factor, *VIP* vasoactive intestinal peptide

(Young et al. 2008) have been associated with ASD, and both also activate mast cells (Kempuraj et al. 2010; Kwon et al. 2002). Additional indirect evidence may link mast cells to autism. CSF and microglia of ASD patients had high levels of macrophage chemoattractant protein-1 (MCP-1) (Vargas et al. 2005), which is also a potent chemoattractant for mast cells (Conti et al. 1997). In contrast, ASD plasma levels of transforming growth factor-beta1 (TGF-β1) were low (Ashwood et al. 2008), which is important in view of the fact that TGF-β1 inhibits mast cell function (Gebhardt et al. 2005).

Other mast cell triggers include bacterial and viral antigens, as well as peptides such as neurotensin (NT) and corticotropin-releasing hormone (CRH), which stimulates selective release of vascular endothelial growth factor (VEGF) (Cao et al. 2005). CRH is typically secreted from the hypothalamus, but it can also be secreted from nerve endings outside the brain, where it exerts pro-inflammatory effects (Chrousos 1995; Slominski et al. 2001; Theoharides et al. 2008). In fact, CRH acts synergistically with NT to increase vascular permeability (Donelan et al. 2006). In this context, it is important that NT levels were increased in the serum of young children with autistic disorder as compared to normal, age-matched controls (Angelidou et al. 2010).

The effect of CRH may be relevant to ASD. ASD patients had high anxiety levels and were unable to handle stress appropriately (Gillott and Standen 2007). Evening cortisol levels positively correlated to daily stressors in children with autism (Corbett et al. 2009). Moreover, increase in age of autistic children correlated with increased cortisol level during social interaction stress (Corbett et al. 2010). However, it should be noted that peripheral CRH release can be independent of hypothalamic–pituitary axis (HPA) activation status (Chrousos 1995) and may serve as a distinct biomarker. In fact, CRH can disrupt the blood–brain barrier (BBB) (Theoharides and Konstantinidou 2007). BBB disruption in autistic children is suggested by the presence of autoantibodies against encephalogenic peptides in as many as 60% of ASD patients (Cabanlit et al. 2007; Goines et al. 2010; Singer et al. 2006; Vojdani et al. 2002; Wills et al. 2008). Mast cell-derived cytokines can also disrupt BBB permeability (Abbott 2000; Theoharides and Konstantinidou 2007). It is intriguing that mast cell-derived IL-9 induces intestinal permeability and predisposes to oral antigen hypersensitivity in children (Forbes et al. 2008), while it also exacerbates newborn brain toxic lesions (Dommergues et al. 2000).

We speculate that perinatal mast cell activation, in response to allergic or non-immune triggers, could disrupt the gut–blood–brain barriers (Theoharides et al. 2008) and permit neurotoxic molecules to enter the brain and result in brain inflammation, thus contributing to ASD pathogenesis (Fig. 2). BBB disruption has been documented in brain inflammatory diseases, such as multiple sclerosis, where it *precedes* any pathological or clinical symptoms (Minagar and Alexander 2003; Soon et al. 2007; Stone et al. 1995).

Conclusion

The papers discussed above often suffered from the use of different methodologies and lack of precise definitions of ASD endophenotypes, thus losing specificity. Moreover, the evidence discussed does not imply a "cause and effect" relationship. Nevertheless, subjects with hypersensitive mast cells and/or ASD susceptibility genes may represent a unique subgroup of patients who are more likely to respond to environmental and stress triggers, leading to precipitating or worsening ASD. It is important to investigate mast cell-associated triggers and mediators in patients with ASD, especially close to the time the diagnosis is made. Such efforts could help unveil novel aspects of the pathogenesis of ASD, identify potential biomarkers, as well as establish new therapeutic targets.

In the meantime, blocking mast cell activation may prove to be useful both for reducing the "allergic-like" symptoms and possibly ASD-related behavior. For instance, the natural mast cell inhibitor luteolin (Kempuraj et al. 2008) has already been shown to decrease IL-6

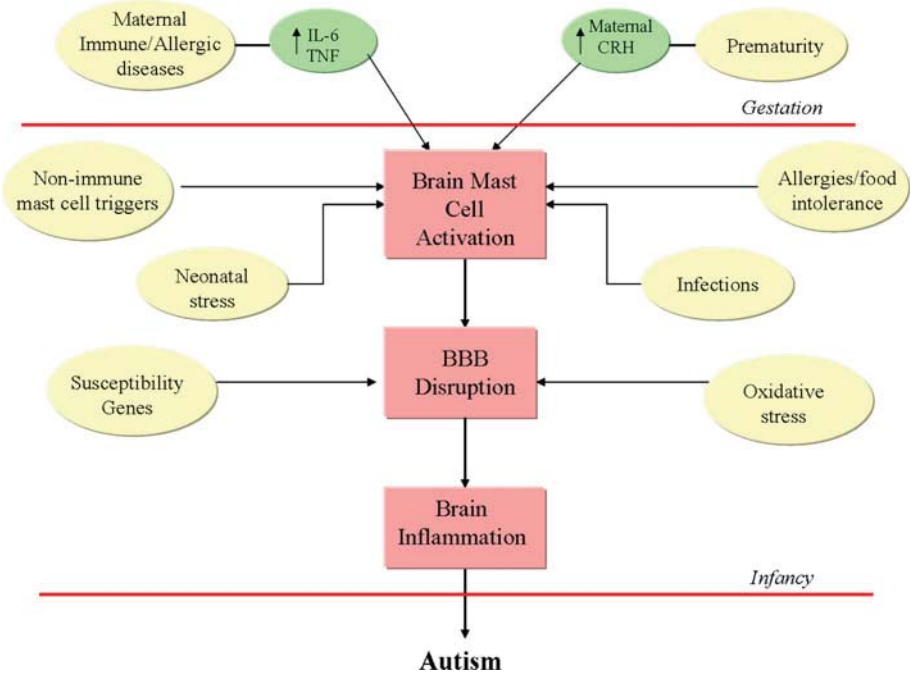

Fig. 2 Schematic representation of the possible steps involved in perinatal mast cell activation by allergic and non-immune triggers, disruption of the blood–brain barrier, and brain inflammation leading to autism. *BBB* blood–brain barrier, *CRH* corticotropin-releasing hormone, *IL* interleukin, *TNF* tumor necrosis factor

release (Jang et al. 2008) and induce an anti-inflammatory phenotype (Dirscherl et al. 2010) in microglia. Luteolin also inhibits an autistic-like behavior in mice (Dirscherl et al. 2010). A unique luteolin formulation with high oral absorption is presently awaiting clinical trials.

Health care providers should be alerted to "allergic-like" symptoms that could be challenging in cases of atypical presentations or non-verbal individuals with ASD. It is imperative that proper epidemiologic studies be conducted to determine the true prevalence of mast cell activation in well-defined ASD populations, and identify its role in the neuropsychiatric manifestations of ASD.

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Conflict of interest TCT is on the Scientific Advisory Board of The Mastocytosis Society. TCT is also the inventor of patent application US 12/534,571 "Methods of diagnosis and treating autism" that covers a new luteolin-containing dietary supplement NeuroProtek® (www.algonot.com).

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