

## EDITORIAL

## AUTISM SPECTRUM DISORDERS AND MASTOCYTOSIS

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**Autism Spectrum Disorders (ASD) are diagnosed in early childhood and include Autism, Asperger's disorder and Pervasive neurodevelopmental disorder - not otherwise specified (PDD-NOS, or atypical autism). ASD are associated with varying degrees of dysfunctional communication and social skills, repetitive and stereotypic behaviors, as well as attention and learning disabilities. Most ASD patients also have food intolerance and other allergic symptomatology indicative of mast cell activation. The number of ASD cases have increased over the last decade to 1/100, but there is no definite pathogenesis or curative therapy. We report that the apparent prevalence of ASD in patients with mastocytosis, a rare disease occurring in 1/4,000 children and characterized by an increased number of hypersensitive mast cells in many organs, is about 1/10 or 10 times higher than the general population. A child with skin mastocytosis [urticaria pigmentosa, (UP)] and regressive autism is presented to illustrate the point. Allergic, infectious, neuroimmune and environmental triggers may activate mast cells to release vasoactive, inflammatory and neurotoxic molecules. These could disrupt the gut-blood-brain-barriers (BBB), and/or activate susceptibility genes, thus contributing to brain inflammation and ASD.**

Autism Spectrum Disorders (ASD) are pervasive developmental disorders, diagnosed in early childhood, that include autistic disorder, Asperger's disorder, and atypical autism, otherwise known as pervasive developmental disorder not otherwise specified (PDD-NOS) (1). These are neurodevelopmental disorders, characterized by varying degrees of dysfunctional communication and social skills, repetitive and stereotypic behaviors, as well as attention, cognitive, learning and sensory defects (1). The diagnosis of ASD has increased more than 10-fold during the last decade to 1/100 (2-5).

Increasing evidence suggests that ASD may be a neuroimmune disorder (6). Allergic symptomatology

and food intolerance is present in most ASD patients (7). A recent paper reported that 87% of Asperger patients had evidence of atopy, as compared to 7% in healthy controls (8). In a National Survey of Children's Health, parents of autistic children reported symptoms of allergies more often than other children, with food allergies showing the greatest difference (2). Food intolerance is also quite prevalent in mastocytosis, a spectrum of rare disorders involving proliferation and activation of mast cells in the skin, intestine and other organs (9). The most common manifestation of mastocytosis is urticaria pigmentosa (UP), which is characterized by small brown-red maculopapules on the skin (10), and allergic-like symptoms such as flushing and

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**Table I.** Mastocytosis patients with ASD.

Patient	Age in 2008	Sex	ASD	Mast cell diagnosis
1	4	M	Stuttering, high functioning	Mastocytoma, solitary
2	15	M	ASD, poor speech	UP, asthma
3	11	M	Asperger's	UP, NF1
4	18	M <sup>†</sup>	ASD, dyslexia	SM
5	44	M <sup>†</sup>	Asperger's	Mastocytosis, UP?
6	21	F	SID	UP
7	21	F	SID	Mastocytosis
8	18	M	Asperger's	Mastocytosis
26	7.5	M	Autism	Mastocytoma, solitary
10	4	M	ASD, ADHD, SID	Mastocytosis, UP?, flushing, GI
11	9	M	Asperger's	UP, hives, rash, GI (brother with masto)
12	3.5	M	PDD-NOS	Mastocytosis
13	46 (father)	M <sup>#</sup>	Asperger's	Hives, asthma
14	10 (daughter)	F <sup>#</sup>	Asperger's	Diarrhea, hives, itching
15	8 (son)	M <sup>#</sup>	Mood problems, ADD	Mastocytosis
16	2.5	F	Autism spectrum, PDD-NOS	UP, SM?
17	17	F	Asperger's	MCD, food intolerance
18	9	M	Asperger's	MCD
19	15	M	Asperger's	asthma
20	23	F	Mild autism, ADD	MCD
21	4	M	Asperger's	Mastocytosis
22	7	M	Asperger's (mild)	UP
23	2	M	ASD, SID	Mastocytosis, Celiac disease
24	21	F	Asperger's	SM
25	4.5	M	ASD, moderate	Mastocytoma, solitary
26	8	F	Asperger's	UP
27	5	F	PDD-NOS	MCD, flushing, milk, intolerance, anxiety
28	2.5	M	Regressive autism	MCD, flushing, food intolerance, acute lymphocytic anemia
29	3.5	M <sup>&amp;</sup>	PDD-NOS, regressive	UP, GI symptoms
30	6.6	M <sup>&amp;</sup>	SID	Food hypersensitivities
31	10.5	M <sup>&amp;</sup>	ADD, Asperger's ?	Food hypersensitivities
32	4	M	PDD-NOS	Mastocytoma, allergies, loose stools
33	4	M	Autism	Mastocytoma
34	7	F	SID	Mastocytoma, flushing headaches
35	12-premature	M	Autism, regressive	Allergies, GI symptoms (skin negative)
36	6	M	Autism	Allergies, asthma, food allergies
37	8	M	Autism	Food allergies, high IgE, mitochondrial d.
38	57	M	Asperger's	Indolent systemic mastocytosis, IC
39	?	F	Asperger's	Indolent systemic mastocytosis, GI Sxs
40	11 months	M	PDD-NOS	UP
41	4-premature (triplets)	M	Asperger's (two of the three)	UP, allergies, GI problems

ADHD=Attention Deficit Hyperactivity Disorder; IC=Interstitial Cystitis; MCD=Mast Cell Disease; PDD-NOS=Pervasive Developmental Disorder-Not Otherwise Specified; NF1=Neurofibromatosis-1; SID=Sensory Integration Dysfunction; SM=Systemic Mastocytosis; UP=Urticaria Pigmentosa; #, & Within the same family

hives (11). About 15% of mastocytosis patients also have a short attention span, difficulty concentrating, forgetfulness, confusion, and irritability (9), all ASD-like symptoms. This apparent symptom overlap prompted us to investigate any possible association between mastocytosis and ASD further.

Data were obtained in response to a question listed below that was sent by the Mastocytosis Society ([www.tmsforacure.org](http://www.tmsforacure.org)) to a database of 400 patients: "Could you please let us know if you or any

of your children have been diagnosed with Autism or an Autism Spectrum Disorder (e.g. Asperger's disorder). Please include your and your child's sex, current age, age at time of diagnosis, and how/where diagnosis was made." The particular type of mastocytosis and other mast cell-related symptoms were also requested, including whether any parent had a diagnosis of mastocytosis. Those who replied were further asked to complete a questionnaire including the precise ASD diagnosis made by a

**Table II.** Mastocytosis parents with children with ASD.

Parent	Age in 2008	Sex	Mast cell diagnosis	Child with ASD-Sex, Age at Dx
1	48	F	Systemic mastocytosis	ADD, Asperger's-M, 5 y/o
2	43	F	MCD	Autism, FCAS-F triplets, 2 y/o
3	45	F	Systemic mastocytosis	Asperger's, Mast cell disease
4	?	F	UP, Systemic mastocytosis	Asperger's, ADD, asthma, M
5	45	F	Systemic mastocytosis	Mild autism, ADD, MCAS, F
6	?	F	Systemic mastocytosis	Asperger's, ADD, M
7	?	F	Mastocytosis	Asperger's, 15 y/o
8	?	F	Systemic mastocytosis	Niece with Asperger's, F
9	42	F	MCD	Asperger's F 10 y/o, ADD M 8 y/o
10	46	F	Indolent SM, UP	Rett syndrome, F, 6 y/o
11	56	F	MCD	Asperger's, F, 5 y/o
12	49	M	Indolent SM	Asperger's, M, 14 y/o
13	41	F	MCD, Flushing, IBS, Psoriasis	PDD-NOS, F, 5 y/o
14	49	F	Indolent SM	Asperger's, M, 4 y/o (two of triplets)

FCAS=Familial Cold Auto-inflammatory Syndrome; MCD=Mast Cell Disease

health professional using either ADOS-G or the criteria set forward in DSM-IV. The survey was e-mailed to 400 mastocytosis patients and resulted in 41 positive responses from patients who had both mastocytosis, and ASD (Table I); this translates to a prevalence of about 10/100, over 10 times higher than the 1/100 recently reported for the general population (4). In three cases, there were two or more members of the same family with both mastocytosis and ASD (Table I).

The ages of the patients varied from 1-46 years, with the mean age being 11.8 years (Table I). There were 31 males and 10 females. The predominant ASD diagnosis was Asperger's syndrome, while the most common type of mastocytosis was UP (Table I). A case in point (#29, Table 1) is presented. This is a 4-year-old Caucasian, non-Latino, male who was diagnosed with UP (Fig. 1A) at age 1 year. The pediatrician at that time suggested that the skin spots would go away with time, but they increased after routine vaccination at age 3 years. Soon thereafter, the child regressed and was diagnosed with PDD-NOS. The child has also often experienced skin rashes that were associated with worsening of his behavioral status, even though it tested negative on skin prick and Rast tests.

There were also a number of parents (3 mothers and 1 father) with mastocytosis before/during

conception, who had one or more children with ASD (Table II).

Our present results indicate a higher prevalence of ASD in mastocytosis patients, as well as in mothers who had mastocytosis during gestation. Even though, this is a preliminary report, the apparent association is intriguing since the prevalence of mastocytosis is estimated to 1/4,000 (11-13). About 15% of mastocytosis patients also have a short attention span, difficulty concentrating, forgetfulness, confusion, "brain fog" and irritability (9), all ASD-like symptoms. It should be emphasized that neuropsychiatric symptoms present in mastocytosis patients do not necessarily present evidence of ASD. Clinical evidence also suggests comorbidity of ASD and mast cell activation as evidenced by allergic symptomatology and food intolerance in ASD patients. A recent paper reported that 87% of Asperger patients had evidence of atopy, as compared to 7% in healthy controls (8). In a National Survey of Children's Health, parents of autistic children reported symptoms of allergies more often than other children, with food allergies showing the greatest difference (2). In another study of 30 autistic children and age-matched controls with other neurologic diseases from the same hospital, 30% of children with ASD had a history of atopy as compared to 2.5% of controls, again with



**Fig. 1.** The back of the patient showing obvious urticaria pigmentosa lesions (solid arrows).

no statistical difference in serum IgE (14). In a brief report of 362 ASD patients, the only statistically significant correlation was with history of allergies (15). A nested case control study of 407 ASD children and 2095 controls showed that there was a greater than 2-fold higher risk of children with ASD born to mothers who had a diagnosis of allergies or asthma during the second trimester of pregnancy (16). Mast cell activation typically leads to allergic reactions (17), but is also involved in immunity (18-19) and in inflammation (20). In addition to allergic stimulation, many other substances originating in the gut or the brain can trigger mast cell secretion (17). These include immunoglobulin-free light chains, bacterial and viral products and superantigens, as well as neuropeptides, such as substance P (SP), and neurotensin (NT). Mast cells, in turn, secrete numerous vasoactive, neurosensitizing and proinflammatory mediators, especially histamine, vascular endothelial growth factor (VEGF), prostaglandins and cytokines, such as IL-6, IL-8, IL-13 and TNF, which increase blood-brain-barrier (BBB) permeability (21-23). Release of such cytokines may be important in the pathogenesis of ASD since TNF was shown to be elevated in the

CSF of autistic children (24), IL-6 expression was increased in brain of autistic patients (25), while IL-6 was shown to induce autistic-like behavior in mice (26). Serum IL-6 was also high in patients with mastocytosis (27).

Mast cells could release mediators other than histamine *selectively* (28), especially VEGF in response to corticotropin-releasing-hormone (CRH) (29), and IL-6 in response to IL-1 (30). It is interesting that postmortem brains, microglia and CSF of ASD patients had high levels of macrophage chemoattractant protein-1 (MCP-1) (31), which is also a potent chemoattractant for mast cells (32). In contrast, plasma levels of transforming growth factor-beta 1 (TGF- $\beta$ 1) were low (33), which is important in view of the fact that TGF- $\beta$ 1 inhibits mast cell function and Fc $\epsilon$ RI expression (34). Serum from autistic children contains a number of autoantibodies against encephalogenic peptides, findings that suggest BBB disruption (35-39). Mast cells can disrupt the BBB in rats (40) through corticotropin-releasing hormone (CRH) (41), secreted under stress. Acute restraint stress also stimulates intestinal mast cells and disrupts the gut-blood barrier in rodents (42), while CRH can increase permeability in normal human colonic biopsies through activation of subepithelial mast cells (43). These findings may be relevant to the gastrointestinal complaints common to many ASD patients (2).

A dysfunctional gut-blood-brain barrier (7) could expose local mast cells to environmental and innate substances triggering the release of vasoactive, inflammatory and neurosensitizing mediators (44-45, 7). These could also activate susceptibility genes leading to ASD. Mastocytosis may represent only a subgroup of patients with ASD, but it points to unique associations worthy of further investigation. A prospective study identifying ASD in mastocytosis patients, with precise diagnoses in each case by the same clinicians, would be important and could also provide biological samples for possible biomarker analysis.

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