

Clinical Communications

Neurocognitive dysfunction and anaphylaxis in pediatric maculopapular cutaneous mastocytosis

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Clinical Implications

- Children with maculopapular cutaneous mastocytosis are unlikely to have higher rates of developmental disorders or anaphylaxis than healthy children.

TO THE EDITOR:

Cutaneous mastocytosis is a group of conditions associated with proliferation of mast cells in the skin. The most common form in children is maculopapular cutaneous mastocytosis (MPCM).¹ Autism spectrum disorders were found to be more than 10-fold higher than baseline rates in patients with any form of mastocytosis,² and learning disabilities have also tended to be more prevalent in the families of children with cutaneous mastocytosis.³ Similarly, systemic mastocytosis overall is associated with high rates of anaphylaxis,⁴ although the risk in pediatric MPCM may be lower. In a large cohort of children with MPCM, we examined the prevalence of anaphylaxis and neurodevelopmental disorders, defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) as conditions with onset in childhood impacting social function or academic achievement.

Data were collected through chart review from patients with MPCM, as defined by Heide et al,⁵ with onset before age 15 years after obtaining institutional review board's approval and parental written informed consent/patient assent as appropriate. Patients had been seen in dermatology clinics at Emory University, Texas Children's Hospital, Seattle Children's Hospital, Mayo Clinic, and the Ann and Robert H. Lurie Children's Hospital of Chicago. Patients with other forms of cutaneous and systemic mastocytosis were excluded. Data on demographics and skin and systemic signs and symptoms were collected from sequential visits when available. Patients without data for a variable were excluded from analysis.

The prevalence of neurodevelopmental disorders was reported for each patient in response to the following: "Any history of: Attention-Deficit/Hyperactivity Disorder (ADHD), developmental delay, autism spectrum disorder, sensory integration disorder, other cognitive disorder?" Diagnoses reported were developmental delay, ADHD, dysgraphia, habitual behaviors, and autism. We were not able to independently verify the reported diagnoses and relied on the patients' medical record. Diagnoses of depression, anxiety, and oppositional defiant disorder were not considered within the definition of neurodevelopmental disorder, as these diagnoses are classified

elsewhere in DSM-5.⁶ Patients undergoing testing for neurodevelopmental disorders were also excluded.

χ^2 testing was performed for categorical variables, whereas Student's *t*-test and Kruskal Wallis tests were used for numerical covariate univariate analysis. Statistical analyses were conducted using SAS statistical package V9.4 (SAS Institute Inc., Cary, NC).

A total of 227 patients were available for analysis. An average of 1.4 visits per patient (range, 1-7) were recorded. The median age of onset of MPCM was 3 months (range, 0-15 years). Patients were predominantly non-Hispanic Caucasian (79%), with fewer Hispanic (10%), Asian/Pacific Islander (3.2%), and African American (1%) patients. Of the 203 patients with available data, 26.1% had a biopsy for diagnostic confirmation.

Nine patients reported anaphylaxis, with 3 after arthropod bites, 1 after ingesting nuts, 1 from midazolam administration, and the remaining 4 from an unknown trigger. Anaphylaxis was associated with a greater number of systemic symptoms ($P < .001$) and skin signs and symptoms, including itch, flushing, bullae, Darier's sign on examination ($P = .004$), but not with age of onset or lesion count. Only 3 of 9 patients reporting anaphylaxis had a reported tryptase level, limiting analysis of the relation between tryptase level and occurrence of anaphylaxis.

Fifteen patients (8.2%) overall were diagnosed with a neurodevelopmental disorder (95% confidence interval [CI], 4.7% to 13.4%), and the risk was higher in patients with data between ages 3 and 18 years (10.5%; 95% CI, 4.9-18.94). Four additional children were undergoing testing, and 4 had concern for developmental delays before age 3 years without further follow-up. The average age at the last follow-up for those with data on neurodevelopmental disorders was 5.5 years (range, 3 months to 28 years). Diagnoses included developmental delay, ADHD, dysgraphia, habitual behaviors, and autism. The number of skin and systemic signs and symptoms reported by the patient did not correlate with the development of neurodevelopmental disorders, nor did the age of onset of MPCM. Antihistamine use was not associated with neurodevelopmental disorders.

We present 227 patients with pediatric onset MPCM from 5 institutions. Onset before age 2 years in our study matches large retrospective analyses of pediatric mastocytosis.¹ Most patients were Caucasian, with African American children representing only 1% of cases, which is not reflective of the demographics of the reporting institutions. It is unclear whether this represents underdiagnosis in more darkly pigmented patients or a lower disease prevalence.

A neurodevelopmental disorder was described in 8.2% of the children, with a higher prevalence when data were available after 3 years of age. A recent European analysis reported that the average age of diagnosis of ADHD is 9.7 years,⁷ suggesting that our data may underestimate the prevalence of neurodevelopmental disorders. Boyle et al⁸ reported that 13.87% of children aged 3 to 18 years in the United States have been diagnosed with neurodevelopmental disorders, whereas in our study the rate in 86 patients of the same age group was 10.5% (95% CI, 4.9-18.94). A future study would require 810 patients to achieve 80% power at the significance level of 0.05 to detect a difference relative to the data reported by Boyle et al.⁸

Adults with systemic mastocytosis have a high rate of anaphylaxis, with reported rates as high as 49%.⁹ In a large meta-analysis, 5.5% of 1747 pediatric patients reported anaphylaxis,¹ a rate similar to the children in our study (4.7%). Heinze et al¹⁰ followed 43 children with MPCM for an average of 8.1 years with no reported anaphylaxis. The most common etiology for anaphylaxis in our study was “unknown,” as in previous studies.⁹ Anaphylaxis was reported as documented in the medical record, and further data on elevation in tryptase during episodes of anaphylaxis, IgE sensitization, and further workup of etiology of anaphylaxis were not available.

Although our cohort was relatively large, a full dataset was not available for each patient, given the retrospective nature of our study. The diagnoses of neurodevelopmental disorders and anaphylaxis were based on clinician report. Although our preliminary data did not suggest an increased rate of neurodevelopmental disorders in MPCM, a larger prospective study with longer follow-up will be essential to address these possible associations.

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