Mast Cell Activation Syndrome in Children: a Nuanced Approach to Diagnosis and Patient Care

A Narrative Review Illustrated by Two Case Reports

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Abstract

Mast cell activation syndrome (MCAS) covers a range of conditions resulting from recurrent mast cell degranulation, sometimes manifesting as anaphylaxis. It is defined by three criteria: a clinical presentation of mast cell activation (clinical criterion), an increase in tryptase levels (biological criterion), and a favourable response to treatment (treatment criterion). A new classification has been developed that includes mast cell activation disorders (MCAD) that do not strictly meet the above criteria (in particular the biological criterion). This leads to an increasing number of patients being detected, some of whom may however benefit from MCAS treatment. MCAS can be divided into primary (clonal), secondary and idiopathic forms. There are also forms that combine MCAS with mastocytosis, hereditary alpha-tryptasemia and/or allergy. This diagnosis of exclusion needs to be assessed by a specialised multidisciplinary team, to avoid over- and under-diagnosis. Moreover, patients often experience a prolonged medical journey, requiring management of the significant psychosocial and financial repercussions for the child and his family.

Introduction

Mast cells are effectors of the innate immune system, whose granules contain numerous vasoactive and inflammatory mediators such as tryptase, prostaglandins and histamine. They are widely and abundantly spread in the human body, particularly in connective and mucosal tissues. Mast cell degranulation results in multisystemic symptoms of variable intensity and may result from both immunological and non-immunological triggers (1). Mast cells are involved in many pathologies, including allergy (ranging from acute urticaria to anaphylaxis), chronic urticaria, mastocytosis, hereditary alpha-tryptasemia (HαT), and mast cell activation syndrome (MCAS) (which is included in the mast cell activation disorders that are discussed within this article).

MCAS encompasses a heterogeneous group of clinical presentations, resulting from the release of mast cell mediators during mast cell activation. MCAS can be evoked in cases of systemic, recurrent, and severe symptoms of mast cell degranulation (sometimes manifesting as anaphylaxis), after exclusion of the various differential diagnoses (2).

To date, the literature defines mast cell activation based on the combination of clinical, biological and response criteria. However, these criteria are rarely fulfilled in paediatric clinical practice. A broader classification of mast cell activation disorders (MCAD) is emerging, yet their management remains a matter of controversy. In this article, we present two cases of suspected paediatric MCAS and their multidisciplinary management (1,2).

Case description

Case 1: A 3-year-old boy was referred to the paediatric allergology department from the emergency department for acute angioedema.

His medical history recorded a resolved non-IgE-mediated cow's milk protein allergy, controlled atopic dermatitis, broccoli and spinach intolerance without allergic sensitisation, and gastroesophageal reflux. Family history revealed occasional episodes of skin oedema, urticaria and joint pain in his father.

The boy is presented to the emergency department with localised pruritus on one thigh and general discomfort, after eating a large amount of various industrial sweets on Halloween. In the morning, he developed multiple oedemas (labial, palpebral, perineal, left hand), followed by coughing and sneezing. The symptoms were relieved by the administration of antihistamines.

At the allergology visit, he was advised to perform a measurement of baseline tryptase and of the tryptase elevation in the event of a new episode consistent with mast cell degranulation. The absence of C1-inhibitor deficiency ruled out hereditary angioedema. During the following month, the patient presented with several episodes of urticaria, and angioedema (face-perineum-hand) associated with abdominal symptoms (pain, and sometimes vomiting or diarrhoea). These events did not seem to be related to specific foods. However, two reactions occurred after taking ibuprofen, which had previously been tolerated.

A thorough anamnesis revealed punctual episodes of joint pain, irritability, sleep disturbances and rare episodes of constipation. The administration of antihistamines provided temporary relief of these symptoms. The association of these signs suggested a mast cell activation disorder. During one of the exacerbations, tryptase was measured at 6.4 ng/ml; however, this value is probably underestimated, as the sample was obtained 6 hours after the onset of symptoms. Baseline tryptase was measured at 2.7 ng/ml. The increase in the symptomatic phase is thus higher than 120% of baseline tryptase +2 ng/ml, which fulfils the MCAS biological criterion. Management was completed by the assessment of several specialists, in order to exclude other diseases. The dermatologist excluded cutaneous mastocytosis, and systemic mastocytosis criteria were not met (including genetic testing for *KIT* mutation). The gastropaediatrician did not report any digestive pathology, and an ENT specialist was consulted for persistent rhinitis. Following this exhaustive multidisciplinary assessment, probable MCAS was suspected and treatment with H1-antihistamines was initiated. The patient showed a favourable evolution within one month.

Our patient thus met the three diagnostic criteria for MCAS, and the diagnosis of idiopathic MCAS was established (in the absence of mast cell clonal disease or underlying pathology explaining the presentation). In addition to medical follow-up, the family received support from the team's dieticians and psychologists.

Case 2: A 3-year-old girl was referred to a combined paediatric gastroenterologist and allergology consultation for chronic abdominal pain.

Her past medical history was unremarkable. Family history revealed an allergy to raw egg white in her mother.

She had suffered from severe digestive discomfort since birth. Her symptoms of abdominal pain and alternating diarrhoea and constipation were followed by a paediatric gastroenterologist, but no digestive pathology was found. The implication of many foods has been suspected, but no allergy hs been demonstrated.

On presentation, the association of these symptoms with skin pruritus, transient perioral eruptions and leg pain raised the suspicion of MCAS. Biological assessment showed a normal baseline tryptase of 4.2 ng/ml. No tryptase was measured in the symptomatic phase, given the absence of clear acute reactions. Despite this absence of biological criteria, MCAS was suspected and treatment with antihistamines and sodium cromoglicate was initiated. The patient and her family also met with the paediatric pain team, as well as a psychologist and a dietician.

The treatment resulted in a rapid and spectacular regression of symptoms, thus fulfilling the response criterion at the follow-up visit 3 months later. The diagnosis is therefore unspecified MCAD, as the biological criterion was missing, that nevertheless showed a favourable response to MCAS treatment.

Discussion

Diagnostic criteria

As illustrated in the above clinical cases, no symptom is specific for mast cell degranulation. MCAS remains a diagnosis of exclusion and consists of the association of a clinical criterion (multisystem clinical signs of mast cell degranulation), a biological criterion (increased tryptase during a reaction) and finally a response criterion (response of symptoms to treatment) (1). Table 1 summarises these criteria.

Importantly, some patients show persistently elevated tryptase levels. Elevation of baseline serum tryptase above >8 ng/ml may suggest other pathologies such as hereditary α-tryptasemia, mastocytosis or other myeloid pathologies (1,7). HαT is autosomal dominant genetic polymorphism and is due to an increased number of *TPSAB1* copies, coding for alpha and beta tryptase. This polymorphism is present in 5-6% of the general population and leads to an elevated basal tryptase level. Most patients remain asymptomatic while a few present with symptoms of mast cell activation (7,8). Mastocytosis corresponds to a clonal expansion of mast cells and results in different symptoms depending on its location and systemic character (7).

Classification

Once diagnosis of MCAS is made, further classification is needed. MCAS are currently classified in primary (including mastocytosis and monoclonal mast cell activation syndrome), secondary (due to autoimmune, allergic or tumoral pathologies) or idiopathic forms (Table 2) (1). Recent articles propose to expand this classification by adding combined forms (associating primary and secondary MCAS) and MCAS + HαT forms (1,2). These combined forms are at higher risk of potentially severe reactions; particularly in patients combining systemic mastocytosis with HαT and IgE-mediated allergy to Hymenoptera venoms, who may experience very severe anaphylaxis (1,6).

Table 1 : MCAS diagnostic criteria.

1. Clinical criterion	= signs of recurrent mast cell degranulation Involvement of at least two organs, not assignable to another pathology (3). - Cutaneous system (involved in 100% of cases): urticaria (62.8%), angioedema (48.8%), pruritus (44.2%), flushing (58.1%). - Digestive system (93%): abdominal pain (83.7%), nausea/vomiting (39.5%), diarrhoea (65.1%), gastroesophageal reflux disease (25.6%), multiple food reactions. - ENT/respiratory system: rhinorrhoea, nasal pruritus, laryngeal oedema, wheezing, conjunctival injection. - Cardiovascular system: tachycardia, hypotension, syncope, incontinence. - Neurological system: sleep disorders (48.8%), asthenia (30.2%), headache, difficulty concentrating, agitation, anxiety/sad mood. Massive degranulation can lead to systemic symptoms of anaphylaxis. Note that the presence of the neurological system in the MCAS criteria is debated. It is more likely to be an accompanying symptom, similar to many other aspecific and chronic symptoms (e.g. osteoarticular pain, pollakiuria, recurrent fever, dysmenorrhea, etc.) which many patients report, but are not included in the diagnostic criteria stricto sensu (4).
2. Biological criterion	= increase of mast cell-derived mediators in blood (tryptase) or urine (N-methyl histamine, methylimidazole acetic acid (MIMA), prostaglandin D2, leukotrienes C4) during the symptomatic reaction (1,4,5). The validated standard test is the temporary elevation during symptoms of serum tryptase ≥ 2ng/ml + 20% above the individual's baseline serum tryptase (BST) (1,6). Tryptase should be measured between 30 min and 2 hours after the onset of symptoms. The patient's baseline tryptase can be measured from 24 hours post-reaction (6).
3. Response criterion	= response of symptoms to treatment targeting mast cell activation, mast cell mediator activation, production, or effects (antihistamines, anti-leukotrienes, sodium cromoglicate).

Table 2 : MCAS classification.

Primary MCAS **(=clonal MCAS)** *ICD-10-CM* code: D89.42	Mast cells are clonal, increased in number and overly reactive to triggers. Clonal MCAS includes mastocytosis, for which the KIT D816V mutation is part of the diagnostic criteria. This genetic mutation results in mast cell expansion which is independent of its growth factor. Other patients present only one or two of the minor criteria of mastocytosis and are classified as Monoclonal Mast Cell Activation Syndrome (MMAS) (2,7,9).
Secondary MCAS *ICD-10-CM* code: D89.43	Due to allergic, inflammatory, tumoral, autoimmune or infectious pathologies.
Idiopathic MCAS *ICD-10-CM c*ode: D89.42	No aetiology is identified. This is the most common MCAS variant, typically manifesting as idiopathic anaphylaxis.
Combined MCAS *MCAS ICD-10-CM* code: D89.40 *HαT ICD-10-CM* code: D89.44 Various possible codes depending on allergy or mastocytosis subtype	MCAS criteria + at least two associations among the following conditions: mastocytosis, allergy/atopy, genetic predisposition (e.g. HαT).
MCAS + HαT	MCAS criteria are met and HαT is identified, but there is no associated mastocytosis or underlying pathology.

Table 3 : Mast cell activation disorders.

Probable MCAS	Mast cells are clonal, increased in number and overly reactive to triggers. Clonal MCAS includes mastocytosis, for which the KIT D816V mutation is part of the diagnostic criteria. This genetic mutation results in mast cell expansion which is independent of its growth factor. Other patients present only one or two of the minor criteria of mastocytosis and are classified as Monoclonal Mast Cell Activation Syndrome (MMAS) (2,7,9).
Other MCAD *ICD-10-CM* code: D89.49	Due to allergic, inflammatory, tumoral, autoimmune or infectious pathologies.
Unspecified MCAD **(= MCA not further specified » = MCA(D)-NOS)** *ICD-10-CM* code: D89.40	No aetiology is identified. This is the most common MCAS variant, typically manifesting as idiopathic anaphylaxis.

Mast cell activation disorders: when MCAS criteria are not met

As shown in our second case, several patients do not meet the MCAS criteria but may respond favourably to MCAS treatment. MCAD can be considered in patients with a clinical presentation of mast cell activation. This term includes MCAS but also less typical presentations (probable MCAS, other MCAD and unspecified MCAD), which are described in table 3 (1,2).

The "International Classification of Diseases -10- Clinical Modification" (ICD-10-CM) has recently created specific codes for these particular conditions. However, their definition and management are not uniform, and will certainly evolve in the future (2).

Expanding the inclusion criteria for MCAS is therefore complex and controversial, as it would significantly increase the number of patients labelled with MCAS (2,4,7).

These types of mast cell disorders that do not meet the strict criteria of MCAS, appear to be predominant in paediatrics. A revision of the paediatric inclusion criteria therefore seems necessary to identify patients who could benefit from a MCAS treatment protocol.

Diagnostic approach

Patients suffering from MCAS generally experience a long medical journey before reaching this diagnosis, which can have a significant psychosocial and financial impact on the child and its family.

Multidisciplinary teams specialised in mast cell disorders are not widespread (e.g. CEREMAST ("centre de référence des mastocytoses") in France), but are essential for the optimal and global management of these patients. These teams should ideally include specialised paediatricians (in allergology, gastroenterology, dermatology, rheumatology, haematology, etc.), psychologists, a pain management team, geneticists, dieticians, etc. MCAS is indeed a diagnosis of exclusion, requiring the expertise of several specialties to rule out other differential diagnoses and thus avoid over- and under-diagnosis (4,7).

The medical assessment obviously includes a detailed medical history and a meticulous clinical examination. Additional investigations are then carried out.

First, a basal and reactive serum tryptase assay is performed.

Second, a blood test will be performed, including a complete blood count, liver enzymes, renal function and ionogram, total IgE assay, *KIT* D816V mutation test or HαT (if mastocytosis is suspected or HαT, where an elevated basal tryptase will be seen) and urine metabolite test (if available in the institution's laboratory).

Finally, depending on the clinical findings, specialist referrals and specific additional investigations will be requested (thyroid and celiac disease investigations in the case of a change in the growth curve, allergological evaluation in the case of suspected allergy, gastroenterological evaluation in the case of signs suggestive of chronic inflammatory bowel disease or eosinophilic oesophagitis, dermatological evaluation to detect signs of cutaneous mastocytosis, etc.).

Treatment and evolution

Treatment is based on a combination of several molecules (1,7);

- H1-antihistamines (desloratadine or cetirizine)
- H2-antihistamines (cimetidine or famotidine)
- Anti-leukotrienes (montelukast)
- Sodium cromoglycate (as a second-line treatment, in the event of mainly dietary reactions or difficulty in stabilising symptoms)

However, there is no consensus on the specific practical details. These depend on the experience of specialised centres. H2-antihistamines and sodium cromoglycate are no longer available in Belgium.

Avoidance of triggers is also recommended, and an epinephrine autoinjector pen could be prescribed depending on the profile of each patient (10).

The response to these therapies serves as a diagnostic test (response criterion). After 3 months of treatment, the evolution of symptoms is assessed. Clinical scores exist but are not currently validated. However, they may be helpful to objectify the therapeutic response and thus to adjust the treatment (3).

Conclusion

Mast cell activation syndrome is characterised by multisystemic clinical symptoms, secondary to the effects of mediators released by mast cell degranulation.

The general classification includes three main categories (primary, secondary, and idiopathic MCAS). However, the association with hereditary alpha-tryptasemia, mastocytosis or allergic/atopic pathology needs to be assessed and complicates this classification.

Three criteria are required to confirm the diagnosis of MCAS: a clinical criterion, a biological criterion and a response criterion. However, many patients do not strictly meet these criteria, typically in the paediatric population. Nonetheless, some of these patients respond favourably to MCAS treatment (based on a combination of H1-, H2-antihistamines, anti-leukotrienes and/or sodium cromoglicate). These "incomplete" variants have recently been added to the classification. However, their definition and management are still not standardised.

The complexity and misunderstanding of these pathologies often leads to delayed diagnosis and a significant psychosocial impact on these children and their families,requiring multidisciplinary management in specialised centres.

Conflicts of Interest

The authors have no conflicts of interest to declare in relation to this manuscript.

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