

ORIGINAL ARTICLE

Autoimmunity and Clinical Immunology

Idiopathic mast cell activation syndrome is more often suspected than diagnosed—A prospective real-life study

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Abstract

Background: Idiopathic mast cell activation syndrome (MCAS) is characterized by three diagnostic criteria: (1) episodic mast cell (MC)-driven signs/symptoms of at least two organ systems in the absence of clonal MC expansion and definite triggers, (2) episodic increase in tryptase, and (3) response to MC-targeted treatment. Many patients believe they have MCAS, but how often this is the case remains unknown.

Methods: We prospectively investigated patients with suspected MCAS ($n = 100$) for the diagnostic criteria including baseline tryptase, KIT D816V mutation, and patient-reported outcome measures (PROMs) over the course of 12 weeks. Comorbid depression and anxiety were explored with the Hospital Anxiety and Depression Scale (HADS).

Results: In 53% of our patients (80% females), suspicion of MCAS was based on self-evaluation. In total, patients reported 87 different symptoms, mostly fatigue ($n = 57$), musculoskeletal pain/weakness ($n = 49$), and abdominal pain ($n = 43$), with overall high disease activity and impact. Two of 79 patients had increased tryptase (by $>20\%$ $+2$ ng/ml) following an episode. Only 5%, with any of the PROMs used, showed complete response to MC-targeted treatment. Depression and anxiety disorders were frequent comorbidities ($n = 23$ each), and 65 patients had pathological HADS values, which were linked to high disease impact and poor symptom control.

Conclusion: Mast cell activation syndrome was confirmed in only 2% of patients, which implies that it is not MC activation that drives signs and symptoms in most patients with suspected MCAS. There is a high need for comprehensive research efforts aimed at the identification of the true underlying pathomechanism(s) in patients with suspected MCAS.

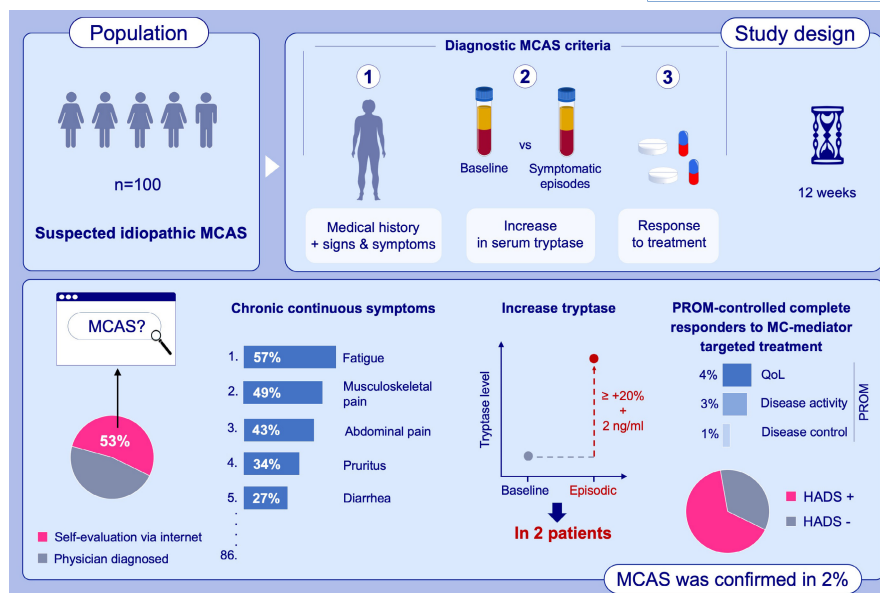
KEYWORDS

mast cell activation syndrome, MCAS, prospective study, real-life, targeted treatment, tryptase

Abbreviations: HADS, hospital anxiety and depression scale; MC, mast cell; MCAS, mast cell activation syndrome; PROM, patient-reported outcome measure; QoL, quality of life.

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GRAPHICAL ABSTRACT

A total of 100 patients with suspected idiopathic MCAS were investigated for the diagnostic criteria over the course of 12 weeks. Suspicion of MCAS was frequently based on self-evaluation. Eighty-seven different mainly chronic continuous symptoms were reported. Two patients had increased tryptase levels following a symptomatic episode; very few benefited from MC-targeted treatment. Psychiatric morbidity was frequent.

Abbreviations: HADS, hospital anxiety and depression scale; MC, mast cell; MCAS, mast cell activation syndrome; QoL, quality of life; PROM, patient-reported outcome measure

1 | INTRODUCTION

The term mast cell activation syndrome (MCAS) describes a condition that, according to the US Academy of Allergy, Asthma & Immunology (AAAAI), “presents with spontaneous episodic signs and symptoms of systemic anaphylaxis concurrently affecting at least two organ systems and resulting from secreted mast cell (MC) mediators”.¹

Primary MCAS is distinguished from secondary and idiopathic MCAS. Primary MCAS is defined by a clonal expansion of MCs and a somatic KIT D816V mutation and/or aberrant CD25 expression on MC, i.e., systemic mastocytosis (SM) or monoclonal MCAS (MMAS). In secondary MCAS, normal MCs get activated due to known triggers, e.g., via IgE. If neither a clonal expansion nor a trigger of aberrant MC activation can be identified, the condition is defined as idiopathic MCAS by (1) typical clinical signs of severe, recurrent (episodic) systemic (involving at least two organ systems) MC activation (urticaria, flushing, pruritus, angioedema, nasal congestion, nasal pruritus, wheezing, throat swelling, hoarseness, headache, hypotensive syncope, tachycardia, abdominal cramping, and diarrhea), (2) involvement of MCs as demonstrated by biochemical analyses, preferable through increase in serum tryptase of $20\% + 2 \text{ ng/ml}$ compared with baseline levels,² and (3) response to treatment with MC-stabilizing agents or drugs targeting the effects of MC mediators.^{3,4}

An increasing number of patients believe to suffer from idiopathic MCAS, in many cases supported by their treating physicians.⁵ In fact, the prevalence of MCAS has been estimated to be as high as up to 17% by some authors.^{6–8} However, the suspicion of idiopathic MCAS often is exclusively based on the presence of a variety of mostly unspecific symptoms.^{9,10} This frequently directs patients

and their treating physicians towards specialists in tertiary centers including allergists, immunologists, and dermatologists, to help with the diagnosis and treatment of suspected idiopathic MCAS.

Patients suspected with idiopathic MCAS are rarely assessed for the three defining diagnostic criteria, thus, the rate of *bona fide* diagnosed MCAS in patients suffering from not otherwise classifiable symptoms remains unknown.⁹ Since not many physicians are familiar with MC-driven diseases, including MCAS, and experienced in how to diagnose them, the number of patients who are suspected or even diagnosed with MCAS is expectedly high. To test patients with suspected MCAS for the three defining diagnostic criteria requires special resources. Also, the spectrum of signs and symptoms patients with suspected idiopathic MCAS present with and their impact on patients' quality of life and their response to treatment remains ill-defined.

To address these knowledge gaps, we performed a prospective study with the aim to determine the proportion of patients that fulfill the three defining diagnostic criteria and to characterize the clinical features, disease burden, and response to treatment in patients with suspected idiopathic MCAS.

2 | METHODS

2.1 | Study design

This 12-week prospective study was part of an outpatient screening program for patients referred to our department from February 2019 to November 2020, approved by the local ethics committee

(EA1/328/19). The program consisted of three visits at intervals of 6 weeks, carried out by two physicians experienced in MC-driven diseases. A standardized medical history, clinical examination, and diagnostic workup were performed, and response to treatment was monitored via patient-reported outcome measures (PROMs) (Figure 1).

2.2 | Study population

Patients (≥ 18 years old) referred with suspected or by others' established diagnosis of MCAS, MCAD, or "unspecific MC activation" were eligible for participation. Patients referred with clear indications for systemic mastocytosis/monoclonal MCAS or anaphylaxis, i.e., to insect venom, were excluded. Patients who stated they had

diagnosed MCAS by themselves after internet research were included after thorough evaluation and exclusion of relevant differential diagnoses.

Of 179 patients suspected to have MCAS and referred to our center, 100 were included in our study (Appendix S1). Reasons for exclusion, in 79 patients, included symptoms that did not point to MCAS as assessed by our team ($n = 25$), impaired health precluded participation ($n = 12$), and unavailability ($n = 26$) and discrepancies in expectations ($n = 9$), geographic distance ($n = 7$), underage ($n = 2$), and withdrawal of consent ($n = 1$).

Of 100 patients, 83 completed the study (until visit 3) and were further evaluated. Early termination, in 17 patients, was due to unavailability ($n = 8$), impaired health ($n = 4$), unwillingness to treat (for fears of worsening or side effects, $n = 4$), and suicide ($n = 1$).

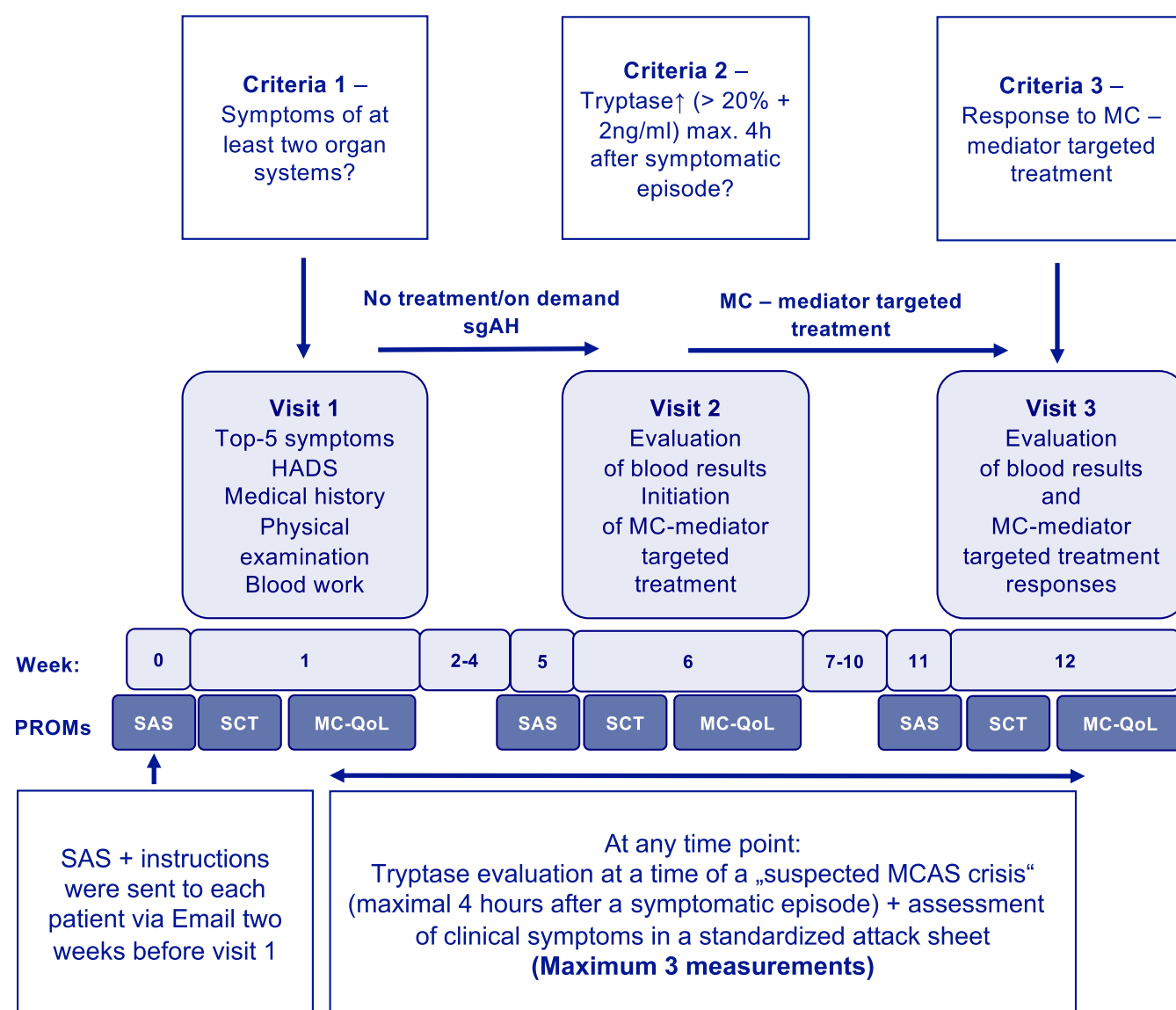


FIGURE 1 Study flow of the outpatient screening program for patients with suspected idiopathic mast cell activation syndrome. SAS, Symptom Activity Score; SCT, Symptom Control Test; sgAH, 2nd generation H1-antihistamine; MC-QoL, Mastocytosis Quality of Life Questionnaire; HADS, Hospital Anxiety and Depression Scale; PROM, patient-reported outcome measure

2.3 | Questionnaires and patient-reported outcome measures (PROMs)

2.3.1 | Top-5-symptoms questionnaire

At visit 1, patients were requested to list the five symptoms they "suffer from most days the week" (Appendix S2). In addition, patients could indicate whether they have "continuous" complaints or suffer from "continuous and intermittent" or "exclusively intermittent" symptoms.

2.3.2 | Symptom activity score (SAS)

The SAS is a modified version of the Mastocytosis Activity Score (MAS),¹¹ a validated 9-item tool for patients with cutaneous or indolent systemic mastocytosis that prospectively assesses the occurrence and severity of signs and symptoms on 7 consecutive days. The SAS consists of 17 items, but patients can also add two more items to the list (Appendix S3). The total and domain raw values were calculated by summing all relevant item values (0–4 points); all raw values were linearly transformed to a 0–100 scale, with higher values indicating a higher burden and activity of symptoms.

2.3.3 | Symptom control test (SCT)

The SCT is a 4-item tool based on the Urticaria Control Test (UCT) validated for patients with chronic urticaria.¹² A score between 0 and 4 is assigned to every answer option, the maximum total score is 16 points. The SCT was used to investigate disease control retrospectively over the last 4 weeks at all three visits (Appendix S4). In contrast to the UCT, "physical symptoms of urticaria" was replaced by "symptoms." In accordance with the UCT, an SCT score ≥ 12 was defined as "controlled disease".¹³

2.3.4 | Mastocytosis quality of life questionnaire (MC-QoL)

The MC-QoL is a validated disease-specific 27-item questionnaire for adult patients with cutaneous or indolent systemic mastocytosis¹⁴ that retrospectively assesses the quality of life impairment in the last 2 weeks. The MC-QoL has a four-domain structure, i.e., symptoms, emotions, social life/functioning, and skin. Each item is scored from 0–4 points; the domain raw scores were calculated by summing all relevant item scores. All raw scores were linearly transformed to a 0–100 scale, with higher values indicating a higher QoL impairment. Total MC-QoL scores were computed from the mean domain scores (Appendix S5).

2.3.5 | Hospital anxiety and depression scale (HADS)

The HADS was used to screen patients for anxiety disorders (HADS-D Anxiety Score, HADS-A) and depressive disorders (HADS-D Depressive Disorder Score, HADS-D).¹⁵ Scores (0–3) for items in each of the HADS were summed to produce an anxiety score (HADS-A) and a depression score (HADS-D). A score of more than 8 points each in anxiety score and depression score is defined as borderline pathological, and more than 11 points as pathological.

2.4 | Diagnostic workup

At visit 1, participants were clinically examined, including signs and symptoms of cutaneous mastocytosis, and screened for routine clinical parameters, KIT D816V mutation^{16,17} and baseline tryptase (the latter was also done at visits 2 and 3). Between visits 1 and 2 (if not possible also until visit 3), participants were requested to have blood taken, at our department or by the referring physician, within 4 h after onset of a symptomatic episode, for serum tryptase measurement. Patients documented the signs and symptoms of their episode by use of a standardized episode documentation sheet (Appendix S6). Post-episodic tryptase levels were compared to the mean basal values.

2.5 | Mast cell mediator-targeted treatment

Treatment was initiated at visit 2 for 6 weeks and consisted of the daily intake of a non-sedating 2nd generation H1-antihistamine (cetirizine, loratadine, levocetirizine, desloratadine, rupatadine, ebastine, or fexofenadine) up to four-fold standard dose, an H2-antihistamine twice daily (famotidine 20 mg or cimetidine 400 mg), the leukotriene-antagonist montelukast 10 mg once daily, and cromolyn 200 mg up to four times daily. Response to treatment was assessed by use of SAS, SCT, and MC-QoL until visit 3. Complete response was defined as $\geq 90\%$ reduction in SAS or MC-QoL or complete symptom control with an SCT of 16 at visit 3 as compared to pre-visit 2 values. Partial response was defined as 30%–90% improvement in SAS or MC-QoL or well-controlled symptoms with an SCT value ≥ 12 and nonresponse as $<30\%$ improvement in SAS or MC-QoL, or SCT values <12 at visit 3 as compared to pre-visit 2.

2.6 | Statistics

Data were summarized descriptively. Categorical variables were displayed as frequencies and percentages, continuous variables as mean \pm standard deviations (SDs), or median with ranges. The

nonparametric Mann–Whitney *U*-test was used to test not normally distributed data for statistical differences; *p*-values <.05 were considered statistically significant. Statistical analysis was carried out by IBM SPSS statistics 25 software.

3 | RESULTS

3.1 | Idiopathic MCAS is mostly suspected in female patients and based on self-evaluation

Of 100 patients suspected to have idiopathic MCAS, 80% were female. Patients, on average, were 41.5 years old (range: 21–76 years), and male patients were significantly younger than female patients (36.6 ± 10.2 vs. 45 ± 13.4 years, $p < .05$). In 53 patients, suspicion of MCAS was based on self-evaluation and internet research. The other 47 patients were diagnosed and referred to us by their treating physicians, and 28 of them had previously undergone extensive assessments for MCAS. The onset of signs and symptoms held to be explained by idiopathic MCAS, in most patients (68%), was in adulthood, whereas 13 and 19 patients reported onset in adolescence and early childhood, respectively (Table 1).

3.2 | Patients suspected to have idiopathic MCAS show high disease activity, marked impact on quality of life, and poor disease control

At the time of the first presentation, all patients showed high disease activity, i.e., symptom burden, markedly reduced quality of life (QoL), and poor symptom control as assessed by the SAS, MC-QoL, and SCT, respectively. SAS values (32.9 ± 15.6) and MC-QoL values (63.8 ± 17.3) at baseline indicated moderate to severe disease on average. In 87 patients who completed the SCT at visit 1, the average value was 4.2 ± 3 of 16, indicative of poor disease control, and all except two patients scored lower than 12 points, the cutoff for well-controlled disease.

3.3 | All patients with suspicion of idiopathic MCAS report signs and symptoms of at least two organ systems

On average, patients presented with a history of signs and symptoms of more than 3 organ systems (3.4 ± 0.9) with at least 2 in

all of them, the first of the three defining criteria of idiopathic MCAS.⁴ Based on their history, all patients had chronic continuous signs and symptoms, with additional episodic exacerbation in 53% of patients. No patient exclusively had episodic signs and symptoms.

When asked for their top-5 signs and symptoms, i.e., those that occur most often in the week (Top-5-questionnaire at visit 1), patients reported a total of 86 different ones. Individual patients had 6 ± 1.4 different signs and symptoms on average. The most common manifestations were fatigue/exhaustion ($n = 57$), musculoskeletal pain/weakness ($n = 49$), abdominal pain ($n = 43$), pruritus ($n = 34$), and diarrhea ($n = 27$) (Figure 2). Swellings ($n = 10$) and wheals ($n = 5$) were less frequent (Appendix S7).

Patients with episodic exacerbation of their disease had 5 ± 1.8 signs and symptoms per episode, and all except one reported involvement of at least two organ systems during episodes (average: 3 ± 1.1). The most frequently reported episodic signs and symptoms at baseline were abdominal pain ($n = 18$), muscle, and joint pain or weakness ($n = 18$), headache ($n = 16$), tachycardia ($n = 15$), and fatigue/exhaustion ($n = 14$) (Figure 2).

3.4 | Blood tryptase levels, in most patients with suspected idiopathic MCAS, do not increase after episodic disease exacerbation

Basal tryptase levels, in 95% of patients were within the normal range limit, and the mean was 5.4 ± 3.3 ng/ml (Appendix S8). No patient had a clinical indication for mastocytosis or monoclonal MCAS based on physical examination, basal tryptase levels (<20 ng/ml in all), and KIT D816V mutation analyses in peripheral blood, which were negative in all.

Patients were assessed, prospectively, for changes in blood tryptase levels linked to episodic exacerbation of their symptoms, and 79% reported at least one episode over the course of up to 12 weeks. The most common signs and symptoms of these episodes were impaired general wellbeing ($n = 73$), headache ($n = 61$), heat sensation ($n = 60$), pruritus ($n = 59$), flatulence ($n = 59$), abdominal pain ($n = 58$), and skin redness ($n = 56$) (Figure 2).

Of 79 patients assessed for increased levels of tryptase after episodic symptom exacerbation, the second of the three defining criteria of idiopathic MCAS,⁴ two patients tested positive, i.e., showed an increase >20% +2 ng/ml as compared to their average basal levels (Appendix S9). These two patients did not exhibit distinct clinical or

TABLE 1 Demographics data of study population

	Male	Female	Total
Gender, %	20	80	100
Age (mean)	36.6	45	43.3
	Self-evaluation	Physician	Total
Suspicion of idiopathic MCAS	53	47	100
	Childhood/adolescence	Adulthood	Total
Presumed onset of disease	32	68	100

FIGURE 2 Frequencies of Top-5 reported symptoms as reported in medical history (on most days of the week and during symptomatic episodes) and prospectively documented during symptomatic episodes (at the time point of blood draw for tryptase)

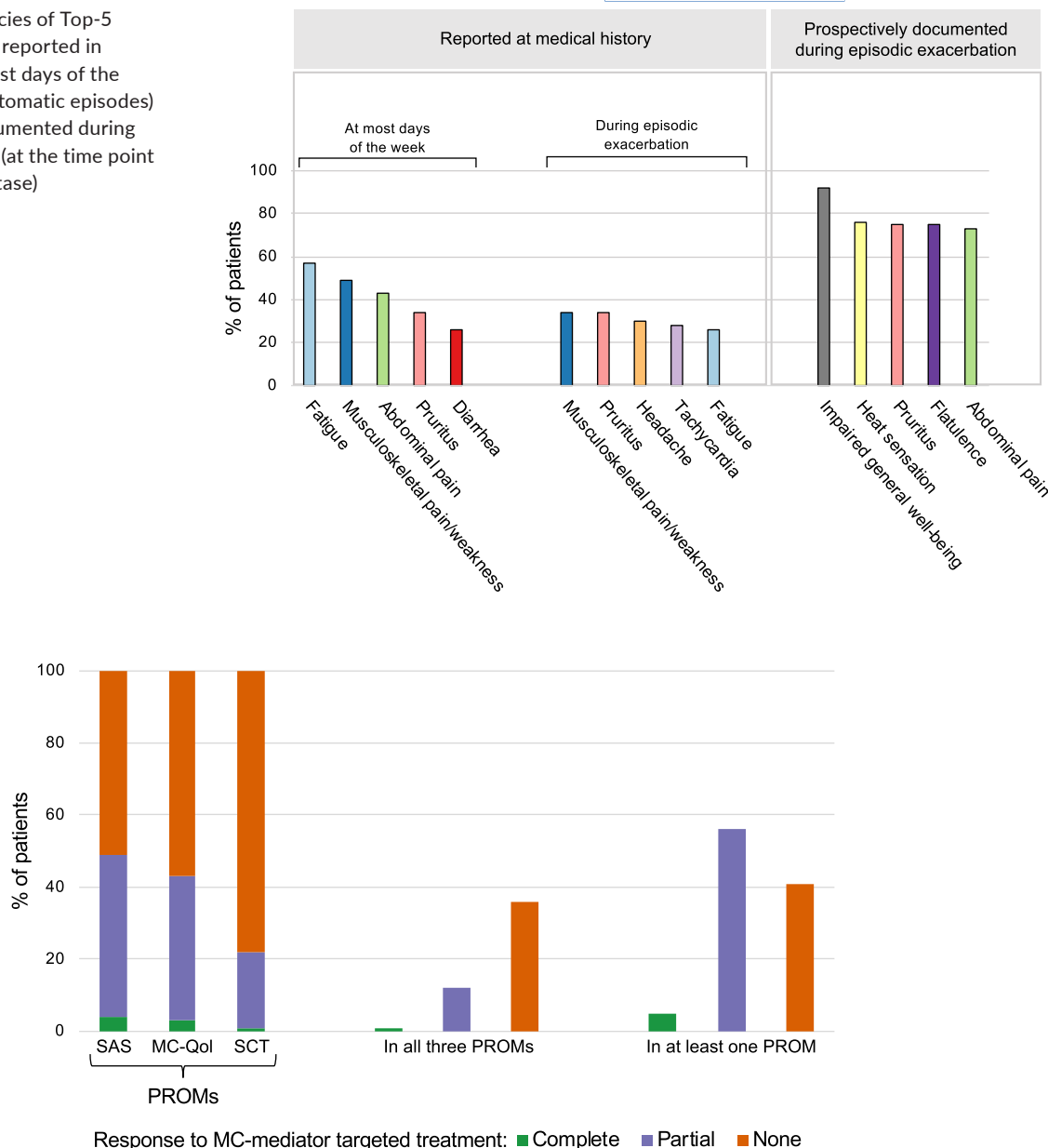


FIGURE 3 Response to mast cell mediator-targeted treatment based on the patient-reported outcome measures (PROMs), SAS (Symptom Activity Score), MC-QoL (Mastocytosis Quality of Life Questionnaire), and SCT (Symptom Control Test) in the study population ($n = 83$). The values before initiation of treatment (visit 2) and after a 6-week mast cell mediator-targeted treatment (visit 3) were compared. Nonresponse in SAS and MC-QoL means less than 30% improvement, partial response means at least 30% but less than 90% improvement, and complete response means at least 90% improvement. For SCT values less than 12 before and at least 12 points after treatment were attributed to partial response (controlled disease), SCT values of 16 points after treatment were considered complete response. Rates of patients that achieved complete, partial, and nonresponse in all three PROMs and in at least one PROM are displayed

demographic characteristics as compared to patients without post-episodic tryptase increase of $>20\% +2$ ng/ml, and there was no indication of secondary MCAS.

In 12 and 6 patients, post-episodic tryptase levels were increased by $\geq 5\% +1$ ng/ml and $\geq 10\% +1$ ng/ml, respectively. This was not linked to distinct demographic or clinical features.

Post-episodic tryptase levels were not assessed in 21 patients. The main reasons reported were “wrong time of day” and “not enough symptoms.”

3.5 | Few patients with suspected idiopathic MCAS benefit from MC mediator-targeted treatment

Next, we assessed patients for their response to MC mediator-targeted treatment, the third of the three defining criteria of idiopathic MCAS.⁴ Of 83 patients subjected to PROM-controlled daily treatment with a high-dose H1-antihistamine, an H2-antihistamine, montelukast, and cromolyn, only 4 patients (5%) showed complete response. Specifically, 4%, 3%, and 1% of patients had complete

response by SAS, MC-QoL, and SCT, respectively, and only one patient was a complete responder to all of them (Figure 3).

Partial response by at least one PROM was achieved in 56% of patients; 45% and 40% of patients, respectively, had partial response by SAS and MC-QoL. Only 21% achieved well-controlled symptoms, i.e., an SCT value of ≥ 12 (Figure 3).

Most patients, with any of the PROMs used, were nonresponders. Specifically, 51%, 57%, and 78% of patients were SAS, MC-QoL, and SCT nonresponders, respectively.

Patients who benefitted from MC mediator-targeted treatment, i.e., partial or complete response for one or more PROMs ($n = 48$, 62%), did not differ in their clinical or demographic profile from those who did not benefit from any of them. Of the 5 patients with wheals as a top-5 manifestation, four achieved partial response in at least one PROM; in three of them chronic spontaneous urticaria (CSU) was a known comorbidity and in two patients concomitant CSU was diagnosed by us.

Both of the patients with post-episodically increased tryptase levels showed partial response in SAS, MC-QoL, and/or SCT.

3.6 | In patients with suspected idiopathic MCAS, psychiatric morbidity is frequent

Depression and anxiety disorders were common in patients with suspected idiopathic MCAS ($n = 23$ each) (Table 2). Other psychiatric conditions included compulsive disorders ($n = 5$), attention deficit hyperactivity disorder ($n = 5$), somatization disorder ($n = 1$), and bipolar disorder ($n = 1$). A male patient with a known compulsive disorder reported recurrent suicidal thoughts. A female patient with poorly controlled disease ($SCT = 7$) committed suicide.

In total, two-thirds (65%) of patients scored above threshold values of ≥ 8 with the HADS-A or HADS-D (HADS-A: 58%; HADS-D: 43%), and a third of patients (35%) scored ≥ 8 for both. Above threshold scores in both HADS-A and HADS-D were linked to poor symptom control and higher disease impact. At visit 1, patients with values ≥ 8 in both HADS-A and HADS-D scored lower SCT values

TABLE 2 Most frequent comorbidities in patients with suspected idiopathic MCAS ($n = 100$)

Comorbidity	Patients
Depression	23%
Anxiety disorders	23%
Food intolerance (fructose and/or lactose)	22%
Chronic gastritis	18%
Irritable bowel syndrome	17%
Asthma	17%
Chronic fatigue syndrome (CFS)	15%
Fibromyalgia	15%
Compulsive disorders	5%
Attention-deficit hyperactivity disorder	5%

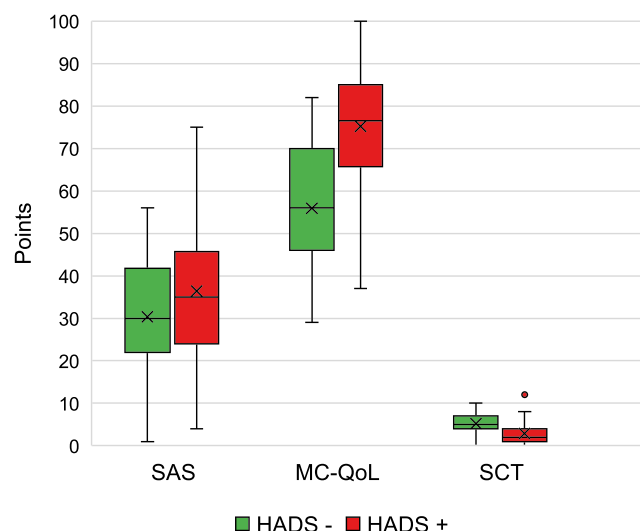


FIGURE 4 Disease activity, quality of life (QoL), and disease control at baseline (visit 1) based on the patient-reported outcome measures (PROMs) SAS (Symptom Activity Score, $n = 93$), MC-QoL (Mastocytosis quality of life questionnaire, $n = 96$), and SCT (Symptom control test, $n = 86$) in patients with suspected idiopathic MCAS with normal values in both HADS-A and HADS-D (HADS -) and above threshold levels in both (HADS +)

(2.9 ± 2.8) and higher MC-QoL values (75.1 ± 13.6) than patients with below threshold values in both HADS-A and HADS-D (5.3 ± 2.4 and 55.4 ± 14 , respectively) (Figure 4). Also, patients with both HADS-A and HADS-D ≥ 8 showed higher rates of nonresponse to MC mediator-targeted treatment, as compared to patients with both HADS-A and HADS-D < 7 (45% vs. 40%).

4 | DISCUSSION

This is the first prospective study to apply the three defining diagnostic criteria of idiopathic MCAS to a population of patients suspected to have this condition. Our results show that in only 2 out of 100 patients referred with suspected idiopathic MCAS the diagnosis could be confirmed according to the three defining criteria during the course of this study. Moreover, this study provides unique and novel insights into the demographics, clinical manifestation, symptom profiles, disease burden, and impact and response to treatment in patients with suspected idiopathic MCAS.

Our study shows that patients with suspected idiopathic MCAS are predominantly middle-aged women, who are severely impaired in their quality of life, have a high symptom burden and poor disease control. Most of our patients searched the internet for help, often after various specialists had failed to find a reason for their symptoms. Indeed, our study shows that the complaints of patients suspected of having idiopathic MCAS are highly heterogeneous, elusive, and, most importantly, unspecific. Fatigue and musculoskeletal pain were the most frequently reported symptoms. Both have multiple reasons, and they are not diagnostic criteria¹⁸ or specific for MCAS¹⁹ or other well-defined MC-driven diseases, i.e.,

IgE-mediated food allergy,²⁰ anaphylaxis,²¹ chronic urticaria,²² and indolent systemic mastocytosis.¹⁴ As it is, information provided on the internet and even some publication make patients think that fatigue and fibromyalgia-like pain are manifestations of MCAS.^{8,19} Our results discourage this notion and support the view of the AAAAI that fatigue and fibromyalgia-like pain "lack precision for diagnosing MCAS."¹ More evidence-based information on MCAS and other MC-driven diseases should be made available through various media including the internet, for both physicians and patients.

The observation that patients with suspected MCAS consistently report several organ systems to be affected suggests systemic rather than organ-specific underlying pathology. The true causes of these patients' complaints remain unclear and need to be investigated and characterized. Clearly, this patient population is severely impaired, and studies are needed to understand the pathogenic drivers and to develop effective treatment options. Ultimately, our results underline that idiopathic MCAS is unlikely to be the cause of the complaints in most patients suspected to have this condition.

Importantly, levels of serum tryptase, in most of our patients, were normal at baseline, which argues against increased numbers of MCs, and tryptase levels did not increase at episodic disease exacerbation.²³ The latter is a strong argument against a key role of MC as driver of signs and symptoms, as the elevation of tryptase is considered the most sensitive marker for severe systemic MC activation, i.e., in anaphylaxis.²

Of note, only a few patients showed marked benefit from MC mediator-targeted treatment in terms of disease activity, symptom control, or quality of life. This also argues against a critical role of MC in the disease burden of these patients. MC mediator-targeted treatment has been demonstrated to be effective in other MC-driven diseases.^{21,22,24} The use of novel therapeutic antibodies that silence MCs, i.e., liletelimab,²⁵ or deplete them, i.e., CDX-0159, can help to better understand in what patients suspected to have idiopathic MCAS MCs actually play a role, and they should be very effective in those with *bona fide* idiopathic MCAS.

A notable finding of our study is that about a quarter of patients suspected of having idiopathic MCAS had psychiatric comorbidity, and two-thirds had above cutoff values in the HADS, a screening questionnaire for depression and anxiety. Tragically, a female study patient (a practicing medical doctor) committed suicide, and another patient, a young man, reported a failed suicide attempt during our study. Although some authors propose psychiatric symptoms to be a manifestation of idiopathic MCAS,⁸ our results do not support this view. What they do support is that psychiatric comorbidity is linked to poor disease control and marked QoL impairment, suggesting that effective treatment of a comorbid psychiatric condition may help patients with suspected idiopathic MCAS to achieve better disease control and QoL. Our study did not specifically investigate the impact of having suspected idiopathic MCAS on psychiatric comorbidities. It is tempting to speculate that the longstanding and high burden of signs and symptoms in these patients, and that their cause cannot be found, not even by specialists, may contribute to depression and anxiety in patients with suspected idiopathic MCAS.

Our study has several strengths and limitations. As or the former, we investigated a sizable patient population, used all of the three proposed consensus criteria, and managed to implement a comprehensive and challenging study protocol, during the COVID-19 pandemic. As for limitations, our study was monocentric, and we exclusively determined tryptase as a marker for MC activation. Other biomarkers for MC activation such as prostaglandin D₂, leukotriene E₄, N-methylhistamine, chromogranin A, and heparin are less specific, not validated, lack thresholds, or are not recommended.^{1,8,18} On the other hand, tryptase may not be sensitive enough to detect minor MC contributions, especially in patients with less severe forms of MC activation or MC-related events restricted to local sites, e.g., patients with less severe allergic reactions or with mastocytosis and mild symptomatology.⁴ In these conditions, it is even more challenging to confirm MC involvement with certainty. Thus, better and more convenient markers for MC activation are needed. In addition, we used PROMs adapted from known MC-driven diseases (chronic urticaria and mastocytosis), but not validated for idiopathic MCAS. Not least, we did not screen our patients suspected to have MC-mediated symptoms for hereditary alpha-tryptasemia (H α T).^{2,26,27}

The entity of idiopathic MCAS has been the subject of critical debate for decades and much has been published in the literature on this topic.^{5,8} It remains to be discussed whether the current diagnostic criteria may be too stringent; however, as shown by our study, unchanged tryptase levels during episodic exacerbation and unresponsiveness to high-dose MC mediator-targeted treatment argue against systemic MC activation as a major driver of signs and symptoms in the investigated patient population. Moving forward, better and easier to measure markers for MC activation and more effective MC-targeted treatments should be developed and brought to patients to clarify the entity of idiopathic MCAS.

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CONFLICT OF INTEREST

Thomas Buttgereit (T.B.): I have no conflicts of interest to declare. Sophie Gu (S.G.): I have no conflicts of interest to declare. Leonor Carneiro-Leão (L.C.L.): I have no conflicts of interest to declare. Annika Gutsche (A.G.): I have no conflicts of interest to declare. Marcus Maurer (M.M.): M.M. is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Amgen, Aralez, ArgenX, AstraZeneca, BioCryst, Blueprint, Celldex, Centogene, CSL Behring, Dyax, FAES, Genentech, GILInnovation, Innate Pharma, Kalvista, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Novartis, Pharming, Pharvaris, Roche, Sanofi/Regeneron, Shire/Takeda, ThirdHarmonicBio, UCB, and Uriach. Frank Siebenhaar (F.S.): I am or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Blueprint, Celldex, CogentBio, GSK, Novartis, Moxie, Sanofi, and Uriach.

AUTHOR CONTRIBUTIONS

T.B., L.C.L, M.M., and F.S. designed the study. T.B., S.G., and F.S. conducted the study. T.B., S.G., A.G., M.M., and F.S. analyzed the data. T.B., F.S., and M.M. wrote the paper with input from all authors.

INFORMED CONSENT

This study was approved by the local ethics committee (EA1/328/19) at Charité – Universitätsmedizin Berlin. Patients provided written informed consent before any assessment was performed.

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