Primary headache syndromes in systemic mastocytosis

Article *in* Cephalalgia · September 2011

DOI: 10.1177/0333102411421683 · Source: PubMed

3 authors, including:

Jonathan H Smith
Mayo Clinic - Scottsdale
68 PUBLICATIONS **711** CITATIONS
SEE PROFILE

Fred Michael Cutrer
Mayo Foundation for Medical Education and Research
102 PUBLICATIONS **4,592** CITATIONS
SEE PROFILE

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
0(0) 1–10

DOI: 10.1177/0333102411421683
cep.sagepub.com

SAGE

Primary headache syndromes in systemic mastocytosis

Jonathan H Smith, Joseph H Butterfield and F Michael Cutrer

Abstract

Aim: To investigate the relationship between clinical mast cell activity and primary headache syndromes.
Methods: We surveyed individuals with systemic mastocytosis, an uncommon disorder associated with increased mast cell activity. Diagnoses of primary headache syndromes in addition to the relationship of headache and symptoms of mastocytosis were ascertained.
Results: A response rate of 64/148 (43.2%) was achieved. Headache diagnoses in our respondents ($n = 64$) were largely migraine (37.5%) and tension-type headaches (17.2%). Typical aura with and without migraine headache was highly represented in our patient population ($n = 25$, 39%). Three individuals met criteria for primary cough headache (4.7%). Symptoms reflective of mast cell activity were significantly greater in individuals reporting headaches. Patients experiencing headache concurrently with mastocytosis flairs were more likely to be male ($p = 0.002$), have histaminergic symptoms, such as itching ($p = 0.02$) and runny nose ($p = 0.03$), and have unilateral cranial autonomic features ($p = 0.04$). However, using standardized International Headache Society criteria, we did not identify individuals with cluster headache or other trigeminal autonomic cephalalgias in this population.
Conclusions: Our observational survey-based data supports a clinical relationship between mast cell activity and primary headache syndromes. Generalizability of our results is limited by the low response rate and possible tertiary referral bias.

Keywords

Mast cell, mastocytosis, headache, pathophysiology

Date received: 15 June 2011; revised: 2 August 2011; 4 August 2011; accepted: 5 August 2011

Introduction

Systemic mastocytosis (SM) is characterized by an increased total burden of mast cells, which can be pathologically demonstrated as multifocal infiltrates of mast cells in either the bone marrow or an extra-cutaneous site. The World Health Organization (WHO) has published criteria for the diagnosis of SM, defining increasingly aggressive subtypes (1). These diagnoses range from the most common and benign form, indolent systemic mastocytosis (ISM), to mast cell leukemia (MCL). A large percentage of patients with ISM possess a specific gain-of-function mutation (D816V) in the mast cell c-Kit receptor, which results in premature mast cell activation (2).

Symptoms in mastocytosis are attributable to paroxysmal mast cell degranulation, either directly into the host tissue or into the bloodstream, and may include flushing, diarrhea, itching, and syncope. A recent case series of individuals with neurological manifestations in mastocytosis has provided additional clinical data to suggest a pathogenic relationship between migraine and mast cell dysfunction (3), building on an earlier detailed case investigation by Ashina (4). Interestingly, other authors have commented on a cluster-like headache phenomenology, but without reference to International Headache Society (IHS) criteria (5,6). While headache in general is known to be a significant contributor to disability in patients with mastocytosis (7), a dedicated study has not been carried out to define the headache sub-types and clinical features in this population.

Mast cells have been most closely studied with respect to the pathophysiology of migraine (8,9),

Mayo Clinic, USA.

Corresponding author:
F Michael Cutrer, Mayo Clinic, Department of Neurology, 200 1st Street SW, Rochester, MN 55905, USA
Email: cutrer.michael@mayo.edu

although they have also been implicated in cluster headaches (10,11). Mast cells are found in varying densities throughout the dura mater, in association with connective tissue, neural, and vascular structures (12,13). A variety of stimuli implicated in migraine pathogenesis have also been associated with mast cell degranulation, including pituitary adenylate cyclase-activating peptide (14), substance P (15), calcitonin gene-related peptide (15), corticotropin-releasing factor (16), and the parasympathetic nervous system (17). More direct evidence comes from the landmark observation that dural mast cell degranulation results in sustained meningeal nociceptor activation, in addition to activation of second order neurons within the trigeminal nucleus caudalis, as measured by c-Fos expression (18).

With the aim of better understanding the clinical relationship between primary headache syndromes and mast cell activity, we obtained detailed survey information from 64 patients with systemic mastocytosis regarding their experience with headaches, if any.

Participants and methods

Patient identification

With Mayo Clinic Institutional Review Board (IRB) approval, the Mayo Medical Index Registry was searched between January 1999 to December 2008, to identify all participants 18 years of age or older who had been assigned a diagnosis of systemic mastocytosis. One-hundred-and-seventy-one consecutive cases of systemic mastocytosis were identified, all meeting WHO consensus criteria (1). A retrospective chart review of neurologic referral across this population has previously been reported (3).

Data collection

All patients were sent a detailed headache survey by mail, designed to assess cross-sectional primary headache diagnoses, according to International Headache Society (IHS) International Classification of Headache Disorders-2 (ICHD-2) criteria (19). The survey further ascertained information regarding the underlying mast cell disease, with attention to current mast cell mediated symptoms. Participants were asked questions regarding the temporal association of their headaches with flairs of their mastocytosis. Patients contradicting themselves in different survey questions, or with unclear answers, were subsequently interviewed by telephone by the primary investigator (JHS) to ensure accurate documentation of the clinical features.

To more completely define the clinical phenotypes, all survey participants were asked to complete the Headache Disability Inventory (HDI), a self-report inventory (20). The HDI is a 25-item questionnaire which assesses both the emotional (E) and the functional (F) impact of headache. We considered the total composite score of both components (E + F) in our analysis, which is scored as a fraction out of a maximal possible score of 100.

Statistical analysis

All analyses were carried out using the JMP statistical software package (Version 8, SAS Institute Inc, Cary, NC, USA). Descriptive statistics were used to describe the cohort. Continuous variables were described as means with standard deviations, and nominal variables as counts and percentages. Groups were compared using Kruskal-Wallis tests to compare continuous variables among three groups, followed by post-hoc pairwise comparisons using Wilcoxon Rank Sum tests when the overall p-value for the three-group comparison was significant. For dichotomous variables, a strategy was applied using chi-square or Fisher's exact tests, as appropriate. Adjustments were not made for multiple comparisons. Results were considered to be statistically significant for $p \leq 0.05$.

Results

Of the 171 surveys distributed by mail, we received notice that 23 of these patients were either no longer residing at the address on record, or had died since their most recent visit to Mayo Clinic. A response rate of 64/148 (43.2%) was achieved. A mean time of 7.2 years had elapsed between the initial diagnosis of systemic mastocytosis and return of the survey. Of 28 patients tested for the D816V c-Kit mutation, 21 were positive. A comparison of the demographics and WHO mastocytosis classifications between survey responders and non-responders is summarized in Table 1. A trend was observed for survey non-responders to have a higher frequency of more aggressive mastocytosis variants (SM-AHNMD and ASM).

Thirty-six patients (56.2%) reported having headaches in general, with 25% of the total cohort reporting either chronic migraine or chronic tension-type headache (TTH). All patients with headaches were classifiable by IHS criteria (see Table 2). Among patients with migraine, two thirds reported an associated aura. An additional nine patients met criteria for typical aura without headache, such that 25 total patients had migraine aura. Patients with aura most frequently reported typical visual auras; however, language and sensory phenomenon were also very common.

Table 1. Comparison of survey responders and non-responders

Characteristic	Responders (n = 64)	Non-responders (n = 84)	p-value
Female, No (%)	37 (57.8)	42 (50)	0.34
Age, years (mean ± SD)	56.4 ± 13.6	58.3 ± 13.7	0.53
Disease duration*, years (mean ± SD)	7.2 ± 3.27	6.89 ± 2.9	0.63
ISM, No (%)	60 (93.8)	70 (83.3)	0.055
SM-AHNMD, No (%)	3 (4.7)	9 (10.7)	0.18
ASM, No (%)	1 (1.5)	5 (5.95)	0.18

*Disease duration defined as the time from tissue diagnosis to either survey return or send date (for non-responders). Abbreviations: ISM = indolent systemic mastocytosis, SM-AHNMD = systemic mastocytosis with an associated hematologic non-mast cell disorder, ASM = aggressive systemic mastocytosis.

Three patients met criteria for primary cough headache, two of whom also had migraine. None of these patients had been treated with indomethacin. No patients met the criteria for cluster headache or other trigeminal autonomic cephalalgias.

Clinical features were compared between groups with no headache, TTH, and migraine (Table 3). Symptoms reflective of mast cell activity were much more common in patients with either TTH or migraine than in patients not reporting headache. Differences between the TTH and migraine group did not reach statistical significance with respect to mast cell mediated symptoms. However, there were several circumstances in which the migraine group dissociated from patients with no headache, when TTH did not (Table 3). At least one unilateral cranial autonomic feature was reported by 14 patients, 10 (41.7%) of whom had migraine and 4 (36.4%) TTH (comparison non-significant, $p = 0.76$). Night-time waking by headaches was reported by ten (41.7%) patients with migraine, and one (9.1%) patient with TTH ($p = 0.054$). No patient met criteria for primary hypnic headache.

Headache patients were divided into two groups consisting of those who had reported headache concurrently with at least 50% of mastocytosis flairs (n = 15), and those who had not noted an association (n = 20). Patients who experienced headache with at least half of their flairs were more likely to be male ($p = 0.002$), have higher HDI scores ($p = 0.02$), and to report itching ($p = 0.02$), runny nose ($p = 0.03$), and unilateral cranial autonomic symptoms ($p = 0.04$). Comparison of all other clinical features, including headache diagnosis, syncope, diarrhea, and flushing, were non-significant.

Table 2. Distribution of headache diagnoses among survey respondents (n = 64)

Characteristic	Patient n (%)
Headache, total	36 (56.2%)
Chronic daily headache	16 (25%)
Migraine, total	24 (37.5%)
With aura	16 (25%)
Without aura	8 (12.5%)
Episodic	11 (17.2%)
Chronic	13 (20.3%)
Typical aura without headache	9 (14%)
Tension-type headache, total	11 (17.2%)
Episodic*	8 (12.5%)
Chronic	3 (4.7%)
Other	
Primary cough headache	3 (4.7%)

*Combined subgroups of both infrequent and frequent episodic TTH.

Discussion

In patients with systemic mastocytosis we find through use of cross-sectional survey-based data that primary headache syndromes are common, disabling, and associated with clinical mast cell activity. We also demonstrate headaches occurring in temporal association with mastocytosis flairs to be associated with greater disability, independent of the headache sub-type. A limitation of this study includes the referral bias possible in the study of a tertiary center cohort, necessitated by the inherent difficulty obtaining a large cohort size in the study of an uncommon disorder. The purpose of this protocol was not to establish whether various primary headache syndromes are comorbidities of mastocytosis, and this conclusion should not be inferred from our data as a control group was not used. A low survey response rate of 43.2% represents an additional potential limitation to our study. However, survey responders more accurately reflected a general mastocytosis population than did survey non-responders, as more aggressive subtypes seemed to be over-represented in the latter group (Table 1) (2). Finally, multiple comparisons were performed, which increases the chance that

Table 3. Clinical features by headache diagnosis

	No HA (n = 19)	TTH (n = 11)	Migraine (n = 24)	p-value	p < 0.05*
Male gender, n (%)	11 (57.8%)	4 (36.4%)	7 (29.2%)	0.15	
Age MC diagnosis, mean ± SD	60.3 ± 12.4	49.7 ± 12	41.1 ± 10.2	<0.0001	a, b
Alcohol use, n (%)	7 (36.8%)	2 (18.8%)	5 (20.8%)	0.39	
HA with $flairs_{50\%}$†, n (%)	–	6 (54.6%)	9 (37.5%)	0.34	
FH Migraine, n (%)	2 (10.5%)	2 (18.2%)	13(54.2%)	0.005	b, c
HDI, mean ± SD	–	0.13 ± 0.14	0.35 ± 0.3	0.02	c
Difficulty concentrating, n (%)	2 (10.5%)	6 (54.5%)	13 (54.2%)	0.007	a, b
Syncope, n (%)	3 (15.8%)	4 (36.4%)	7 (29.2%)	0.41	
Flushing, n (%)	6 (31.6%)	9 (81.8%)	21 (87.5%)	0.0003	a, b
Warmth, n (%)	5 (26.3%)	8 (72.7%)	14 (58.3%)	0.027	a, b
Itching, n (%)	11 (57.9%)	6 (54.5%)	17 (70.8%)	0.55	
Runny nose, n (%)	4 (21.1%)	3 (27.3%)	13 (54.2%)	0.062	
Abdominal pain, n (%)	4 (21.1%)	6 (54.5%)	17 (70.8%)	0.005	b
Diarrhea, n (%)	8 (42.1%)	9 (81.8%)	16 (66.7%)	0.075	
Chest tightness, n (%)	0 (0%)	2 (18.2%)	10 (41.7%)	0.005	b
Bone pain, n (%)	4 (21.1%)	5 (45.5%)	15 (62.5%)	0.025	b
Pathologic fracture, n (%)	1 (5.3%)	1 (9.1%)	3 (12.5%)	0.72	

Abbreviations: HA = headache, TTH = tension-type headache, MC = mast cell, FH = family history.
*Multiple comparisons abbreviated as a: TTH differs from no HA, b: Migraine differs from no HA, c: Migraine differs from TTH.
†Headache reported to be concurrent with at least 50% of mastocytosis flair.

some of the observed statistically significant relationships could be due to chance.

In our survey, patients with both migraine and TTH more frequently experienced symptoms reflective of mast cell activity than individuals not reporting headache. In other words, the likelihood of having headache in our study cohort was related to the clinical activity of the underlying mast cell disorder. Dural mast cell activity may be a nonspecific means for generating pain in both headache conditions; however, the mechanisms underlying our findings will need to be addressed in further studies (16,21,22). A direct temporal relationship between headache and clinical mast cell activity was reported by only 44% of those with headaches, implying that systemic degranulation alone may not be sufficient to trigger headache. Along these lines, headache is recorded by only a minority of individuals (<4%) during an anaphylactic reaction (23). A more protracted exposure to an increased mast cell burden may contribute to headache susceptibility and chronification. However, headache and abdominal pain are also common symptoms of mast cell activation syndrome (MCAS), which is not associated with tissue infiltration (24). Future study of individuals with mastocytosis may yield insights into the relative contributions of dural versus peripheral mast cell populations.

With regard to the known functions of mast cells, it is of interest that primary cough headache was found to be over-represented in our cohort (4.7%), in comparison with the 1% prevalence observed in both a population and clinic-based study (25,26). This high prevalence needs to be confirmed in a controlled population-based protocol. Although the pathogenesis of cough headache has not been well defined, transient increases in intracranial pressure transmitted from Valsalva maneuvers are certainly an important component (27). The dura has long been appreciated to be sensitive to mechanical stimuli (28). However, it has only recently been demonstrated that mast cell degranulation can persistently sensitize meningeal nociceptors to mechanical stimulation, an effect mediated at least in part by serotonin, prostaglandin I_2, and histamine (29). Proteinase-activated receptor 2 (PAR2), which can be activated by mast cell tryptase, may also contribute to meningeal mechanosensitization (30). Increased dural sensitivity to mechanical stimuli in our patients with systemic mastocytosis may have been pathogenic in the development of a pain response to coughing.

An unexpected result of our study was the common occurrence of aura either with or without typical migraine headache (39%), representing an approximate fivefold excess of what would be expected from the sum lifetime prevalence of aura in a general population (2.3% for migraine aura without headache and 5% for migraine with aura) (31,32). Whether meningeal or systemic mast cell-derived products influence the

development or propagation of cortical spreading depression (CSD) is not known, but if proven to be true, this would represent a novel insight into the current model of migraine aura (33–37).

Patients in our cohort who experience headache during flairs are more likely to be male, have histaminergic symptoms, and unilateral cranial autonomic features. This may account for the confusion in the literature that patients with mastocytosis may experience cluster-like headaches (5,6). Using standardized IHS criteria, we do not find evidence for cluster headache or other trigeminal autonomic cephalalgias in this population. Interestingly, that these headaches with autonomic features occur in association with mastocytosis flairs further implicates mast cells at the crossroads of pain and autonomic dysfunction (38).

In conclusion, we have described the distribution of primary headache syndromes among a cohort of individuals with systemic mastocytosis, in an effort to broaden our understanding of the contributions of mast cells to headache pathophysiology. Our findings will require confirmation, but are hypothesis generating, in that we implicate for the first time mast cells in the pathogenesis of primary cough headache and provide intriguing new data suggesting a fivefold increase in the occurrence of migraine aura in patients with mastocytosis.

Funding

This research was partially supported by the Center for Translational Science Activities (CTSA) at Mayo Clinic. This center is funded in part by a grant from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH) (RR024150 PI: Rizza). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of CTSA, NCRR, or NIH.

References

1. Swerdlow SH International Agency for Research on Cancer. *World Health Organization. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th edn. Lyon, France: International Agency for Research on Cancer, 2008.
2. Metcalfe DD. Regulation of normal and neoplastic human mast cell development in mastocytosis. *Trans Am Clin Climatol Assoc* 2005; 116: 185–203; discussion 4.
3. Smith JH, Butterfield JH, Pardanani A, DeLuca GC and Cutrer FM. Neurologic symptoms and diagnosis in adults with mast cell disease. *Clin Neurol Neurosurg* 2011; 113(7): 570–574.
4. Ashina S and Ashina M. Headache in systemic mastocytosis: a case report with pathophysiological considerations. *Cephalalgia* 2005; 25: 314–316.
5. Horan RF and Austen KF. Systemic mastocytosis: retrospective review of a decade's clinical experience at the Brigham and Women's Hospital. *J Invest Dermatol* 1991; 96: 5S–13S. (discussion S–4S, 60S–65S).
6. Castells M and Austen KF. Mastocytosis: Mediator-related signs and symptoms. *Int Arch Allergy Imm* 2002; 127: 147–152.
7. Hermine O, Lortholary O, Leventhal PS, Catteau A, Soppelsa F, Baude C, et al. Case-control cohort study of patients' perceptions of disability in mastocytosis. *PLoS One* 2008; 3: e2266.
8. Theoharides TC, Donelan J, Kandere-Grzybowska K and Konstantinidou A. The role of mast cells in migraine pathophysiology. *Brain Res Brain Res Rev* 2005; 49: 65–76.
9. Levy D. Migraine pain, meningeal inflammation, and mast cells. *Curr Pain Headache Rep* 2009; 13: 237–240.
10. Liberski PP and Prusinski A. Further observations on the mast cells over the painful region in cluster headache patients. *Headache* 1982; 22: 115–117.
11. Dimitriadou V, Henry P, Brochet B, Mathiau P and Aubineau P. Cluster headache: ultrastructural evidence for mast cell degranulation and interaction with nerve fibres in the human temporal artery. *Cephalalgia* 1990; 10: 221–228.
12. Dimlich RV, Keller JT, Strauss TA and Fritts MJ. Linear arrays of homogeneous mast cells in the dura mater of the rat. *J Neurocytol* 1991; 20: 485–503.
13. Strassman AM, Weissner W, Williams M, Ali S and Levy D. Axon diameters and intradural trajectories of the dural innervation in the rat. *J Comp Neurol* 2004; 473: 364–376.
14. Seebeck J, Kruse ML, Schmidt-Choudhury A and Schmidt WE. Pituitary adenylate cyclase activating polypeptide induces degranulation of rat peritoneal mast cells via high-affinity PACAP receptor-independent activation of G proteins. *Ann N Y Acad Sci* 1998; 865: 141–146.
15. Ottosson A and Edvinsson L. Release of histamine from dural mast cells by substance P and calcitonin gene-related peptide. *Cephalalgia* 1997; 17: 166–174.
16. Theoharides TC, Spanos C, Pang X, Alferes L, Ligris K, Letourneau R, et al. Stress-induced intracranial mast cell degranulation: a corticotropin-releasing hormone-mediated effect. *Endocrinology* 1995; 136: 5745–5750.
17. Delepine L and Aubineau P. Plasma protein extravasation induced in the rat dura mater by stimulation of the parasympathetic sphenopalatine ganglion. *Exp Neurol* 1997; 147: 389–400.
18. Levy D, Burstein R, Kainz V, Jakubowski M and Strassman AM. Mast cell degranulation activates a pain pathway underlying migraine headache. *Pain* 2007; 130: 166–176.
19. The International Classification of Headache Disorders. 2nd edition. *Cephalalgia* 2004; 24(Suppl 1): 9–160.
20. Jacobson GP, Ramadan NM, Aggarwal SK and Newman CW. The Henry Ford Hospital Headache Disability Inventory (HDI). *Neurology* 1994; 44: 837–842.
21. Spierings EL, Ranke AH and Honkoop PC. Precipitating and aggravating factors of migraine versus tension-type headache. *Headache* 2001; 41: 554–558.

22. Theoharides TC, Singh LK, Boucher W, Pang X, Letourneau R, Webster E, et al. Corticotropin-releasing hormone induces skin mast cell degranulation and increased vascular permeability, a possible explanation for its proinflammatory effects. *Endocrinology* 1998; 139: 403–413.
23. Decker WW, Campbell RL, Manivannan V, Luke A, St Sauver JL, Weaver A, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol* 2008; 122: 1161–1165.
24. Hamilton MJ, Hornick JL, Akin C, Castells MC and Greenberger NJ. Mast cell activation syndrome: A newly recognized disorder with systemic clinical manifestations. *J Allergy Clin Immunol* 2011; 128: 147–52, e2.
25. Rasmussen BK and Olesen J. Symptomatic and nonsymptomatic headaches in a general population. *Neurology* 1992; 42: 1225–1231.
26. Chen PK, Fuh JL and Wang SJ. Cough headache: a study of 83 consecutive patients. *Cephalalgia* 2009; 29: 1079–1085.
27. Cutrer FM and Boes CJ. Cough, exertional, and sex headaches. *Neurol Clin* 2004; 22: 133–149.
28. Ray BS and Wolff HG. Experimental studies on headache: pain-sensitive structures of the head and their significance in headache. *Arch Surg* 1940; 41: 813–856.
29. Zhang XC, Strassman AM, Burstein R and Levy D. Sensitization and activation of intracranial meningeal nociceptors by mast cell mediators. *J Pharmacol Exp Ther* 2007; 322: 806–812.
30. Zhang XC and Levy D. Modulation of meningeal nociceptors mechanosensitivity by peripheral proteinase-activated receptor-2: the role of mast cells. *Cephalalgia* 2008; 28: 276–284.
31. Rasmussen BK and Olesen J. Migraine with aura and migraine without aura: an epidemiological study. *Cephalalgia* 1992; 12: 221–8; discussion 186.
32. Russell MB, Rasmussen BK, Thorvaldsen P and Olesen J. Prevalence and sex-ratio of the subtypes of migraine. *Int J Epidemiol* 1995; 24: 612–618.
33. Charles A and Brennan K. Cortical spreading depression-new insights and persistent questions. *Cephalalgia* 2009; 29: 1115–1124.
34. Gomez-Choco M, Capurro S and Obach V. Migraine with aura associated with reversible sulcal hyperintensity in FLAIR. *Neurology* 2008; 70: 2416–2418.
35. Nemeth A, Magyar P, Herceg R and Huszti Z. Potassium-induced histamine release from mast cells and its inhibition by ketotifen. *Agents Actions* 1987; 20: 149–152.
36. Skaper SD, Facci L, Kee WJ and Strijbos PJ. Potentiation by histamine of synaptically mediated excitotoxicity in cultured hippocampal neurones: a possible role for mast cells. *J Neurochem* 2001; 76: 47–55.
37. Rosenblum WI. A possible role for mast cells in controlling the diameter of arterioles on the surface of the brain. *Brain Res* 1973; 49: 75–82.
38. Drummond PD. Mechanisms of autonomic disturbance in the face during and between attacks of cluster headache. *Cephalalgia* 2006; 26: 633–641.

Appendix 1. Survey questionnaire

Name (Please print): _____

Age: _____

General Questions

Do you get headaches? Yes/No

Do you get headaches on at least 15 days of every month? Yes/No

Do your headaches occur exclusively (100% of the time) in the context of flair of your mastocytosis? Yes/No

Do your headaches coincide with the majority ($\geq$ 50%) of your mastocytosis flair? Yes/No

Over the past year, circle which of the following symptoms have occurred with at least 50% of your mastocytosis flair?:

Difficulty concentrating,

"brain fog",

flushing,

warmth,

itching,

runny nose,

abdominal pain,

diarrhea,
bone pain,
chest tightness,
shortness of breath,
light-headedness,
syncope (passing out),
Other(s): _____

If you get bone pain, please circle all the locations that apply (Pelvis, ribs, hands, feet, spine, femur (thigh bone), humerus (arm bone), face, skull).

Have you ever had a fracture from only minor injury or been told that it was related to your mast cell disease? Yes/No

Do you drink alcohol (≥ 3 drinks per week)? Yes/No

If you do get headaches, please proceed to the remainder of the survey.

Headache type #1

1. Have you had 5 or more headaches which untreated or unsuccessfully treated lasted from 4 to 72 hours?	Yes /No
IF NO, go to question 5.	
2. If yes, were at least 5 of these headaches:	
Unilateral (one side of your head)	Yes/No
Throbbing/pulsatile (pounding)	Yes/No
Of moderate to severe intensity	Yes/No
Worsened by or cause to avoid routine physical exertion	Yes/No (walking, climbing stairs)
3. Were at least 5 of these headaches accompanied by:	
Nausea and/or vomiting	Yes/No
Sensitivity to light or sound	Yes/No
4. How often do these headaches occur? (< 15 days per month OR ≥ 15 days per month) (circle one)	
5. Have you ever had at least two episodes (with or without headache) consisting of temporary:	
Visual disturbance: (flickering lights, spots, zigzagging lines, blind spots)	Yes /No
(**NOT** just visual blurring or snow like-symptoms)	
If yes, did the visual disturbance:	
Gradually develop over at least 5 minutes	Yes/No
Persist from 5 to 60 minutes	Yes/No
Affect the same part of vision on both eyes	Yes/No
Sensory disturbance: (tingling, ''needles & pins'' &/or numbness)	Yes/No
If yes, did the sensory disturbance:	
Gradually develop over at least 5 minutes	Yes/No
Persist from 5 to 60 minutes	Yes/No

Affect one half of the body (arm, leg &/or face) Yes/No

Language disturbance: (inability or slowed to think or the correct word, difficulty with reading or writing) Yes/No

If yes, did the language disturbance:

Gradually develop over at least 5 minutes Yes/No

Persist from 5 to 60 minutes Yes/No

6. Please check all of the family members who have recurrent headaches that make them nauseated or light and sound sensitive:

Father ___ Mother ___ Sister ___ Brother ___ Daughter ___ Son ___ None of my family members_____

Headache type #2

7. Have you had at least 10 headache episodes that were:

Lasting between 30 minutes and 7 days Yes/No

Bilateral (both sides of the head) Yes/No

Of mild to moderate intensity Yes/No

Pressing or tightening in quality Yes/No

Not made worse with exertion Yes/No

8. Were any of these headaches accompanied by:

Nausea and/or vomiting Yes/No

Sensitivity to light or sound Yes/No

9. How often do these headaches occur? (< 15 days per month OR ≥ 15 days per month) (circle one)

Headache type #3

10. Have you had at least five headache attacks around or above one eye or one side of the head, and lasting between 15 to 180 minutes? Yes/No

11. If yes, were at least five of these headaches:

Severe or very severe in intensity Yes/No

12. Were at least five of these headaches associated with any of the following only on the same side as the headache:

Tearing from one eye Yes/No

Runny nostril Yes/No

Stuffy nostril Yes/No

Swollen eyelid Yes/No

Sweating on one side of the face Yes/No

Droopy eyelid Yes/No

Restlessness or agitation Yes/No

13. During attack periods, do the headaches occur between once every other day to eight times per day?

Yes/No

Headache type #4

14. Within a period of just three days, did you start getting daily headaches that lasted for at least three months? Yes/No

Headache type #5

15. Do you get headaches that wake you up from sleep? Yes/No
16. If yes, does this occur at least 15 times per month? Yes/No
17. Do these headaches last at least 15 minutes after waking up? Yes/No

Headache type #6

18. Have you had at least 20 attacks of severe pain around or above one eye, or on one side of the head? Yes/No
19. Are these headaches associated with on one side: eye tearing, redness, runny nostril, stuffy nostril, eyelid swelling, droopy eyelid, or facial sweating? (Circle what occurs)
20. During attack periods do they occur at least 5 times per day for at least half the time? Yes/No

Headache type #7

21. Do you get headaches that only begin suddenly (not just made worse by coughing) because of or during a bout of coughing? Yes/No
22. Do these headaches last between one second and thirty minutes? Yes/No
23. Does this type of headache ever occur in the absence of cough? Yes/No

Please circle YES, SOMETIMES, NO depending on how each of the following statements applies to you:

1. Because of my headaches I feel handicapped. [YES, SOMETIMES, NO]
2. Because of my headaches I feel restricted in performing my routine daily activities. [YES, SOMETIMES, NO]
3. No one understands the effect my headaches have on my life. [YES, SOMETIMES, NO]
4. I restrict my recreational activities (e.g., sports, hobbies) because of my headaches. [YES, SOMETIMES, NO]
5. My headaches make me angry. [YES, SOMETIMES, NO]
6. Sometimes I feel that I am going to lose control because of my headaches. [YES, SOMETIMES, NO]
7. Because of my headaches I am less likely to socialize. [YES, SOMETIMES, NO]
8. My spouse (significant other), or family and friends have no idea what I am going through because of my headaches. [YES, SOMETIMES, NO]
9. My headaches are so bad that I feel that I am going to go insane. [YES, SOMETIMES, NO]
10. My outlook on the world is affected by my headaches. [YES, SOMETIMES, NO]
11. I am afraid to go outside when I feel that a headaches is starting. [YES, SOMETIMES, NO]
12. I feel desperate because of my headaches. [YES, SOMETIMES, NO]
13. I am concerned that I am paying penalties at work or at home because of my headaches. [YES, SOMETIMES, NO]
14. My headaches place stress on my relationships with family or friends. [YES, SOMETIMES, NO]
15. I avoid being around people when I have a headache. [YES, SOMETIMES, NO]
16. I believe my headaches are making it difficult for me to achieve my goals in life. [YES, SOMETIMES, NO]
17. I am unable to think clearly because of my headaches. [YES, SOMETIMES, NO]
18. I get tense (e.g., muscle tension) because of my headaches. [YES, SOMETIMES, NO]
19. I do not enjoy social gatherings because of my headaches. [YES, SOMETIMES, NO]
20. I feel irritable because of my headaches. [YES, SOMETIMES, NO]
21. I avoid traveling because of my headaches. [YES, SOMETIMES, NO]

22. My headaches make me feel confused. [YES, SOMETIMES, NO]
23. My headaches make me feel frustrated. [YES, SOMETIMES, NO]
24. I find it difficult to read because of my headaches. [YES, SOMETIMES, NO]
25. I find it difficult to focus my attention away from my headaches and on other things. [YES, SOMETIMES, NO]