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Elevation in histamine and tryptase following exercise in patients with mastocytosis

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Clinical Implications

Patients with mastocytosis exhibit an increase in serum levels of mast cell-related mediators with exercise and therefore should be guided regarding management of mast cell-associated symptoms to improve safety and quality of life.

TO THE EDITOR:

Mastocytosis is a disorder of clonal mast cell proliferation with clinical features that include episodic flushing, pruritus, abdominal pain, diarrhea and syncope (1). The clinical manifestations of mastocytosis are thought in part to be a result of the effects of mediators released from activated mast cells (2). Physical factors, such as heat, mechanical stimulation and exercise, have been reported to increase symptoms. In some patients with mastocytosis exercise has been reported to provoke anaphylaxis (3).

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Conflict of Interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Elevated baseline serum trypase levels are observed in patients with indolent systemic mastocytosis (ISM) and generally correlate with clinical severity of the disease (4). While increases in both histamine and tryptase have been reported in association with systemic allergic reactions, the effect of physical exercise on the release of mast cell mediators in patients with mastocytosis has not been explored. We thus sought to determine if exercise could trigger release of mast cell mediators in patients with systemic mastocytosis and compare these results to mediator levels following exercise both in a patient with cholinergic urticaria (CU) and normal volunteers (NV).

Following informed consent on NIH protocols 09-I-0126 and 02-I-0277, 8 patients diagnosed with indolent systemic mastocytosis (based on WHO criteria (5)), 1 patient with CU (verified before testing) and 2 NVs underwent treadmill exercise challenge (See Table 1 for patient demographics). Prior to the challenge, an intravenous catheter was placed in the basilic vein of the forearm. Blood was serially drawn at baseline and designated time points during and up to 2 hours following exercise challenge (Figure 1A). Blood samples were drawn into serum separation tubes, with serum aliquots stored at -20°C until analyzed. All subjects performed treadmill running/jogging or walking for a minimum of 25 minutes. Subjects were monitored to increase their heart rate to $> 50\%$ maximum (50% of $220 - \text{age}$) as well as for visible perfuse facial sweating. Serum histamine was measured using a competitive enzyme immunoassay (SPI-Bio/Bertin Pharma, Montigny-le-Bretonneux, France). Serum tryptase was measured using the ImmunoCAP 100 System (Phadia Inc., Uppsala, Sweden).

The absolute mean increase from baseline in serum histamine following challenge was greater in patients with ISM for all time points compared to NVs (Figure 1B). As a positive control, we included a patient with CU that exhibited papular urticaria and a sharp rise in serum histamine levels as has been reported following exercise challenge (6). We similarly found that there was a significant difference (Wilcoxon matched-pairs signed rank test, $p=0.0078$) in the serum histamine post-exercise peak among patients with ISM when compared to baseline (Figure 1C), an observation not seen in the NVs. The absolute mean increases in tryptase following exercise were less striking than with histamine, although patients with ISM did exhibit an increase in tryptase post exercise (Figure 1D). Similar to histamine, post exercise peak values of serum tryptase in patients with ISM were significantly higher ($p=0.0234$) compared to baseline (Figure 1E). Furthermore, when using the Mast Cell Activation tryptase index (20% plus 2 ng/ml over the baseline level), 2 of the 8 patients (ISM-2, ISM-4, Table 1) with ISM exhibited an increase in serum tryptase levels following exercise that would meet criteria for the diagnosis of systemic mast cell activation (7) which was not detected in patients with CU or NVs. Although ISM patient #4 (ISM-4, Table 1) exhibited the most dramatic increase in serum histamine and tryptase levels following exercise, the differences between baseline and post-exercise peak mediator levels remain significant when removing this subject from the ISM patient data set (histamine, $p=0.0078$ with #4, $p=0.0156$ without #4 and tryptase, $p=0.0234$ with #4, $p=0.0469$ without #4). Consistent with this, ISM patient #4 has been avoiding strenuous exercise due to increase in symptoms. As expected, we found a significant correlation between the absolute change from baseline to post-exercise peak levels of serum histamine and that of tryptase (Supp. Figure 1, $r=0.9628$, $p=0.0001$).

We next investigated whether histamine and tryptase release parallels mastocytosis severity and found that the extent of mast cell bone marrow infiltration was associated with absolute post-exercise serum mediator level increases (Suppl. Figure 2 A, B). Other manifestations of systemic mastocytosis such as osteoporosis did not show any evidence of association with higher increases in histamine or tryptase levels following exercise (Suppl. Figure 2 C,D). Patients described the various symptoms that were experienced either during or directly after exercise challenge (Table 1). We found that there was a trend towards an association between a greater absolute increase in serum histamine/tryptase levels and gastrointestinal symptoms as well as pruritis following exercise (Suppl. Figure 2 E-H).

We have presented evidence that patients with ISM exhibit a significant and intercorrelated rise in histamine and tryptase following exercise consistent with the conclusion that physical activity can induce mast cell mediator release. Furthermore, the increase of these mediators in circulation was associated with an exacerbation of mast cell mediator-related symptoms in the ISM cohort. Our current study in patients with ISM corroborates an accumulating body of evidence that suggests physical exercise can trigger mast cell degranulation. Indeed, exercise is considered a significant augmenting factor in as much as 10% of food related anaphylactic reactions (8) and has recently been reported to cause local release of histamine and tryptase from skeletal muscle (9). In conclusion, our findings suggest that clinicians managing patients with systemic mastocytosis should instruct their patients regarding the effects of exercise and provide guidance in the judicious use of mast cell mediator receptor antagonists that may provide relief of symptoms as well as the self-administration of epinephrine for the treatment of anaphylaxis should it occur.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIGURE 1.

The effect of exercise on serum histamine and tryptase levels in patients with mastocytosis.

A, Exercise challenge depicting blood draws (1 - 7). **B**, Mean ± SE change in serum histamine from baseline (time point 1) at time points 2 - 7. **C**, Baseline and peak post-exercise serum histamine levels (mean ± SE for each group). Same for tryptase (**D**,**E**). Data was derived from 3 technical replicate measurements at each time point.

NV - Normal volunteer, **CU** - Cholinergic urticaria patient, **ISM** - Indolent systemic mastocytosis patient. A two-tailed Wilcoxon matched-pairs signed rank test was used to

compare baseline and post-exercise peak levels of serum histamine (C) and tryptase (E) among individuals in the ISM patient cohort. ** $p < 0.01$ * $p < 0.05$

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TABLE 1.

t demographics and results

Age Sex		Characteristics associated with ISM			Baseline symptoms (further increased with exercise)				Serum histamine			Serum tryptase		MCA Tryptase index* (ng/ml)
		History of anaphylaxis	Osteoporosis	GI	Headache	Pruritis	Bone pain	Baseline (nM)	Post-exercise peak (nM)	Relative change † (% of baseline)	Baseline (ng/ml)	Post-exercise peak (ng/ml)	Relative change † (% of baseline)	
30	F	✓		✓		✓		9.6	16.4	71	7.74	11.8	52.5	11.3
62	M		✓					12.2	15.4	26	98.2	99.5	1.3	119.8
60	M		✓					14	18.4	30.6	44.3	42.9	-3.2	55.2
41	F	✓		✓		✓		17.2	111.3	545.7	48.9	65.2	33.3	60.7
56	F		✓			✓		59.1	75	26.9	38.1	41	7.6	47.7
42	F			✓	✓	✓	✓	19.5	23.9	22.7	19.6	21.3	8.7	25.5
42	M	✓		✓				10.7	12.9	20.9	18	20	11.1	23.6
34	M		✓			✓		34.3	50.3	46.7	25.8	29.9	15.9	33
34	M							3.9	3.5	-10.1	2.9	3.4	19.9	5.4
56	M							5.7	9	57.9	4.4	6.7	51.8	7.3
21	M							7.7	7.9	3.5	4.5	5.2	16.1	7.4

Idolent systemic mastocytosis, NV: normal volunteer, CU: cholinergic urticarial

e change from baseline calculated as (post-exercise peak \m=x\ baseline) / (baseline) × 100

ell activation (MCA) tryptase index (baseline serum tryptase × 1.2 + 2) represents the minimum serum tryptase concentration for each patient (following an acute increase) needed in order to be red indicative of systemic mast cell activation (ref. 7)