

Urinary N-methyl histamine levels relate to the presence of angioedema and decrease with the duration of chronic urticaria



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Clinical Implications

- Elevated urinary N-methyl histamine relates to the occurrence of angioedema in chronic urticaria and shorter duration of disease at presentation. Predictive algorithms using this easily measureable biomarker may help in prognosis.

TO THE EDITOR:

Chronic urticaria (CU) defined as hives lasting more than 6 weeks¹ is a challenging disease to treat due to its unpredictable nature, the lack of prognostic predictors, and minimal data on predictors of treatment response. CU affects between 0.5% and 5% of the population with the estimated incidence rate of 1.4% per year.¹ Quality of life of patients with CU is significantly poor² with associated angioedema (in approximately 40% of cases³) perceived as a particularly alarming symptom. Hives commonly last 3-5 years with 85% of patients reporting resolution of urticaria within 5 years.⁴

Clinical predictors of CU include coexisting angioedema, disease severity, and positivity to an autologous serum test associated with a longer duration of disease.⁴ Poor control with an H1 antihistamine was reported with dermatographism, a physical urticaria, and neutrophilic infiltrates on skin biopsy, whereas the presence of thyroid autoantibodies predicted greater control.⁵ Recent data are emerging on the role of biomarkers as prognosticators of disease;^{6,7} we retrospectively sought to investigate whether urinary N-methyl histamine (uNMH) could be associated with disease duration and presence of angioedema.

This was a 2-year retrospective study of patients seen at an adult tertiary outpatient allergy clinic (2013-2015). Data on patient demographics, clinical symptoms, medical history, family history, basic laboratory evaluation, and medication use were collected. Of 75 patients screened, 10 patients were excluded for an unknown duration of urticaria or urticaria <6 weeks. Of the 65 patients, 32 patients had clinical impression of chronic idiopathic urticaria, had no additional workup performed, and were not included in analysis. The remainder (n = 33) had symptoms suggestive of a mast cell activation (eg, palpitations, diarrhea, episodes of light headedness or dizziness, etc.) and therefore underwent further assessment including serum tryptase and 24-hour uNMH. One patient had serum tryptase >20 ng/mL and was excluded; thus the final number for analysis was 32. Thus patients with CU who underwent 24-hour uNMH and serum tryptase measurement as part of assessment for mast cell activation but resulted normal were analyzed. This study was approved by the

TABLE I. Characteristics of subjects in the study

Patient characteristics	
Number	32
Age, median (IQR), y	43.5 (35.5-56)
Gender	
Female (%)	20 (62)
Male (%)	12 (37)
Body mass index, median (IQR)	32.8 (27.7-68.2)
Duration of hives, median (IQR), wk at the time of first visit	46 (16-180)
Clinical characteristics of hives	
Hives severe enough to affect quality of sleep (n = 24)	19 (79)
Hives associated with angioedema (n = 31)	25 (80)
Presence of abdominal pain and cramping during flare (n = 28)	4 (14)
There was an infectious episode preceding the onset of hives (n = 25)	6 (24)
Presence of a diagnosis of autoimmune disease as comorbidity (n = 31)*	9 (29)
Presence of diagnosis of thyroid disease as comorbidity (n = 30)	9 (30)
Association with any physical trigger (n = 29)	12 (41)
Lab features of cohort	
	Median (IQR)
Blood eosinophil count, cells/mm ³ (n = 31)	130 (70-190)
Blood basophil count, cells/mm ³ (n = 31)	20 (10-30)
TSH, mIU/L (n = 29)	1.6 (0.8-2.9)
TPO, IU/mL (n = 21)	1.2 (0.4-1.9)
Serum tryptase, ng/mL (n = 31)	4.7 (3-7.9)
Twenty-four-hour urinary N-methyl histamine, mcg/g Cr (n = 32) (normal range: 30-200)	124.5 (86-154)
Medication scoring system	
	Score (number of patients)
No medication or as needed	0 (8)
Antihistamines H1RA only (varying doses, up to 4 times per day)	1 (9)
Combination of H1RA, H2RA, and/or montelukast	2 (10)
Use of omalizumab in addition to score 0-2 medications	3 (1)
Use of immunomodulators in addition to score 0-3 medications	4 (4)

IQR, Interquartile range; TPO, thyroid peroxidase antibodies; TSH, thyroid stimulating hormone.

*Diagnoses included granulomatous polyangiitis (1, clinically suspected), rheumatoid arthritis (1), autoimmune hypothyroid disease (4), Hashimoto's thyroiditis (1), and Graves' disease (2).

Institutional Review Board at Mayo Clinic. The 2-sided *P* value of less than .05 was considered statistically significant. The Wilcoxon test was used for univariate comparison. The correlation coefficient was calculated on pairwise correlations of log-transformed data. Statistical and graphic software are JMP 10.0 (SAS, Cary, NC) and Microsoft Office 2010 (Redmond, WA).

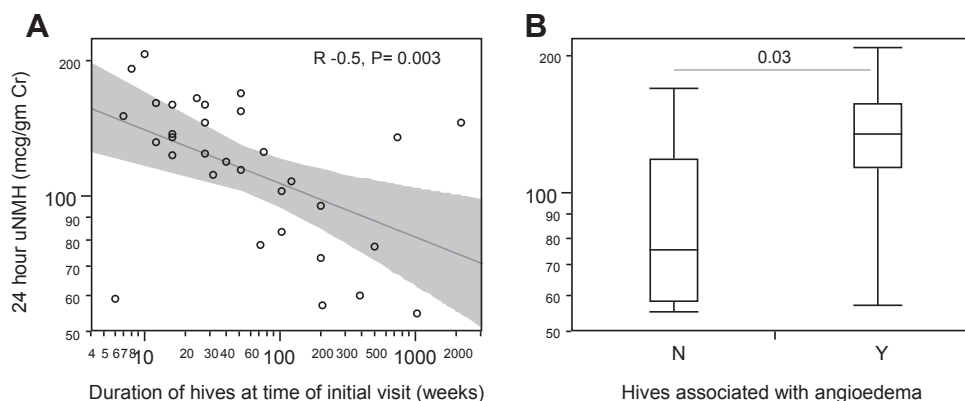


FIGURE 1. **A**, Correlation plot of 24-hour urinary N-methyl histamine (uNMH) excretion (mcg/g Cr) versus duration of hives at the time of initial visit (weeks). The line represents a transformed fit in Log-Log mode. The shaded area shows confidence limits for the expected value. **B**, Comparison of uNMH excretion between those who did not report associated angioedema (N) and those who did (Y).

Table I shows the characteristics of the study population. The median duration of hives was 46 weeks (interquartile range [IQR] 16-180). The median blood eosinophil, basophil, thyroid stimulating hormone (TSH), tryptase level, and 24-hour uNMH level were within normal limits. The 24-hour uNMH levels inversely correlated with duration of urticaria at the time of presentation (Figure 1, $R = -0.5$, $P = .003$). Patients with angioedema had higher but normal uNMH (median 135 mcg/g Cr, IQR 113-157.5) compared with those without angioedema (median 75.5 mcg/g Cr, IQR 58-119.5; $P = .03$) (Figure 1). Serum tryptase did not exhibit such relation. We found no association between uNMH and body mass index, age, gender, severity of urticaria (as reflected by urticaria affecting quality of sleep), autoimmune disease, thyroid disease, or association with a physical trigger. Patients with abdominal cramping as a symptom with CU tended to have higher uNMH (median 150.5 mcg/g Cr, IQR 135.5-182.7) than those without (median 124.5, IQR 98.2-157.7) but did not reach significance ($P = .13$). There was no correlation between uNMH and peripheral eosinophil or basophil count, TSH, or thyroid peroxidase (TPO) antibody titers. To analyze medication use and its relation to variables in the study, we classified the medication use by applying a “medication scoring” system to convert the heterogeneous textual data to a numeric scale (Table I). There was a moderate and significant increase in the intensity of the medication use with longer lasting urticaria corresponding with greater medication use ($R = 0.36$, $P = .04$). However, in this cohort, the medication score had a weak and insignificant correlation ($R = 0.174$, $P = .34$) with the uNMH excretion.

Higher N-methyl histamine excretion has been reported in aspirin and food additive challenge in patients with CU⁸ as well as variation in methyl histamine excretion noted in relation to timing of onset of challenge-induced hives.⁹ We sought to examine if uNMH, a metabolite of histamine, could reflect the clinical features of disease severity or duration. We found that elevated uNMH relates to the occurrence of angioedema in CU and shorter duration of disease at presentation. We recognize some limitations of this analysis. First, our cohort was small and

may not be sufficiently powered to delineate differences between other variables. Second, we were unable to factor the exact role of medications on histamine excretion. Future studies would be needed to investigate the relationship of higher urinary histamine and response to increased antihistamines or if uNMH could be used as a marker of medication-induced suppression. Third, the study was retrospective and hence limited by the shortcomings of such design, and serial testing to conclusively rule out an underlying mast cell-related condition was not available. However, the study has its strengths. For example, clinical data were obtained prospectively using a standard questionnaire tool allowing for harmonization and consistent comparisons. To our knowledge, this is the first comprehensive evaluation of 24-hour uNMH, an easily obtainable marker, with broad clinical correlates in CU. Whether the reduced excretion with duration reflects a change in histamine-based responses in long-term CU needs to be further elucidated. Patients with CU and angioedema had higher levels of uNMH excretion though uNMH levels were still within the normal range for both groups. This suggests that increased urinary histamine excretion may be a predictor of short duration of CU and tendency for the development of angioedema; though larger prospective studies are needed in this regard.

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Conflicts of interest: B. Patel declares no relevant conflicts of interest. R. Divekar is employed by Mayo Clinic, and has received revenue from Google.com for an unrelated Web blog.

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