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# Value of urinary *N*-methylhistamine measurements in childhood mastocytosis

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**Background:** Histamine is an indicator of mast cell activation. *N*-methylhistamine (NMH) is a metabolite of histamine that can be measured in urine.

**Objective:** Our purpose was to assess the usefulness of determining urinary NMH levels for the diagnosis and follow-up of patients with mastocytosis.

**Methods:** Urinary NMH levels were determined in 44 patients and were correlated with disease activity and extension. The control group consisted of 24 children without mastocytosis or any other skin disease.

**Results:** A significant negative correlation was found between NMH and age in patients with active mastocytosis and in the control group. Adjusted for age, NMH values were significantly higher in patients with active mastocytosis. There was a significant difference in NMH values between patients with diffuse cutaneous mastocytosis, patients with active urticaria pigmentosa, and patients with active mastocytomas. However, there was a substantial overlap of NMH values in the different subgroups.

**Conclusion:** Urinary NMH values tend to decrease with age. Urinary NMH values correlated with the extent and the activity of the disease. High NMH values suggest more extensive involvement.

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Mastocytosis consists of an array of clinical and biochemical abnormalities that are a consequence of tissue infiltration by an excess of mast cells and the release of various biologically active mediators from these cells.<sup>1-4</sup> Patients with mastocytosis are usually classified according to the extent of the skin abnormalities. Children with less than five distinct skin lesions are placed in the group of mastocytomas and those with five or more lesions are classified as having urticaria pigmentosa. The term *diffuse cutaneous mastocytosis* is used when the skin is diffusely involved.

*N*-Methylhistamine (NMH) is a degradation prod-

**Table I.** Distribution of the study patients in the different subgroups of mastocytosis

Subgroup	Active mastocytosis (No.)	Nonactive mastocytosis (No.)
Mastocytomas ( <i>n</i> = 14)	12	2
Urticaria pigmentosa ( <i>n</i> = 27)	21	6
Diffuse cutaneous mastocytosis ( <i>n</i> = 3)	3	0
Total patients with mastocytosis ( <i>n</i> = 44)	36	8

uct of histamine, one of the main excretion products of mast cells. An increased plasma level of histamine in patients with mastocytosis has been reported.<sup>6, 7</sup> However, measurement of plasma and urinary histamine levels appears to be less accurate than the measurement of the urinary NMH level.<sup>8, 9</sup> We investigated the usefulness of urinary NMH in the diagnosis and follow-up of children with mastocytosis.

## MATERIAL AND METHODS

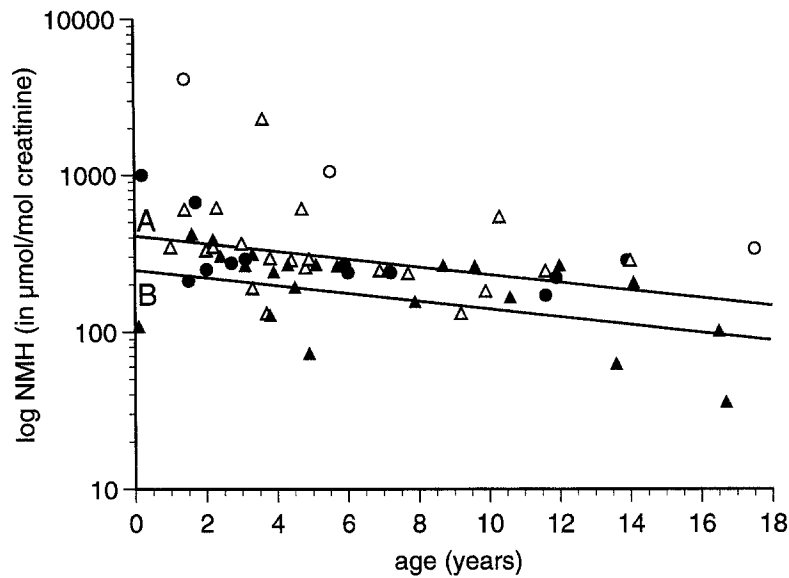
Forty-four patients and 24 control subjects were enrolled into this study. The patients' ages ranged from 2

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**Fig. 1.** NMH values (after log transformation) of all patients with active mastocytosis and of the controls, showing the decline with age. Upper line (A) is regression line for patients with active mastocytosis; lower line (B) is regression line for control subjects. ●, Active mastocytomas; ○, diffuse cutaneous mastocytosis; △, active urticaria pigmentosa; ▲, controls.

**Table II.** Comparison of urinary NMH values in our control group with normal values according to Schulze et al.<sup>12</sup>

	Study control group	Schulze et al.
<4 yr	272.3 (109-423) (n = 8)	213 (101-524) (n = 19)
4-10 yr	225.2 (73-270) (n = 10)	181 (79-375) (n = 20)
>10 yr	140.3 (36-267) (n = 6)	134 (50-247) (n = 18)

Data expressed as mean (range given in parentheses) in micromoles of NMH per mole of creatinine.

months to 17 years. The control group consisted of children without mastocytosis or any other skin disease. The age distribution of the control group was the same as that of the patient population.

The patients were placed into subgroups according to the extent of their skin abnormalities. In addition, the activity of their disease was assessed by history (reports of conditions such as flushing) and clinical examination (Darier's sign). On the basis of these findings the groups were further subdivided of those children with active and inactive mastocytosis.

The NMH levels in the urine samples were determined in duplicate with a double antibody radioimmunoassay (Pharmacia, Woerden, The Netherlands). The concentrations of NMH were expressed as micromoles of NMH per mole of creatinine in the urine.

Statistical analyses were conducted by means of the

**Table III.** Mean, median, and range of the urinary NMH values in the different subgroups

	Mean	Median	Range
Mastocytosis (n = 44)	453	262	82-4182
Active mastocytosis (n = 36)	516	288	132-4182
Active mastocytoma(s) (n = 12)	318	257	171-1000
Active urticaria pigmentosa (n = 21)	424	293	132-2320
Diffuse cutaneous mastocytosis (n = 3)	1858	1054	338-4182
Inactive mastocytosis (n = 8)	168	162	82-247
Control subjects (n = 24)	219	248	36-423

Data expressed in micromoles of NMH per mole of creatinine.

Spearman rank correlation<sup>10</sup> and multiple regression analysis.<sup>11</sup>

## RESULTS

The distribution of the patients in the different subgroups with active and inactive disease is shown in Table I. This distribution is in agreement with the relative occurrence of the different forms of the disease.<sup>3</sup>

Systemic complaints were present in one patient with mastocytoma, in one patient with urticaria pigmentosa, and in all patients with diffuse cutaneous

mastocytosis. Contact urticaria induced by peanuts was present in one patient with active urticaria pigmentosa. This patient also had severe atopic dermatitis.

The values of NMH excreted in the urine samples from our control group were similar to the normal values found by Schulze et al.<sup>12</sup> (Table II).

Fig. 1 shows the decline of NMH (after log transformation) with age in the control group and in the group of patients with active mastocytosis. Mean, median, and range of the values of NMH excreted in the urine samples of the patients in different groups are shown in Table III. A substantial overlap between the concentrations of NMH in the different subtypes is evident.

A significant negative rank correlation was found between NMH and age in patients with active mastocytosis ( $r_s = -0.452$ ;  $p = 0.006$ ;  $n = 36$ ) as well as in the control subjects ( $r_s = -0.510$ ;  $p = 0.011$ ;  $n = 24$ ) ( $r_s =$  Spearman rank correlation coefficient).

With multiple regression analysis to adjust for age, a significant difference in NMH (after log transformation) was found between patients and control subjects. NMH values in patients were, on average, 70% higher than those of the control subjects ( $p = 0.0023$ ).

This average effect (adjusted for age) can be further specified in the different subgroups of patients as follows: the NMH values in patients with active mastocytomas were 49% higher than in the control subjects ( $p = 0.032$ ), 64% higher in patients with active urticaria pigmentosa ( $p = 0.002$ ), and 573% higher in patients with diffuse cutaneous mastocytosis than in the control subjects ( $p = 0.000$ ).

NMH decreased by 6.1% per year of age ( $p = 0.001$ ); there was no evidence that this age effect differed between the groups ( $p = 0.338$ ).

## DISCUSSION

The results of this study showed that urinary NMH values, adjusted for age, were higher in children with active mastocytosis than in the age-matched control group. We found that the more extensive the skin lesions, the higher the average values of the urinary NMH and the more significant the difference between the control group and the re-

spective subgroup of patients with active mastocytosis. Therefore high levels of NMH suggest more severe and extensive disease and possible systemic involvement. In systemic disease NMH levels can be useful to follow the evolution of mastocytosis.

On the other hand, the distribution of NMH levels in the various subgroups and in the control group substantially overlapped. In part this is a consequence of the age dependency of the NMH levels with higher (normal) values during early childhood.<sup>12, 13</sup>

We suggest that in childhood mastocytosis, measurement of the urinary NMH level may be useful at the time of diagnosis. It should only be repeated later in patients in whom the initial value was high or if new signs or symptoms, indicating activation of the mastocytosis, appear.

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