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Blood histamine levels (BHL) in infants and children with respiratory and non-respiratory diseases

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Background: Blood histamine levels are decreased after severe allergic reactions and in various chronic diseases.
***Aims:* To study blood histamine levels in infants and children with acute infectious and non-infectious, non-allergic, disease.**
***Methods:* Blood histamine levels were investigated by a fluorometric method in infants and children admitted to hospital with bronchiolitis, non-wheezing bronchitis, acute infections of the urinary tract, skin and ear–nose–throat, gastroenteritis, or hyperthermia of unknown aetiology. Results of blood histamine levels and white blood cell counts were compared with those obtained for children recovering from benign non-infectious, non-allergic illnesses.**
***Results:* As compared with control children, white blood cell numbers were significantly increased in children with acute infections of the urinary tract, skin and ear–nose–throat, and were significantly decreased in children with gastroenteritis. Blood histamine levels were significantly lower in children with gastroenteritis and hyperthermia than in children with other diseases and control children. It was not possible to correlate blood histamine levels and the number of blood basophils.**
***Conclusions:* BHL are significantly decreased in infants and children with acute gastroenteritis and hyperthermia of unknown aetiology. The mechanisms responsible for the decrease in blood histamine levels in children with gastroenteritis and hyperthermia are discussed.**

Key words: Blood histamine, Bronchiolitis, Bronchitis, Gastroenteritis, Hyperthermia, Infant, Child

Introduction

Histamine plays an important role in physiological homeostasis and in the pathogenesis of various diseases via its regulatory effects on smooth muscle contraction, vascular tone and permeability, gastric secretion, neurotransmission, the immune system and inflammation.[1,2]

Plasma histamine levels (PHL) increase in pathological conditions associated with mast cell and/or basophil activation, such as severe atopic dermatitis,[3,4] exercise-induced asthma,[5] severe asthma,[6] food allergy,[7,8] anaphylaxis and anaphylactoid reactions,[9–11] and in chronic, non allergic diseases, such as sickle cell anemia,[12] chronic renal failure and nephrotic syndrome,[13] and polytraumatized patients.[14] However, PHL determinations are very dependent on sampling procedure and on short half-life of histamine in plasma, leading to numerous false positive and false negative results.[15]

In humans, blood histamine is almost entirely contained in basophils,[16–19] and whole blood histamine levels (BHL) are closely related to the number of circulating basophils.[20] Thus, BHL are independent of sampling conditions.[21] BHL are significantly decreased in conditions associated with massive blood basophil degranulation, such as anaphylaxis and anaphylactoid reactions,[21] and in chronic non-allergic diseases, such as malignant solid tumours in adults[22] and infection with human immunodeficiency virus (HIV) in infants and children.[20]

BHL have not been studied in infants and children with acute infectious and non-infectious, non-allergic diseases. We therefore investigated BHL in infants and children admitted to hospital with various acute infectious diseases or hyperthermia of unknown aetiology. Results were compared with those obtained for hospitalised children recovering from acute non-infectious, non-allergic benign illnesses.

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Table 1. Characteristics of the infants and children, and results of blood histamine determinations and white blood cell counts

Group	Children			Blood histamine (ng/ml: mean±SEM)	WBC counts (nb/mm^3±SD)
	N	Sex	Age: range (mean)		
1	29	20 M + 9 F	1–10 m (8 m, 10 d)	44.9 ± 24.4	13686 ± 5740
2	18	13 M + 5 F	1–33 m (13 m, 1 w)	53.8 ± 30.7	15483 ± 4876
3	15	8 M + 7 F	1–26 m (6 m, 2 w)	41.9 ± 17.6	17180 ± 9463*
4	24	16 M + 8 F	10 d–32 m (8 m)	19.6 ± 11.0*	10995 ± 4033*
5	16	8 M + 8 F	1–36 m (8 m, 3 w)	22.9 ± 6.8*	13125 ± 7148
6	26	17 M + 9 F	3 d–24 m (5 m, 3 w)	53.3 ± 23.2	13869 ± 6313

Abbreviations: d (day), m (month), w (week).
Statistical significance assessed by the test of Mann & Whitney: *p<0.01 as compared with control children (group 6).

Material and methods

Children

128 children (46 F + 82 M) admitted to hospital for acute illnesses were investigated. The children were aged from 3 days to 32 months (mean: 14 months). Children were classified according to diagnosis:

- group 1: bronchiolitis;
- group 2: non-wheezing bronchitis;
- group 3: infections of the urinary tract, skin, or ear–nose–throat (ENT);
- group 4: acute gastroenteritis (GE);
- group 5: transient hyperthermia of unknown aetiology;
- group 6 (controls): children recovering from benign non-infectious, non-allergic conditions such as faintness, crying, oedema of unknown aetiology, difficult bottle-feeding, spasms, and gastroesophageal reflux.

The demographic characteristics of the children are shown in Table 1.

Histamine determination and blood cell counts

Blood samples for white blood cell (WBC) counts and BHL determination were taken at the same time as for other tests (e.g. electrolyte determination), after informed consent has been obtained from the parents of the children.

To take into account possible diurnal variations in BHL,[23] blood was always taken between 9.00 and 11.00 h and treated as described previously.[22] Briefly, 800 µg 0.15 M NaCl and 1 ml 0.8 N perchloric acid were added to 200 µl of heparinised venous blood. The mixture was vigourously shaken and centrifuged, and supernatants were stored in polystyrene tubes until assay. Histamine was assayed using the fluorometric method of Shore *et al.*,[24] automated as described by Siraganian and Brodsky,[25] and modified as described by Lebel.[26] The results were expressed as nanograms of histamine base per millilitre blood (ng/ml: mean±SEM).

The non parametric test of Mann & Whitney (U test) was used for statistical analysis.

Results

Mean BHL and WBC counts for each group of children are shown in Table 1. BHL were significantly lower in children with GE and hyperthermia ($p = 0.01$) than in control children. No significant differences were observed between control children and the other groups of children. BHL did not differ significantly between boys and girls (Table 2), and were independent of age (Table 3).

WBC numbers were not significantly different in control children and in children with bronchiolitis, bronchitis, and hyperthermia. As compared with control children, mean number of WBC was significantly increased in children with non-pulmonary infections ($p < 0.01$), and was significantly decreased in children with GE ($p < 0.01$). The number of blood basophils was very low, and below the detection threshold in most of the children

Discussion

BHL are significantly correlated with the number of circulating basophils,[20] and decrease after the activation of blood basophils in patients with severe allergic

Table 2. Results of blood histamine determination (ng/ml: mean±SEM) according to the sex of infants and children

Group	Male	Female
1	46.8 ± 26.4	42.7 ± 16.2
2	52.8 ± 33.1	56.6 ± 26.5
3	34.7 ± 9.1	48.2 ± 21.3
4	21.4 ± 12.7	15.9 ± 5.4
5	22.6 ± 5.6	23.1 ± 8.2
6	52.8 ± 13.1	53.5 ± 27.4

Table 3. Results of blood histamine determinations (ng/ml: mean±SEM) according to the age of infants and children

Group	<3 months	3–6 months	>6 months
1	48.8 ± 25.1	54.1 ± 36.4	41.0 ± 15.6
2	64.5*	70.0 ± 14.2	48.5 ± 34.3
3	48.1 ± 21.7	**	34.9 ± 7.9
4	23.5 ± 11.1	19.1 ± 14.5	17.7 ± 10.6
5	21.0 ± 5.8	26.7 ± 3.9	22.0 ± 7.4
6	46.4 ± 16.1	56.5 ± 33.2	63.6 ± 27.1

*2 infants only. **no child.

reactions such as anaphylaxis and anaphylactoid reactions.[21] We have also shown that BHL and blood basophil numbers decrease significantly in chronic non-allergic diseases such as malignant tumours in adults,[22] and HIV infection in infants and children.[20] The mechanisms involved in the decrease in BHL and blood basophils in these patients are unknown. They may be related to a chronic IgE-dependent activation of basophils by antigens from HIV and/or opportunistic pathogens in HIV-infected patients,[27-29] and to the inhibition of basophil differentiation in the bone marrow of tumour-bearing patients.[22]

In this study, we report the results of investigations in infants and children with acute infectious and non-infectious, non-allergic diseases. BHL in control children were similar to those reported in previous studies,[20] and were consistent with the blood basophil numbers usually found in infants and children,[30,31] and with the reported mean histamine content of blood basophils.[32] Our results are consistent with those of previous studies showing that BHL are independent of age and sex in healthy newborns, infants and children.[20,33] WBC number in control children was consistent with the total leukocyte numbers usually found in infants and children.[31]

BHL did not differ significantly between control children and children with infections of the urinary tract, skin, and ENT, non-wheezing bronchitis and bronchiolitis.

Respiratory viruses, such as respiratory syncytial virus (RSV), induce Th2-type immune responses in infected infants and children.[34] Welliver *et al.* detected virus-specific IgE in the nasopharyngeal secretions of infants infected with *para-influenzae* virus and RSV.[35,36] Histamine levels are high in nasal secretions of infants with RSV-induced bronchiolitis,[36] and levels of virus-specific IgE and histamine are significantly and positively correlated with the severity of bronchiolitis, and with the subsequent development of wheezing.[37,38] Although virus-specific IgE are predominantly found in nasopharyngeal secretions,[37] they are also detected in the serum of RSV-infected infants.[39] Moreover, plasma histamine levels (PHL) are high in infants with acute bronchiolitis and in children with viral respiratory infections.[40,41] However, the increase in PHL reported in these studies probably results from histamine release due to IgE-dependent activation of bronchial and pulmonary mast cell by virus antigens because we found no convincing evidence for *in vivo* blood basophil activation in children with bronchiolitis, although *in vitro* IgE-dependent activation of blood basophils by viral antigens has been reported in RSV-infected infants.[42]

BHL were normal in children with non-wheezing bronchitis and infections of the urinary tract, skin, and ENT. Most of these infections are due to viruses (bronchitis) and bacteria (infections of the urinary tract, skin, and ENT). Mean WBC number was significantly increased in children with non bronchopulmonary infections, consistent with the bacterial origin of the infections of the urinary tract, skin and ear–nose–throat. With the exception of *Mycoplasma pneumoniae*, which induces the production of specific IgE in asthmatic patients,[43] and other bacteria such as *Haemophilus influenzae* and *para-influenzae*, and *Pseudomonas aeroginosa*, which induce mast cell activation *in vivo*, and non-specific histamine release *in vitro*,[44] these pathogens induce an inflammatory reaction, with no evidence of mast cell and/or basophil activation.

BHL were significantly lower in children with GE and hyperthermia than in control children. Unfortunately, it was not possible to correlate BHL and basophil numbers because the number of blood basophils was very low, and often below the detection threshold in most of the children. It has been shown that corticosteroid treatment causes a significant decrease in BHL.[16,23] However, most of the children in our study, including children with hyperthermia and gastroenteritis, were not treated with corticosteroids. Moreover, we have previously shown that the decrease in BHL and blood basophils in tumour-bearing patients and in HIV-infected infants and children is significantly and inversely correlated with the severity of the disease, and is independent of chemotherapy, radiotherapy, and corticosteroids.[20,22]

Hyperthermia results from the release of mediators and cytokines such as prostaglandin E_2, endogenous pyrogen, interleukins 1, 6 and 8, C-C chemokines, tumour necrosis factor-α, and interferon-γ.[45,46] Most of these cytokines also induce mast cell and basophil activation,[47–49] and may therefore decrease BHL. However, WBC numbers did not differ significantly between children with hyperthermia and control children. Most children with hyperthermia recovered spontaneously in a few days, suggesting that hyperthermia resulted from viral infection. However, most cases of bronchiolitis, bronchitis and GE also resulted from viral infections, and most of these children were also hyperthermic at the time of BHL determination, although fever was generally milder and/or of shorter duration in these children than in children with hyperthermia of unknown aetiology.

In western countries, most cases of acute GE in infants and children result from viral infections of the digestive tract, although a few cases are attributed to bacteria, such as enteropathogenic *Escherichia coli*. Enteric viruses and bacteria induce major inflammation of the digestive tract mucosa, associated with large losses of water and electrolytes, and with a transient malabsorption syndrome. Previous studies have shown that PHL increase significantly in children with acute GE, but return to normal after recovery.[50,51] The authors suggested that the increase in PHL resulted from mast cell activation in the intestine by factors released from the inflammed gut mucosa. The release of inflammatory mediators from the digestive tract, known to recruit and activate basophils and mast cells, such as complement factors,[52,53] factors of the kinin system,[54] and chemokines,[47–49,55–57] may account for the decrease in BHL in infants and children with acute GE. Preactivated human basophils have also been shown to release histamine and leukotriene C4 in response to stimulation with secretory immunoglobulin A (sIgA).[58] As sIgA is the most abundant immunoglobulin isotype in gut mucosa and mucosal secretions, this suggests that blood basophils are recruited and activated in the digestive tract during acute GE. However, several other mechanisms may also be involved: (1) IgE-dependent activation of circulating basophils by microbial antigens. However, in contrast to the situation for bronchiolitis, there are no reports concerning specific IgE against enteric pathogens in patients with GE. (2) Fever, because most infants and children with GE were hyperthermic at the time of BHL determination (see above).

Conclusion

BHL decrease significantly in infants and children with acute gastroenteritis and hyperthermia of unknown aetiology. The mechanisms involved, and the possible pathophysiological significance of the decrease in BHL in these diseases are unclear.

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