Advs Exp. Medicine, Biology - Neuroscience and Respiration
DOI 10.1007/5584_2017_81

Serum Diamine Oxidase in Pseudoallergy in the Pediatric Population

Joanna Kacik, Barbara Wróblewska, Sławomir Lewicki, Robert Zdanowski, and Bolesław Kalicki

Abstract

Histamine intolerance (pseudoallergy) is a poorly investigated type of food hypersensitivity. The main enzyme responsible for histamine degradation in the extracellular matrix is diamine oxidase (DAO). Disturbances in the concentration or activity of DAO may lead to the development of clinical signs of allergy. The aim of the present work was to assess the DAO concentration, peripheral blood morphology, lymphocytes phenotyping (CD3+, CD4+, CD8+, CD19+, NK cells, NKT cells, and activated T-cells), and natural regulatory Treg (nTregs) cell population (CD4+, CD25+, CD127low, and FoxP3) in 34 pediatric patients with histamine-dependent syndromes. Patients were divided into two groups: classical allergy and pseudoallergy on the basis of IgE concentration. The investigation was based on the analysis of peripheral blood samples. A significantly lower serum DAO, both total and specific IgE, concentration was found in the pseudoallergy group compared with the allergy group. There were no significant differences in blood morphology or lymphocyte populations. A similar level of nTreg lymphocytes was also found in both groups, although it was lower than that present in healthy individuals. The findings suggest that the serum DAO is responsible for the symptoms of histamine intolerance. Moreover, a general decrease in nTreg cells in comparison with healthy individuals may lead to symptom aggravation.

J. Kacik (✉) and B. Kalicki
Department of Pediatrics, Pediatric Nephrology and Allergology, Military Institute of Medicine, 128 Szaserów, 04-141 Warsaw, Poland
e-mail: jkacik@wim.mil.pl

B. Wróblewska
Department of Immunology and Food Microbiology, Institute of Animal Reproduction and Food Research, Polish Academy of Sciences, Olsztyn, Poland

S. Lewicki and R. Zdanowski
Department of Regenerative Medicine and Cell Biology, Military Institute of Hygiene and Epidemiology, Warsaw, Poland

Keywords
Allergy • Angioedema • Dermal lesions • Headache • Immunological disorders • Stomachache

1 Introduction

Histamine intolerance is a poorly understood type of food hypersensitivity mimicking an allergic reaction. It is referred to as pseudoallergy. In both histamine intolerance and allergy, the factor responsible for the development of symptoms is histamine (β-imidazolyl-4-ethylamine), acting on numerous receptors present in various cells. Histamine-dependent symptoms develop in the alimentary system (stomachache, diarrhea, nausea, and flatulence), skin (rashes, angioedema, reddening, and itching), cardiovascular system (arrhythmias and hypotension), nervous system (headaches and fainting), and in other organs (Karpińska-Gasztoł et al. 2014; Millichap and Yee 2003).

In case of allergy, immunological reaction triggers a release of histamine into the blood. The reaction involves the IgE cross-linking on mast cells or basophiles following an allergen provocation, leading to a rapid release of histamine from those cells (Maintz et al. 2006). A trace amount of an allergen is sufficient to evoke the reaction. In case of histamine intolerance, a non-immunological pathway leads to the accumulation of histamine in excess of the body tolerance threshold due to an excessive ingestion of histamine-rich food with insufficient mechanisms of its degradation or, to a lesser extent, due to a number of factors triggering a release of histamine from cellular reserves (Table 1) (Smolinska et al. 2014; Czerwionka-Szaflarska and Zielińska-Duda 2009).

There are only two pathways of histamine metabolism in humans (San Mauro Martin et al. 2016; Górski 2007). The principal enzyme responsible for histamine degradation in the extracellular space and for preventing its excessive absorption is diamine oxidase (DAO) (Schwelberger et al. 2013, Maintz et al. 2006). Disorders of histamine degradation by DAO may result from the enzyme deficiency or its impaired function due to the action of pharmaceuticals, intestinal flora disorders, inflammatory diseases, and malignancies of the alimentary tract (Table 2) (Skypala et al. 2015; Maintz and Novak 2007). Another enzyme capable of degrading histamine, N-methyltransferase, acts intracellularly and plays no significant role in the metabolism of histamine supplied with food. The role of N-methyltransferase in the diagnostic and therapeutic procedures involving histamine intolerance seems negligible, despite its presence in various cells, including the respiratory epithelial cells.

When histamine-dependent symptoms are present, the diagnostics focus on confirming the allergic background of the ailment. The guidelines have been developed, along with the interpretation of readily available diagnostic methods, including the determination of total IgE and specific IgE and skin-prick tests (Høst et al. 2003). New diagnostic tools are also under development such as the determination of platelet-activating factor or mastocytic tryptase level (Vadas 2016; Vitte 2015; Sala-Cunill and Cardona 2015; Lieberman 2014; Akin et al. 2007). On the other hand, there is striking lack of a reliable diagnostic tool in case of a suspected histamine intolerance.

Demarcation between histamine intolerance and allergy is a challenge. Frequently, patients presenting histamine-dependent symptoms are classified as allergic, even though the allergic background has not been confirmed. This misinterpretation is associated with lasting consequences, particularly in children. The pseudoallergy is often suspected subsequent to a long-term observation in patients who exhibit at least two histamine-dependent symptoms that improve after a 4-week low-histamine diet or

Table 1 Food products high in histamine content and histamine releasing

Products high in histamine	Products stimulating histamine release
Alcoholic beverages (red wine, red, beer, champagne)	Alcoholic beverages (wine, beer)
Fish, including marinated, smoked, tinned	Marinated, salted and smoked fish
Seafood (crabs, oysters, caviar, mussels)	Tinned meat
Red meat and highly processed meat products (pepperoni, salami), tinned meat, offal	Milk and dairy products
Fermented dairy products	Certain herbs (mint, chamomile, linden, sage, pansy, willow)
Mushrooms	Mushrooms
Cheese (processed, mouldy, hard and semi-hard)	Pickled vegetables
Preserved and pickled vegetables	Certain vegetables (spinach, pepper, lettuce, potato, tomato, cucumber, peas, radish, courgette, leek, corn, carrot, beetroot)
Certain vegetables (beans, peas, lentils, spinach, lettuce, tomato, cabbage)	Certain fruits (berries, currants, citrus fruits, kiwi fruit, apple, plums, cherries, banana, melon, watermelon, pineapple, peach, grapes, apricot)
Certain fruits (berries, plums, grapes, avocado, pineapple, citrus fruits)	Preserved and dried fruits (raisins, figs, apricot, plums)
Preserved and dried fruits (raisins)	Carbonated drinks, fruit and vegetable juice
Sweets (chocolate, jam, marzipan, nougat)	Sweets (chocolate, honey, caramel, nougat)
Drinks (coffee, tea, cola)	Vinegar, mayonnaise, ketchup, oils, olive oil
Vinegar, mayonnaise, ketchup	Cereal products, seeds and nuts (soy, peanuts, almonds)
Certain spices (curry) Cereal products and yeast-based products	Food additives (colorants, preservatives, antioxidants, flavor enhancers)

Table 2 Factors inhibiting diamine oxidase (DAO) activity

DAO inhibitors
H_2 receptor antagonists (e.g., cimetidine)
Certain antibiotics (e.g., cefuroxime, clavulanic acid)
Antiarrhythmics (e.g., propafenon)
Antihypertensives (e.g., verapamil)
Analgesics (e.g., morphine, metamizole)
Radiological contrast media
Anesthetics (e.g., thiopental)
Antispasmodics
Motility agents (e.g., metoclopramide)
Diuretics (e.g., amiloride)
Mucolytics and broncholytics (e.g. acetylocysteine, ambroxol, aminophyline)
Other factors that inhibit DAO activity
Intestinal microflora disorders (excessive intake of probiotics, chemotherapy)
Excessive intake of biogenic amines (tyramine, putrescine)
Gastrointestinal tract disorders (inflammatory diseases, neoplastic diseases)

antihistamine medications (Kovacova-Hanuskova et al. 2015; Weidenhiller et al. 2012).

It is estimated that approximately 1% of the general population presents symptoms of histamine intolerance caused by DAO deficiency (Jarisch 2004). However, there are no reliable publications indicating the ratio of those patients in the overall group presenting histamine-dependent symptoms, or frequency of histamine intolerance and allergies coinciding. There are also no in-depth reports focusing on the pediatric population. Therefore, the present study seeks to

define a link between reduced serum DAO level and histamine intolerance in children. Attention was drawn to the plausible association of histamine intolerance with changes in peripheral blood cell counts and in subpopulations of regulator lymphocytes in a hope of identifying a reliable and rapid method enabling the diagnosis of histamine-dependent symptoms.

2 Methods

2.1 Patients

The study was approved by the Bioethics Committee of the Military Institute of Medicine in Warsaw, Poland (permit no. 141/16). The parents of qualified children gave written informed consent. Thirty four children with histamine-dependent symptoms were enrolled into the study. They were divide into two groups: allergy group (inclusion criteria: high concentration of total IgE or specific IgE compared to the age-matched healthy population) – 26 patients, aged 7 months to 17 years, and the pseudoallergy group (inclusion criteria: low concentration of total IgE or specific IgE compared to the age-matched healthy population) – 8 patients, aged 18 month to 11 years. Standard diagnostic interviews were conducted to assess the histamine-dependent symptoms and the probability of allergy. Patients or parents filled out the questionnaire by ticking yes or no answer. The results were shown as a percentage of positive answers.

2.2 Hematological Investigation

The blood, 500 μl taken into EDTA tubes, was investigated using the hematology systems (Sysmex XN 1000, Kobe, Japan and Advia 2102i, Siemens Healthcare GmbH, Erlangen, Germany) to determine the following parameters: white blood cells (WBC), red blood cells (RBC), hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW%), red cell distribution width absolute (RDW-a), platelets (PLT), and mean platelet volume (MPV).

The determination of WBC phenotype was performed as described previously (Kalicki et al. 2013). Briefly, cells in 100 μl of whole blood were labeled with the appropriate antibodies in the dark for 20 min (BD Simultest™ – IMK Plus Kit, BD Biosciences, Warsaw, Poland). Next, erythrocyte lysis was performed in room temperature for 10 min (FACS Lysing Solution, BD Biosciences). Afterward, the cells were washed twice with 2 ml of phosphate buffer solution (PBS) and fixed in 200 μl of 1% v/v paraformaldehyde/PBS solution. Phenotypic analysis was performed with flow cytometry (FACS Calibur; BD Biosciences) and analyzed with CellQuest Pro software (BD Biosciences). Three thousand counts of lymphocytes finished the acquisition. Results were expressed as means ±SE%.

The determination of nTreg cell population and gating restriction were performed as described previously (Lipińska-Opałka et al. 2017). Briefly, the cells in 100 μl of whole blood were stained with primary antibodies CD4-PerCP, CD25-APC, and CD127-FITC (extracellular staining; BD Bioscence, Warsaw, Poland) or with the appropriate isotype control with the addition of ally CD4-PerCP antibody. After 20 min, erythrocyte lysis was performed (FACS Lysing Solution, BD Biosciences) followed by fixation and permeabilization (Fixaton/Permeabilization buffer BD Pharmingen, Warsaw, Poland). The cells were then stained with FoxP3 PE or isotype IgG1 kappa PE antibody for 45 min in the dark in room temperature. The cells were acquired in flow cytometry. Ten thousand counts of CD 4 PerCP positive cells finished the acquisition. Results were analyzed by CellQuest Pro software (BD Biosciences) and expressed as means ±SE %.

2.3 Biochemical Investigations

Total IgE concentration was determined in the serum samples using a solid-phase enzyme-linked immunosorbent assay (Sandwich ELISA), calibrated with commercially available IgE standards. DAO content was measured in the serum samples using an ELISA assay kit for D-amino acid oxidase (Cloud-Clone Corp, Katy, TX). Results were expressed as means ±SE IU/ml.

2.4 Statistical Elaboration

Data distribution was evaluated using the Shapiro-Wilk test. Differences between the allergy and psudoallergy groups were evaluated with Student's *t*-test or Mann-Whitney U test as required. A p-value <0.05 defined the statistically significant changes. The analyses were performed with a commercial GraphPad Prism v5 software package (GraphPad Software, La Jolla, CA).

3 Results

3.1 Allergy vs. Pseudoallergy

The main criterion for the differentiation of allergic from pseudoallergic children was the serum concentration of IgE immunoglobulin. The difference in the total IgE content was outstanding (Fig. 1), enabling further elaboration of clinical aspects in clearly demarcated groups of children.

3.2 Symptoms

Generally, there were no significant differences in the manifestation of specific histamine-dependent systemic symptoms in the children with allergy and pseudoallergy. However, there was a tendency for a lower incidence of skin symptoms in children with pseudoallergy. We also observed the appearance of symptoms after ingestion of food nearly twice as often in children with pseudoallergy (Table 3).

3.3 Serum DAO Concentration

In the group of patients with allergy, the mean serum DAO concentration amounted to 83.01 ± 6.73 IU/ml. In the pseudoallergic group, the mean DAO concentration was significantly lower 46.40 ± 7.19 IU/ml ($p = 0.0016$) (Fig. 2).

There were no significant differences in the majority of blood morphological indices in the children with allergy and pseudoallergy. The notable exceptions were a significantly greater absolute and relative levels of eosinophils in the allergy than pseudoallergy group and somewhat smaller mean corpuscular volume and concentration of hemoglobin in the latter group (Table 4).

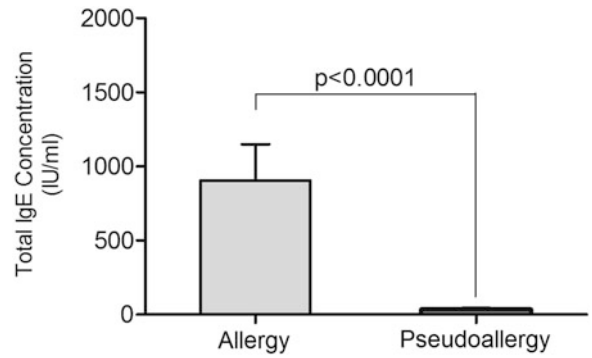

Fig. 1 Serum total IgE concentration; data are means ±SE

Table 3 Patient symptoms (% of cases)

	Allergy	Pseudoallergy
Skin (atopic dermatitis, pruritus, urticaria, erythema)	76.9%	50.0%
Neural system (pain and dizziness, nausea)	7.4%	0%
Digestive system (diarrhea, bloating, vomiting, lips and tongue swelling)	22.2%	25.0%
Respiratory system (runny nose, sneezing, wheezing, dyspnea)	70.4%	75.0%
Circulatory system (arrhythmias, syncope, dizziness)	0%	0%
Seasonality	29.6%	12.5%
Symptoms appearing after food ingestion	22.2%	50.0%
Symptoms appearing after drug use	3.7%	12.5%

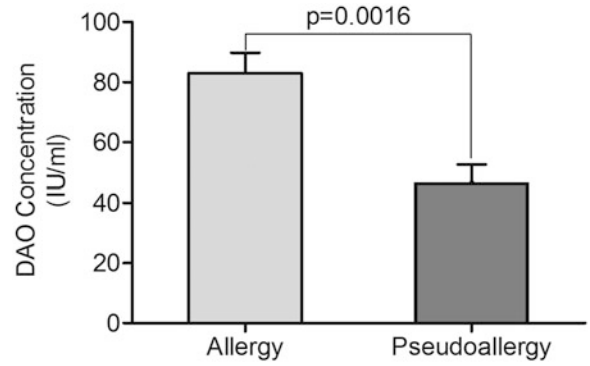

Fig. 2 Serum DAO concentration; data are means ±SE

In both allergy and pseudo-allergy groups, there were no significant differences in the percentage of the following lymphocyte subpopulations: B-cells, T-cells, CD4, CD8, CD4/8 ratio, NK cells, NKT cells, and activated T-cells (Fig. 3). Nor were there any significant differences between the percentages of nTregs (CD4+, CD25+, CD 127low, and FoxP3+).

4 Discussion

Attempts to examine the role of histamine and reduced serum DAO activity in the diagnostics of food intolerance have been made in the 1980s and 1990s. Provocation tests, intestinal biopsy, and a determination of serum DAO following heparin injections were the procedures of choice at that time; which, however, were apt to produce numerous adverse effects (Wantke et al. 1994; Wantke et al. 1993; Lessof et al. 1990).

New methods for diagnosing pseudoallergy are currently sought. Mušič et al. (2013) have examined a correlation between serum DAO activity in patients with suspected histamine intolerance and the effect of a low-histamine diet in a group of 316 adults. A similar study has been conducted by Manzotti et al. (2016) in 14 adults presenting histamine-dependent symptoms, following the exclusion of the allergic background of observed symptoms and of factors leading to the enzyme dysfunction. Both studies confirm the existence of a correlation between reduced DAO activity and the development of histamine intolerance. There are reports suggesting the applicability of skin-prick tests with histamine-soaked flakes as a diagnostic method (Kofler et al. 2011).

Clinical studies on histamine intolerance in children are scarce or involve small groups of patients (Hoffmann et al. 2013; Rosell-Camps et al. 2013; Millichap and Yee 2003). Therefore, there are no reliable data determining a correlation between DAO concentration and histamine intolerance symptoms; not to mention the

Table 4 Blood hematological indices

	Allergy	Pseudoallergy	*p*-value
WBC# (×10^9/l)	7.5 ± 0.4	8.3 ± 0.9	0.778
RBC# (×10^12/l)	4.8 ± 0.1	4.9 ± 0.1	0.298
HGB (g/dl)	13.0 ± 0.2	12.7 ± 0.2	0.224
HCT%	38.6 ± 0.6	37.9 ± 0.7	0.755
MCV (fl)	80.2 ± 0.6	77.9 ± 0.8	0.062
MCH (pg)	27.2 ± 0.2	26.0 ± 0.3	**0.004**
MCHC (g/dl)	33.9 ± 0.2	33.4 ± 0.3	**0.009**
PLT# (×10^9/l)	313.4 ± 17.1	343.7 ± 23.4	0.348
MPV (fl)	8.5 ± 0.3	8.0 ± 0.8	0.898
PCT%	0.26 ± 0.02	0.27 ± 0.03	0.439
PDW (fl)	10.7 ±1.4	13.1 ±1.5	0.316
PDW%	26.6 ±5.1	32.8 ±8.4	0.741
RDW-SD (fl)	36.3 ±0.5	36.4 ±1.2	0.965
RDW-CV%	12.7 ±0.1	12.9 ±0.5	0.584
LUC# (×10^3/μl)	0.12 ±0.03	0.17 ±0.05	0.528
LUC%	1.6 ±0.3	2.3 ±0.6	0.800
LY#	3.1 ±0.2	4.0 ±0.9	0.546
LY%	42.6 ±1.7	45.2 ±5.1	0.671
NE# (×10^3/μl)	3.2 ±0.2	3.4 ±0.5	0.919
NE%	42.8 ±1.8	43.1 ±4.9	0.966
MO# (×10^3/μl)	0.52 ±0.04	0.51 ±0.06	0.809
MO%	6.9 ±0.4	6.4 ±0.7	0.842
EO# (×10^3/μl)	0.43 ±0.06	0.22 ±0.03	**0.007**
EO%	5.6 ±0.7	2.8 ±0.4	**0.004**
BA# (×10^3/μl)	0.04 ± 0.0	0.04 ± 0.01	0.897
BA%	0.54 ± 0.04	0.57 ± 0.08	0.968
P-LCR (×10^3/μl)	21.0 ± 3.9	33.9 ± 6.5	0.144

Data are means ±SE; $p < 0.05$ denoting significant changes between the two groups in *bold*
WBC white blood cells, *RBC* red blood cell count, *HGB* hemoglobin, *HCT* hematocrit, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration, *PLT* platelet count, *MPV* mean platelet volume, *PCT* platelet crit, *PDW* platelet distribution width, *PDW%* relative platelet distribution width, *RDW-SD%* relative red blood cell distribution width, standard deviation, *RDW-CV%* relative red blood cell distribution width, coefficient of variation, *LUC#* large unstained cells – absolute content, *LUC%* large unstained cells – relative content, *LY#*,lymphocytes – absolute content, *LY%* lymphocytes – relative content, *NE#* neutrophils – absolute content, *NE%* neutrophils – relative content, *MON#* monocytes – absolute content, *MON%* monocytes – relative content, *EO#* eosinophils –absolute content, *EO%* eosinophils – relative content, *BA#* basophils –absolute content, *BA%* basophils – relative content, P-*LCR* ratio of large platelets

influence on the results of patients' age which could also factor in the present findings.

The present findings demonstrate that in addition to the known correlation between the development of pseudoallergy symptoms and reduced DAO activity, a similar correlation exists for the reduced serum DAO content. The correlation is present in the pediatric population, which suggests the use of a serum DAO measurement as a diagnostic tool in suspected cases of pseudoallergy in children. Moreover, a significantly greater ratio of eosinophils in the peripheral blood was notable in the group classified as allergy. A statistically significant difference in the hemoglobin indices, MCH and MCHC, could be a result of a small size of the study group and its low differentiation. Although a similar level of nTregs (CD4+, CD25+, CD 127low, and FoxP3) was found in both study groups, it was lower than that present in the healthy pediatric population (Lipińska-Opałka et al. 2017). This finding points to the plausibility of immunological dysfunction in both histamine intolerance and allergy. Further exploration of a

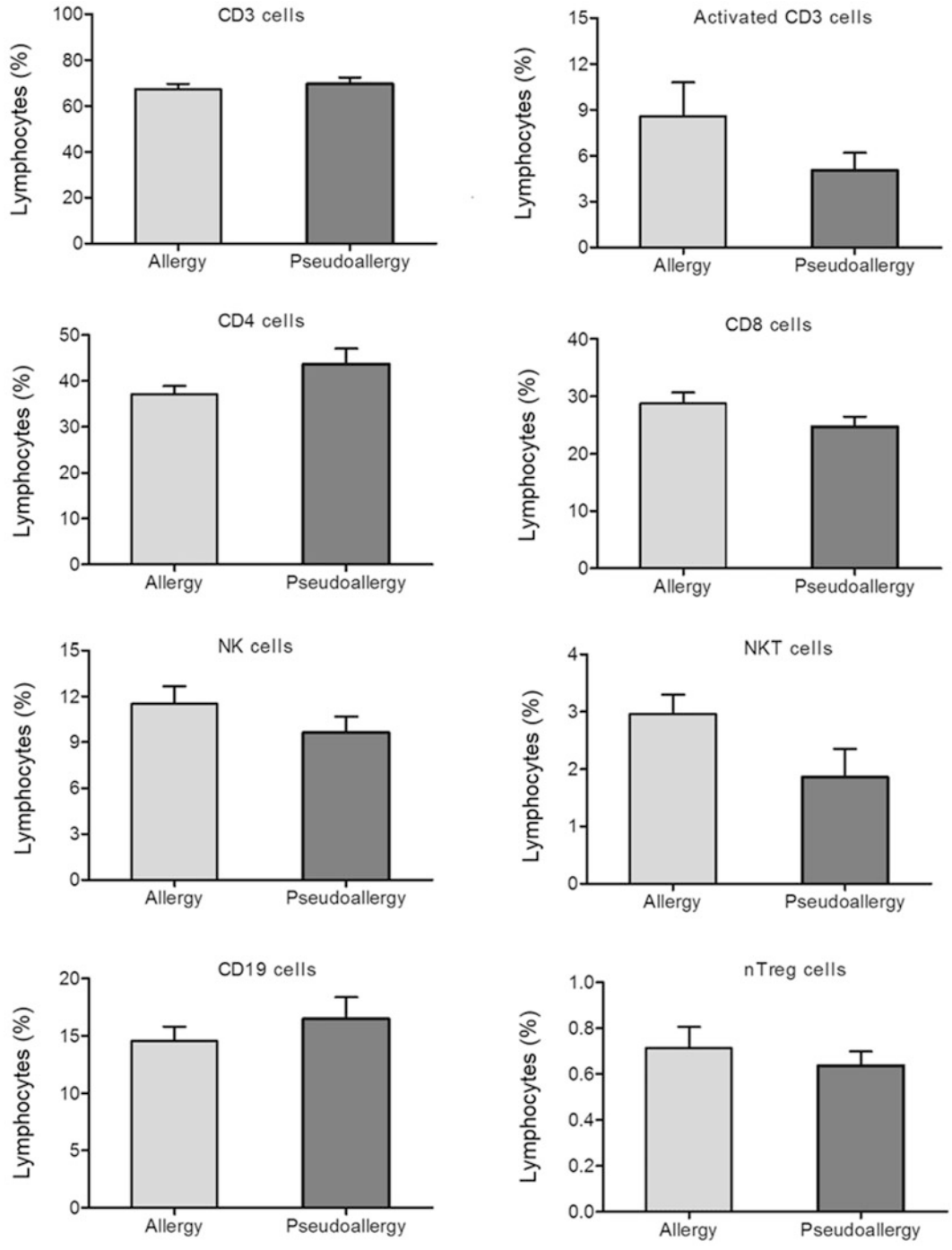

Fig. 3 Lymphocytes phenotyping in peripheral blood; data are means ± SE

link between serum DAO and regulatory lymphocytes is required to determine their mutual influence on the development of histamine dependent symptoms.

When considering the variability of pediatric organisms, a small sample size in the present study could interfere with the interpretation of results. Therefore, the study is a mere introduction to further explorations, including the determination of both serum concentration and activity of diamine oxidase in various age-groups.

Acknowledgments We thank Mr. Piotr Murawski, Head of ICT Department of the Military Institute of Medicine for assistance in statistical elaboration.

Conflicts of Interest The authors declare no conflicts of interest in relation to this article.

References

Akin C, Scott LM, Kocabas CN, Kushnir-Sukhov N, Brittain E, Noel P, Metcalfe DD (2007) Demonstration of an aberrant mast-cell population with clonal markers in a subset of patients with 'idiopathic' anaphylaxis. Blood 110(7):2331–2333

Czerwionka-Szaflarska M, Zielińska-Duda H (2009) Allergy and food intolerance in children. Fam Med Prim Care Rev 11:577–584

Górski P (2007) Histamine- a mediator the longer known the more unknown. Alergia 4:33–35

Hoffmann KM, Gruber E, Deutschmann A, Jahnel J, Hauer AC (2013) Histamine intolerance in children with chronic abdominal pain. Arch Dis Child 98 (10):832–833

Høst A, Andrae S, Charkin S, Diaz-Vázquez C, Dreborg S, Eigenmann PA, Friedrichs F, Grinsted P, Lack G, Meylan G, Miglioranzi P, Muraro A, Nieto A, Niggemann B, Pascual C, Pouech MG, Rancé F, Rietschel E, Wickman M (2003) Allergy testing in children: why, who, when and how. Allergy 58 (7):559–569

Jarisch R (2004) Histamin-Intoleranz. Histamin und Seekrankheit, 2nd edn. Georg Thieme Verlag, Stuttgart/New York

Kalicki B, Lewicki S, Stankiewicz W, Jung A, Rustecka A, Turkowska M, Rutkowski P, Bodera P, Zdanowski R (2013) Examination of correlation between vitamin D-3 (25-OHD3) concentration and percentage of regulatory T lymphocytes (FoxP3) in children with allergy symptoms. Cent Eur J Immunol 38(1):70–75

Karpińska-Gasztoł E, Gutowska M, Zdunowski P, Zgliczyńskiet W (2014) Plethoric facies – multidisciplinary problem. Histamine intolerance secondary to reduced diamine oxidase activity. Post N Med 27 (12):843–846. (Article in polish)

Kofler L, Umler H, Kofler H (2011) Histamine 50-skin-prick test: a tool to diagnose histamine intolerance. ISNR Allergy 2011:353045. doi:10.5402/2011/353045

Kovacova-Hanuskova E, Buday T, Gavliakova S, Plevkova J (2015) Histamine, histamine intoxication and intolerance. Allergol Immunopathol (Madr) 43 (5):498–506

Lessof MH, Gant V, Hinuma K, Murphy GM, Dowling RH (1990) Recurrent urticaria and reduced diamine oxidase activity. Clin Exp Allergy 20(4):373–376

Lieberman PL (2014) Idiopathic anaphylaxis. Allergy Asthma Proc 35(1):17–23

Lipińska-Opałka A, Wawrzyniak A, Lewicki S, Zdanowski R, Kalicki B (2017) Evaluation of immune indices and serum vitamin D content in children with atopic dermatitis. Adv Exp Med Biol. doi:10.1007/5584_2017_20

Maintz L, Bieber T, Novak N (2006) Histamine intolerance in clinical practice. Dtsch Arztebl 103(51–52): A3477–A3483

Maintz L, Novak N (2007) Histamine and histamine intolerance. Am J Clin Nutr 85:1185–1196

Manzotti G, Breda D, Di Gioacchino M, Burastero SE (2016) Serum diamine oxidase activity in patients with histamine intolerance. Int J Immunopathol Pharmacol 29(1):105–111

Millichap J, Yee M (2003) The diet factor in pediatric and adolescent migraine. Pediatr Neurol 28(1):9–15

Mušič E, Korošec P, Šilar M, Adamič K, Košnik M, Rijavec M (2013) Serum diamine oxidase activity as a diagnostic test for histamine intolerance. Wien Klin Wochenschr 125(9–10):239–243

Rosell-Camps A, Zibetti S, Pérez-Esteban G, Vila-Vidal-M, Ferrés-Ramis L, García-Teresa-García E (2013) Histamine intolerance as a cause of chronic digestive complaints in pediatric patients. Rev Esp Enferm Dig 105:201–206

Sala-Cunill A, Cardona V (2015) Biomarkers of anaphylaxis, beyond tryptase. Curr Opin Allergy Clin Immunol 15(4):329–336

San Mauro Martin I, Brachero S, Garicano Vilar E (2016) Histamine intolerance and dietary management: a complete review. Allergol Immunopathol (Madr) 44 (5):475–483

Schwelberger HG, Ahrens F, Fogel WA, Sánchez-Jiménez F (2013) Histamine metabolism. In: Stark H (ed) Histamine H4 receptor: a novel drug target in Immunoregulatory and inflammatory diseases. Versita, London, pp 63–101

Skypala IJ, Williams M, Reeves L, Meyer R, Venter C (2015) Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. Clin Transl Allergy 5:34. doi:10.1186/s13601-015-0078-3

Smolinska S, Jutel M, Crameri R, O'Mahony L (2014) Histamine and gut mucosal immune regulation. Allergy 69(3):273–281

Vadas P (2016) The platelet-activating factor pathway in food allergy and anaphylaxis. Ann Allergy Asthma Immunol 117:455–457

Vitte J (2015) Human mast cell tryptase in biology and medicine. Mol Immunol 63:18–24

Wantke F, Gotz M, Jarisch R (1994) The red wine provocation test: intolerance to histamine as a model for food intolerance. Allergy Proc 15:27–32

Wantke F, Götz M, Jarisch R (1993) Histamine-free diet: treatment of choice for histamine-induced food intolerance and supporting treatment for chronic headaches. Clin Exp Allergy 23(12):982–985

Weidenhiller M, Layritz C, Hagel AF, Kuefner M, Zopf Y, Raithel M (2012) Histamine intolerance syndrome (HIS): plethora of physiological, pathophysiological and toxic mechanisms and their differentiation. Z Gastroenterol 50(12):1302–1309