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Magdalena Kleszyk[1], Elżbieta Mizgała-Izworska[2], Anna Góra[1], Maciej Przybył[1], Edyta Machura[1]

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Multifactorial aetiology of recurrent respiratory tract infections in children

Wieloczynnikowa etiologia nawracających infekcji układu oddechowego u dzieci

[1] Department of Paediatrics in Zabrze, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland
[2] Department of Family Medicine in Zabrze, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland
Correspondence: Magdalena Kleszyk, MD, PhD, Department of Paediatrics, Professor Stanisław Szyszko Independent Public Clinical Hospital No. 1 in Zabrze, Medical University of Silesia in Katowice, 3 Maja 13–15, 41-800 Zabrze, Poland, tel.: +48 32 370 42 67, e-mail: madzia.am@gmail.com

Abstract

Recurrent respiratory tract infections in children are a common health problem. Exposure to harmful environmental agents and coexistence of chronic diseases affect the severity and rate of infections. Ineffective outpatient treatment is an indication for a more comprehensive diagnostic workup. The aim of the study was to determine the cause of recurrent respiratory tract infections in children. The study group included 130 children aged 3–17 years who were referred for diagnostic investigation to determine the cause of recurrent respiratory tract infections. The eligibility criterion for the study group was the occurrence of 8 or more respiratory tract infections a year in children aged up to 6 years and 5 or more infections a year in children aged 7–17 years. The study group was subdivided into the following age groups: 3–5 years (n = 60), 6–9 years (n = 35), 10–13 years (n = 11) and 14–17 years (n = 24). The presence of potential risk factors for recurrent infection was analysed on the basis of questionnaires. Tests and examinations were also performed in order to exclude allergies, ear, nose and throat disorders and gastroesophageal reflux disease. Selected laboratory values (complete blood count, vitamin D concentration, immunoglobulin levels) were compared with those obtained from 86 healthy children from the control group. The majority of children had risk factors for recurrent respiratory tract infections. Adenoid hypertrophy was diagnosed in 44.6% of children, asthma in 36.9%, vitamin D deficiency in 30.7%, gastroesophageal reflux disease in 16.2% and immunodeficiency in 9.2% of children. Multimorbidity was found in 34.6% of the subjects. In the study group, there were higher vitamin D levels [study group: 25.6 ng/mL (25^{th} percentile = 17; 75^{th} percentile = 33.3), control group: 22.84 ng/mL (25^{th} percentile = 16.3; 75^{th} percentile = 28.7); $p < 0.044$] and higher leukocyte levels [study group: 7.5×10^3/μL (25^{th} percentile = 5.9; 75^{th} percentile = 9.1), control group: 6.4×10^3/μL (25^{th} percentile = 5.3; 75^{th} percentile = 7.7); $p < 0.02$]. The results indicate that children with recurrent respiratory tract infections are a heterogeneous group of patients. The youngest children were the largest group (n = 60). In the majority of children, the onset of symptoms was associated with the beginning of nursery/preschool or school attendance. In 1 in 3 children, a combined presence of a few diseases was found which increase susceptibility to recurrent respiratory tract infections.

Keywords: child, respiratory tract infections, diagnosis

Streszczenie

Nawracające infekcje układu oddechowego u dzieci są częstym problemem zdrowotnym. Narażenie na niekorzystne czynniki środowiskowe oraz współistnienie chorób przewlekłych rzutują na ciężkość i częstość infekcji. Nieskuteczne leczenie ambulatoryjne jest wskazaniem do pogłębionej diagnostyki. Celem pracy było ustalenie przyczyny nawracających infekcji dróg oddechowych u dzieci. Grupę badaną stanowiło 130 dzieci w wieku 3–17 lat skierowanych do diagnostyki w celu ustalenia przyczyny nawrotowych infekcji układu oddechowego. Za kryterium kwalifikacji do grupy badanej przyjęto występowanie minimum 8 infekcji dróg oddechowych w roku u dzieci do 6. roku życia i minimum 5 infekcji w roku u dzieci w wieku 7–17 lat. Dokonano podziału badanych na podgrupy wiekowe: 3–5 lat (n = 60), 6–9 lat (n = 35), 10–13 lat (n = 11), 14–17 lat (n = 24). Na podstawie badań kwestionariuszowych analizowano obecność potencjalnych czynników ryzyka nawrotowych infekcji oraz przeprowadzono diagnostykę w celu wykluczenia alergii, schorzeń laryngologicznych i refluksu żołądkowo-przełykowego. Wybrane parametry laboratoryjne (morfologia krwi, stężenie witaminy D, stężenie immunoglobulin) porównano z wartościami uzyskanymi u 86 dzieci zdrowych z grupy kontrolnej. U większości dzieci istniały czynniki ryzyka nawrotowych infekcji układu oddechowego. Przerost migdałka gardłowego rozpoznano u 44,6%, astmę u 36,9%, niedobór witaminy D u 30,7%, refluks żołądkowo-przełykowy u 16,2%, a niedobór odporności u 9,2% dzieci. Wielochorobowość dotyczyła 34,6% badanych. W grupie badanej stwierdzono wyższe stężenie witaminy D [grupa badana: 25,6 ng/ml (25. percentyl = 17; 75. percentyl = 33,3), grupa kontrolna: 22,84 ng/ml (25. percentyl = 16,3; 75. percentyl = 28,7); $p < 0,044$] oraz wyższe wartości leukocytów [grupa badana: 7,5 tys./μl (25. percentyl = 5,9; 75. percentyl = 9,1), grupa kontrolna: 6,4 tys./μl (25. percentyl = 5,3; 75. percentyl = 7,7); $p < 0,02$]. Wyniki potwierdzają, że dzieci z nawrotowymi

infekcjami układu oddechowego to heterogenna grupa pacjentów. Najliczniejszą grupę stanowiły dzieci najmłodsze (n = 60). U większości dzieci początek objawów powiązany był z rozpoczęciem uczęszczania do żłobka/przedszkola lub szkoły. U 1/3 dzieci stwierdzono współistnienie kilku chorób predysponujących do nawrotowych objawów ze strony układu oddechowego.

Słowa kluczowe: dziecko, infekcje układu oddechowego, rozpoznanie

INTRODUCTION

Respiratory tract infections, particularly in the youngest children (up to 3 years of age), are a common health problem. These are usually mild upper respiratory tract infections, while lower respiratory tract infections account for 10–30% of cases[1,2]. Frequent infection recurrence may have a negative impact on a child's general health and quality of life. It can increase the frequency of outpatient appointments and/or hospitalisation, force parents to be absent from work and cause secondary infections in parents and siblings[2–4].

The number of infection episodes that can be considered the norm in otherwise healthy children with no additional medical problems varies considerably. According to some authors, the number of mild respiratory tract infections that can be regarded as normal is the following: 11 episodes/year in infants and small children (0–2 years), 8 episodes/year in preschool children (3–5 years) and 4 episodes/year in school children (6–12 years)[5]. Epidemiological research shows that nursery/preschool attendance, a short breastfeeding period/lack thereof, having siblings, low socioeconomic status, poor housing conditions, tobacco smoke exposure, being unvaccinated, male sex and malnutrition are some of the potential risk factors associated with recurrent respiratory tract infections[6,7]. Research from recent years shows that apart from affecting calcium and phosphorus homeostasis, vitamin D has a pleiotropic effect on the immune system; thus, vitamin D deficiency may predispose individuals to recurrent infections[8–10].

Apart from being affected by harmful environmental agents, the rate and severity of respiratory tract infections may also be determined by abnormal function of complex mechanisms associated with or unrelated to the host's immune system and by concomitant chronic diseases[6].

A more comprehensive diagnostic investigation is considered to be required in children with severe infection, lack of improvement following treatment, presence of atypical infection-causing pathogens (e.g. *Pneumocystis jiroveci*), low body weight and/or height for age, delayed psychomotor development, significant chest deformities, abnormal auscultatory findings present always on the same side of the thoracic cavity, persistent wheezing and symptoms that may be related to a heart defect, autoimmune diseases, family atopy, respiratory tract defects and coexistence of chronic diseases[11]. It is known that the common symptoms of infection such as cough and rhinitis are not associated with a single disease entity and may not necessarily be caused by a respiratory tract infection.

Contrary to popular opinion and parents' concerns, primary immunodeficiency is a rare cause of recurrent respiratory tract infections (4–10% according to various sources)[12]. The Jeffrey Modell Foundation Medical Advisory Board developed the "10 Warning Signs of Primary Immunodeficiency," which help to identify children in need of a more comprehensive immunological investigation. These signs include: 4 or more new ear infections, 2 or more serious sinus infections within 1 year, 2 or more months on antibiotics with little effect, 2 or more pneumonias within 1 year, failure of an infant to gain weight or grow normally, recurrent deep skin or organ abscesses, persistent thrush in mouth or fungal infection on skin, the need to use intravenous antibiotics to clear infections, 2 or more deep-seated infections (such as sepsis, encephalitis, bone infections and skin infections) and a family history of primary immunodeficiency[13].

AIM OF THE STUDY

The aim of the study was to establish the cause of recurrent respiratory tract infections in children who were referred by the primary care physician to the General Paediatric Ward to undergo tests and examinations for recurrent respiratory tract infections.

MATERIALS AND METHODS

Materials

The study group (SG) included 130 children in total (68 girls, 62 boys) aged 3–17 years (median 7.51 ± 4.42 years) who were referred to the General Paediatric Ward, Department of Paediatrics of the Independent Public Clinical Hospital No. 1 (SP SK1) in Zabrze, Medical University of Silesia (SUM) in Katowice, Poland, in 2013–2015 due to recurrent respiratory symptoms. In these patients, the treatment prescribed by a paediatrician turned out to be ineffective and outpatient diagnostic tests did not reveal the cause of recurrent complaints. The eligibility criterion for the SG was the occurrence of 8 or more respiratory tract infections within a year in children aged up to 6 years and 5 or more infections within a year in children aged 7–17 years. Antibiotic therapy was used in all children during infection. The presence of an autoimmune disease or a chronic inflammatory

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condition was an exclusion criterion for the study group. The patients were recruited directly based on history, physical examination and basic laboratory test results excluding acute infection during hospitalisation (complete blood count with differential and C-reactive protein, CRP). Based on questionnaire results, the presence of potential risk factors for recurrent infections was analysed.

The control group (CG) included 86 patients (44 girls and 42 boys) aged 3–17 years (median 8.52 ± 4.68 years) without a history of recurrent respiratory symptoms (sporadic mild upper respiratory tract infections were allowed with a frequency of up to 5 a year in children up to 6 years of age and up to 3 times a year in older children). The CG included healthy children with no symptoms of inflammatory or allergic diseases.

Children from the SG and the CG were divided into the following age subgroups: 3–5 years (SG: $n = 60$, CG: $n = 33$), 6–9 years (SG: $n = 35$, CG: $n = 20$), 10–13 years (SG: $n = 11$, CG: $n = 13$), 14–17 years (SG: $n = 24$, CG: $n = 20$).

Laboratory and other diagnostic tests and examinations

Patients had the following tests performed: complete blood count with differential, absolute eosinophil count, CRP level, vitamin D concentration and immunoglobulin levels (IgA, IgG, IgM and IgE). Vitamin D concentration was determined using electrochemiluminescence immunoassay (ECLIA) with the use of Elecsys Vitamin D total assay and the Cobas 6000 device (Cobas e601 module). The analytical sensitivity of the test was 7.5 nmol/L (3.0 ng/mL).

The total serum IgA concentration was determined using latex-enhanced immunoturbidimetry. The method's analytical sensitivity was 0.10 G/L. Total IgG and IgM levels were determined based on the reaction between these antibodies and the relevant antigens. The resultant agglutination was measured with turbidimetry. The analytical sensitivity of the tests was: 0.30 g/L (2.00 µmol/L) for IgG and 0.01 g/L (0.01 µmol/L) for IgM. The total IgE concentration was determined with ECLIA using Elecsys IgE II immunoassay that utilises antihuman IgE monoclonal antibodies. The test was conducted on the Cobas 6000 device (e601 module). The analytical sensitivity of the test was 0.1 IU/mL (0.24 ng/mL).

All patients underwent ear, nose and throat (ENT) examination and allergy tests, i.e. skin prick tests (SPT) and/or specific IgE immunoassay (sIgE). In 69 individuals a chest radiograph was taken (CXR), in 43 spirometry was performed and in 35 a pH test was conducted.

Statistical methods

Statistical analysis of selected laboratory values was performed using licensed Statistica 10.0 software (StatSoft Polska). Quantitative variables were expressed as a median (*Me*) and a range between the 1st and 3rd quartile (25th and 75th percentile). Groups were compared using the Mann–Whitney *U* test. Correlation analysis involved the use of Spearman's correlation coefficient.

In accordance with the Declaration of Helsinki, the subjects and their parents/legal guardians were informed of the research purpose, nature and method. Written informed consent was obtained from the parents or legal guardians of children and from the subjects themselves who were aged 16 years or more.

The study received approval of the Medical University of Silesia, Katowice, Poland, Ethics Committee (No. KNW/0022/KB1/77/14).

RESULTS

Possible risk factors for recurrent respiratory tract infections in children

The majority of children (83%) had at least 2 risk factors for recurrent infections (Tab. 1).

Basic laboratory markers and serum immunoglobulin levels (Tab. 2)

Children from the SG were found to have a higher peripheral blood leukocyte count (expressed as $10^3/\mu L$). This was the case for children aged 3–5 years [SG: $Me = 8.6 \times 10^3/\mu L$ (6.75;10.08) vs. CG: $Me = 6.38$ (5.59;6.93); $p < 0.02$], children with adenoid hypertrophy (AH) [AH: $Me = 8.1$ (6.4;9.5) vs. no AH: $Me = 7.1$ (5.6;8.6); $p = 0.03$], children with lung abnormalities [CXR+: $Me = 9.5$ (8.1;10.9) vs. CXR−: $Me = 6.8$ (5.6;8.5); $p = 0.04$], children with allergy

Parameter	Number of patients	% of patients
Sex (girls/boys)	68/62	52/48
Onset of symptoms associated with the beginning of nursery/preschool/school attendance	74	56.92
Exposure to animal fur	64	49.23
Family history of allergy	60	46.15
Poor housing conditions – mould exposure	41	31.54
Tobacco smoke exposure	37	28.46
No information on tobacco smoke exposure	35	26.92
Prematurity	16	12.31
Short breastfeeding period (up to 1 month of age)	39	30.00
Caesarean birth	36	27.69
Positive perinatal history (respiratory distress syndrome, congenital pneumonia, mechanical ventilation)	10	7.69
No risk factors mentioned above	6	4.62
More than one risk factor	108	83.07

Tab. 1. Characteristics of the study group based on questionnaire data

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[SPT/sIgE+: *Me* = 8.3 (6.1;10.3) vs. SPT/sIgE–: *Me* = 6.6 (5.8;8.5); $p = 0.02$]. The percentage of eosinophils was higher in children with allergy confirmed with SPT/sIgE tests [SPT+: *Me* = 3.0 (2.0;6.0) vs. SPT–: *Me* = 2.0 (1.0;3.0); $p = 0.02$]. IgE concentration and eosinophil percentage were higher in children with asthma/allergic rhinitis (AR) than in children without these diseases [IgE in children with allergy: *Me* = 112.2 (34.1;415.5) vs. IgE in children with no allergy: *Me* = 31.9 (10.8;67.4); $p = 0.000033$; eosinophil percentage in children with allergy: *Me* = 3.0 (2.0;5.5) vs. eosinophil percentage in children with no allergy: *Me* = 2.0 (1.0;3.0); $p = 0.008$]. IgG, IgA, IgM and IgE levels did not differ between the groups (the whole SG vs. the whole CG). However, children in whom immunodeficiency was found ($n = 12$) were younger [immunodeficiency: *Me* = 4.5 years (3.5;6.0) vs. no immunodeficiency: *Me* = 6.0 years (4.0;11.0)] and had lower levels of immunoglobulins (expressed as g/L): IgG [immunodeficiency: *Me* = 6.8 (5.3;7.8) vs. no immunodeficiency: *Me* = 9.1 (8.0;10.9); $p < 0.001$], IgA [immunodeficiency: *Me* = 0.42 (0.17;0.8) vs. no immunodeficiency: *Me* = 1.2 (0.78;1.6); $p < 0.001$], IgM [immunodeficiency: *Me* = 0.69 (0.55;0.99) vs. no immunodeficiency: *Me* = 0.97 (0.74;1.3); $p = 0.048$].

In all children with recurrent respiratory tract infections, a statistically significant higher median serum vitamin D concentration was observed in comparison with the control group ($p = 0.044$). When the division into age subgroups was taken into account, no statistically significant differences were found between the groups. Vitamin D deficit (0–20 ng/mL) was found in 40 children from the SG (30.8%) and in 32 subjects from the CG (37.3%); suboptimal concentration (20–30 ng/mL) was observed in 46 children from the SG (35.4%) and in 37 subjects from the CG (43%). The optimal vitamin D concentration (30–50 ng/mL) was found in 43 children from the SG (33.1%) and 15 from the CG (17.4%). There was 1 child from the SG (0.8%) and 2 from the CG (2.3%) with a high vitamin D concentration. The highest percentage of children with vitamin D deficiency or a suboptimal vitamin D level was found among 14–17-year-olds both in the SG and CG (SG: $n = 19$; 79.17%, CG: $n = 19$; 95%). Among subjects aged 3–5 years, there was the largest percentage of children with optimal vitamin D concentration (SG: $n = 26$, 43.3%, CG: $n = 9$, 27%). No differences were observed in vitamin D concentration between children with adenoid hypertrophy, asthma and allergy and children without these diseases. Regression analysis revealed a negative correlation between vitamin D concentration and age (R: –0.3; $p = 0.0003$), IgG and IgA levels (R: –0.2; $p = 0.01$, R: –0.3; $p = 0.004$, respectively) and the presence of at least 2 risk factors for recurrent infections (R: –0.26; $p = 0.002$). In 8 children, chest radiography revealed peribronchial abnormalities (4 children with asthma, 4 with adenoid hypertrophy). In 21 children, the result of an oesophageal pH test was abnormal and 42 children had a positive SPT and/or sIgE result.

Parameter	SG ($n = 130$)	CG ($n = 86$)	*p*
Sex (girls/boys)	$n = 44/42$, 51%/49%	$n = 68/62$, 52%/48%	
Age [years]	6.0 [4.0;10.0]	6.0 [5.0;13.0]	0.16
Leukocytes [10^3/µL]	7.5 [5.9;9.1]	6.4 [5.3;7.7]	0.005
CRP [mg/L]	0.67 [0.3;1.3]	0.86 [0.44;1.54]	0.197
Eosinophils [%]	2.0 [1;4.0]	3.0 [2.0;3.0]	0.9
Eosinophils [µL]	198 [102;286]	166 [104;208]	0.3
IgA [g/L]	1.1 [0.7;1.55]	0.9 [0.67;1.15]	0.1
IgM [g/L]	0.96 [0.72;1.3]	0.9 [0.67;1.15]	0.28
IgG [g/L]	8.94 [7.8;10.8]	9.6 [8.4;10.9]	0.13
IgE [IU/mL]	44.6 [13.7;123.2]	31.78 [18.0;72.1]	0.34
Vitamin D [ng/mL]	25.6 [17;33.3]	22.84 [16.3;28.7]	0.04
Data expressed as the median (*Me*) and the 25th and 75th percentile [Q1;Q3].			
CRP – C-reactive protein; **IgA, IgE, IgG, IgM** – immunoglobulin classes: A, E, G and M.			

Tab. 2. Laboratory findings in the SG and the CG

Clinical diagnosis in children from the study group

The most common clinical diagnosis in patients with recurrent respiratory tract infections was adenoid hypertrophy (44.62% of patients) and the least common one was immunodeficiency (9.23%), which was found in the youngest children (3–6 years). In 48 children (36.92%), asthma and/or AR were diagnosed. In 40 children with asthma (83.3%), symptoms of AR were also present; for this reason, children with asthma and AR were treated as one group.

Gastroesophageal reflux disease (GERD) was diagnosed in 21 children (16.15%), with 12 children having concomitant AH and 4 concomitant asthma. Children with AH were younger [AH: *Me* = 5.0 years (4.0;6.0) vs. no AH: *Me* = 6.0 years (5.0;14.0); $p = 0.00025$], while those with asthma and/or AR were older [*Me* = 6.0 years (5.0;13.0) vs. *Me* = 5.0 years (4.0;9.0); $p = 0.031$]. In 12 patients (9.23%) the cause of recurrent respiratory tract infections remained undetermined (Tab. 3).

DISCUSSION

In this study, it was documented that the aetiology of recurrent respiratory tract infections in children is a complex one. It was confirmed that exposure to harmful environmental agents, adenoid hypertrophy, asthma, gastroesophageal reflux disease and vitamin D deficiency are associated with frequent infection recurrence. In addition, multimorbidity was revealed in 1 in 3 study subjects.

The present study included more than one age group on purpose, i.e. all children aged 3–17 years who were referred for diagnostic investigation. The intention behind it was to be able to determine which age group is associated with diagnostic difficulties to the most extent. The youngest children (aged 3–5 years) were the largest group in the study, which may corroborate the relationship between recurrent infections and respiratory and immune system immaturity.

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Diagnosis	SG (*n* = 130)	% of patients
AH	58	44.62
Asthma and/or allergic rhinitis	48	36.92
Vitamin D deficiency	40	30.77
Gastroesophageal reflux disease	21	16.15
Immunodeficiency	12	9.24
• IgG deficiency	6	4.62
• Quantitative abnormalities in lymphocyte subpopulations	3	2.31
• IgA deficiency	2	1.54
• Mixed immunoglobulin deficiency	1	0.77
Multimorbidity	45	34.62
No cause of symptoms	12	9.23

Tab. 3. Clinical diagnoses established based on clinical symptoms and test results in patients with recurrent respiratory tract infections

Similar to other studies, it was determined that the onset of infections was associated with the beginning of nursery/preschool attendance in more than half of the children[6,7]. Nearly 1 in 3 parents/legal guardians admitted to smoking cigarettes, whereas a certain proportion did not provide any answer to this question at all; thus, it is difficult to assess the actual exposure of the children to tobacco smoke[4]. The majority of epidemiological research shows that passive smoking is a risk factor not only for otitis media, bronchitis and pneumonia, but also for lower respiratory symptoms such as cough and wheezing, which are typical symptoms of asthma[2,14].

There are not many studies into the risk factors for recurrent respiratory tract infections in children, particularly in developed countries. Various risk factors are assessed depending on geographical area and social structure and affluence. Studies usually include relatively small groups of children aged up to 3 years and the repeatability of the results is insufficient[2,4,6,7].

In the majority of patients diagnosed by the present authors (90.8%), the potential causes of recurrent respiratory tract infections were established. The diagnosis of AH was the most prevalent one and it was made for nearly half of the subjects. According to various sources, 34.6–46% of children and adolescents are affected by AH, which leads to posterior choanal obstruction, snoring, sleep apnoea and recurrent infections[15,16]. Recurrent infections associated with AH are due to impaired mucociliary clearance and decreased ciliary beat frequency, which is additionally reduced by tobacco smoke exposure[17,18]. The predisposing factors for adenoid hypertrophy include allergy, tobacco exposure, vitamin D deficiency and GERD, which were also found in children included in the present study[15,19–22]. The association between allergic diseases and recurrent respiratory tract infections is the subject of many publications[23].

In the current study, 48 patients with recurrent respiratory symptoms (36.9%) were diagnosed with asthma and/or AR. Nearly half of the children had a family history of atopy and/or were exposed to fur-bearing animals (46.15% and 49.23%, respectively). It is known that recurrent viral and bacterial infections during infancy and early childhood, which are associated with respiratory tract immaturity and immune system abnormalities, may induce lung lesions and contribute to the development of asthma[24,25]. In turn, a defect of the respiratory epithelium and innate immunity present in asthma (impaired type I and II interferon production, among others) may predispose an individual to recurrent infections[26].

Gastroesophageal reflux disease was diagnosed in 16% of children. It was usually associated with AH, which is consistent with the observation that adenoid hypertrophy and reflux often coexist[19].

It is believed that pepsin from the stomach is responsible for tonsillar and adenoid hypertrophy. It activates lymphocytes and monocytes and increases local expression of proinflammatory cytokines[27].

It is common for asthma and GERD to coexist, which suggests a pathophysiological link between the 2 conditions. Gastroesophageal reflux disease was demonstrated in 32–80% of patients with asthma[28]; however, in the present study, the co-occurrence of asthma and reflux was found in only 4 children. It is proposed that the release of proinflammatory cytokines in GERD and the associated damage to the mucous barrier can make it easier for food and environmental allergens to penetrate the respiratory epithelium and thus predispose an individual to allergic hypersensitivity and to clinical manifestation of atopic diseases as a further consequence. Asthma, in turn, promotes reflux episodes through an increase in pressure gradient between the chest and the abdominal cavity[28].

Despite the fact that laboratory tests were performed in a period with no infections, leukocyte count was higher in children with AH, allergy, abnormal lung imaging findings and in preschool children than in healthy children. IgE concentration and eosinophil percentage were higher in children with allergy, asthma and/or AR.

The study confirms that vitamin D deficiency is a common problem since in the study group as a whole and in all age subgroups, the mean and median serum vitamin D levels were below the concentration that is optimal for the substance to have pleiotropic effects, i.e. 30 ng/mL. In both the study group and the control group, there was a significant percentage of patients with a vitamin D concentration that is lower than optimal (66.2% of patients from the SG and 80.3% of patients from the CG). In the subgroup of 10–13-year-olds, 72.73% of children from the SG and 76.92% of children from the CG had a vitamin D level of <30 ng/mL. The current study shows a lower percentage of children with vitamin D deficiency compared with the results of a Polish multicentre study in which 90% of children aged 9–13 years were deficient in vitamin D during spring[29]. Similar to other studies, vitamin D concentration decreased with age[29,30] and was significantly lower in

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children with at least 2 of the recurrent infection risk factors under consideration. A higher vitamin D concentration in the whole SG without breakdown into age subgroups may thus be due to the youngest children accounting for a higher percentage of children with recurrent respiratory tract infections.

Vitamin D suppresses the proliferation and differentiation of B-cells, activity of effector cells and differentiation of dendritic cells, thus decreasing the synthesis of immunoglobulins (Ig), expression of major histocompatibility complex II (MHC) and synthesis of proinflammatory cytokines [IL-1, IL-6, IL-8, IL-12, tumour necrosis factor alpha (TNF-α) and granulocyte-macrophage colony-stimulating factor (GM-CSF)][10]. Vitamin D also boosts the body's defence mechanisms by increasing chemotaxis, phagocytosis and the synthesis of defensins and cathelicidins[10]. In the current study, there was a negative correlation between vitamin D concentration and IgA and IgG levels, which was corroborated by other studies as well[31].

Vitamin D deficiency in children with respiratory tract infections, particularly upper respiratory tract infections, was observed in the majority of studies on the subject to date[8,9]. The current study did not analyse the impact of season of the year on vitamin D concentration (53.85% of the patients were hospitalised from October to April, while 46.15% from May to September). It did not look into vitamin D supplementation either due to a lack of reliable data. No differences were found in terms of vitamin D concentration in children with allergy/asthma and recurrent respiratory tract infections compared to children with no history of allergy, which may stand in contradiction with the findings of other authors[32]. In 12 patients (9.23%), abnormal Ig or lymphocyte subpopulation levels were found, which confirms that an Ig deficit is observed in a small percentage of children with mild recurrent respiratory tract infections[11,30]. There were 45 patients (34.62%) who were found to have a few comorbid conditions. There are few studies which indicate the coexistence in children of asthma with other diseases, which are not limited to allergic ones[33,34]. Multimorbidity can make diagnosis and the selection of the right treatment difficult. As mentioned before, symptoms such as rhinitis, cough and breathing difficulties are found in inflammatory and non-inflammatory respiratory diseases. Even though all children were referred to the General Paediatric Ward for recurrent infections, the data regarding the symptoms and the therapy administered was obtained from their parents, with no possibility to verify outpatient medical records.

CONCLUSIONS

The current study confirms that children with recurrent respiratory tract infections are a heterogeneous group of patients. In the majority of children, the onset of symptoms is associated with the beginning of nursery/preschool or school attendance. In 1 in 3 children, the presence of a number of diseases is found which make one susceptible to respiratory symptom recurrence. The majority of children are deficient in vitamin D, regardless of their recurrent infection status, with the lowest levels being found in older children.

Conflict of interest

The authors do not report any financial or personal affiliations to persons or organisations that could adversely affect the content of or claim to have rights to this publication.

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