Respiratory Pathology in Children Inhalationally Exposed to Irritating Substances

Nina Zaitseva, Alfiya Aminova [*], Olga Ustinova, Alevtina Akatova

Federal Scientific Center for Medical and Preventive Health Risk Management Technologies

**** Corresponding Author:*** Alfiya Aminova
Address: 82 Monastyrskaya St, Perm, 614045, Russia
Email: aminova@fcrisk.ru

Abstract

Background: The investigation of the features of the course of the respiratory pathology in children who are chronically exposed to fine dust is an issue of current importance due to high prevalence of respiratory diseases and unfavorable environmental conditions.

Aim: To scrutinize clinical features of the clinical course of respiratory diseases in children who are chronically exposed to fine dust (PM_{10}) and irritating chemicals (nitrogen dioxide, ammonia, hydrogen chloride).

Methods: We used a set of clinical laboratory testing and instrumental examination (rhinomanometry, spirography) methods. We examined a total of 180 children (aged 3 to 7 years) with allergic rhinitis (J30.3) and hypertrophy of the palatine and nasopharyngeal tonsils (J35.0 and J35.2) (44.9% of the patients were girls, 55.1% were boys), who were residing in areas with high levels of ambient air pollution by particulate matter (PM_{10}) and chemicals such as nitrogen dioxide, hydrogen chloride and ammonia (a study group). A control group included 100 children with a similar pathology, residing in relatively unpolluted areas. The age and sex distributions were similar in both groups.

Results: We observed a higher prevalence of upper respiratory tract diseases in the area with high levels of air pollution by fine dust and the chemicals having an irritating effect (nitrogen dioxide, hydrogen chloride and ammonia) in comparison with relatively unpolluted areas. We have determined the features of the clinical course of the upper respiratory tract pathologies – a combination of respiratory symptoms with signs of asthenic and neurotic syndrome, the absence of seasonality of exacerbations, resistance to standard treatment methods, clinical signs of hypoxia and intoxication, lymphadenopathy, increased lipid peroxidation, decreased AOA in the blood and reduced superoxide dismutase activity, increased malondialdehyde (MDA) and methaemoglobin levels, mild inflammatory changes on the complete blood count, reduced non-specific resistance, the imbalance of cellular and humoral immunity, a reduction in the total nasal airflow rate according to a rhinomanometry examination, mild restrictive and obstructive signs of impaired respiration function, inflammatory changes in the mucous membranes of the paranasal sinuses such as swelling, exudation and fibrous changes.

Conclusion: The identified features of the clinical course of respiratory diseases indicate a more severe course of respiratory pathologies in the children who are chronically exposed to fine dust and irritating chemicals (nitrogen dioxide, ammonia and hydrogen chloride) and the necessity to use a comprehensive approach when providing treatment and prevention.

Key words: respiratory diseases, irritating substances, fine dust, children, ambient air

Introduction

In 2009, the prevalence of respiratory diseases in Russia in adults and children amounted to 163.2 ‰ and 1308.8 ‰, respectively. Furthermore, the incidence of respiratory pathologies accounted for 58.94% from the total disease incidence in children.[2,3,5,6] The highest frequency of respiratory diseases is observed in areas with unfavorable environmental conditions.[3,5] According to the Federal Environmental Monitoring Information Fund, among the major air pollutants in 2005-2009 (exceeding the average daily MPCs by 5 times or more) were nitrogen dioxide and particulate matter (PM). In 2009, 871,608 and 290,338 individuals in Russia were exposed to high levels (exceeding the average daily MPCs by 5 times or more) of nitrogen dioxide and suspended matter, respectively.[5]

Fine dust (PM_{10}) is known to include particulate matter of 10 microns in diameter and to have an effect on the respiratory system, to cause damage to the lung tissue, to increase the risk of lung cancer and to cause premature death from cardiovascular diseases.[12,15,16,17] PM_{10} particles exacerbate the course of acute respiratory infections and bronchial asthma. The most "vulnerable groups" are children, the elderly and individuals with asthma or bronchitis.[8,9,10,11] In addition, health effects from exposure to fine dust can be aggravated by a combined impact of irritating chemicals, such as nitrogen dioxide, ammonia, hydrogen chloride, on the respiratory system.[4,14] Along with pathological effects on the upper respiratory tract epithelium, these substances have a moderate resorptive effect which accounts for their systemic effects - this must be considered in the treatment and prevention in areas with high levels of ambient air pollution by particulate matter and irritating chemicals.[1,7,13] Nitrogen dioxide (IV), when entering the human body, induces the formation of methemoglobin, increasing the phenomena of hypoxia and hypoxemia. Methemoglobin is converted to hemoglobin in the liver by means of glucuronic acid, the synthesis of which requires methionine. The resorption of ammonia can contribute to the development of transient hyperammonemia, the duration and intensity of which depends on the detoxifying function of the liver.[4,8,9]

Thus, in areas with high levels of ambient air pollution by particulate matter (fine dust) and irritating chemicals, the risk of chronic diseases of the upper respiratory tract is increasing, which indicates the necessity to study the pathogenetic features of the onset of respiratory pathologies to develop diagnostic criteria.[7]

Objective

The objective of the study was to scrutinize clinical features of the course of respiratory diseases in children chronically exposed to fine dust (PM_{10}) and irritating chemicals (nitrogen dioxide, ammonia, hydrogen chloride).

Materials and Methods

We used a set of clinical and laboratory examination methods: clinical laboratory testing (complete blood count - leukocytes, eosinophils, lymphocytes), biochemical testing (AST AOA, MDA, lipid hydroperoxide, nitric oxide, superoxide dismutase, methemoglobin) immune testing (indicators of non-specific immunity - phagocytic activity, cellular immunity - CD3+, CD4+, CD8 +, CD19 +, CD56 +, and humoral immunity - total IgE, IgA, IgG).

Clinical laboratory diagnosis was carried out using an Abakus Junior automatic hematology analyzer (Austria), a Stat Fax-2600 biochemistry analyzer (USA) and a Stat Fax 1904 Plus biochemistry photometer (USA).

Lymphocyte phenotyping was performed using a FACSCalibur flow cytometer (Becton Dickinson, USA) with CellQuest Pro software on a Macintosh computer. Lymphocyte populations and subpopulations were determined using membrane immunofluorescence and labeled monoclonal antibodies to CD-receptors (Becton Dickinson, USA).

Total IgE was tested by ELISA using a ELx808 microplate reader and HEMA assay kits (Russia). IgA and IgG were determined by radial immunodiffusion (Mancini). Phagocytic activity of blood cells (absolute and relative phagocytosis, the percentage of cells having performed phagocytosis, phagocytic index) was examined using formalinized sheep erythrocytes. Interleukin (IL-6, IL-10, IFN-Y) levels were determined by ELISA using the ELx808 microplate reader and Vector-Best assay kits (Russia).

A dynamic assessment of nasal patency in children was carried out by measuring trans-nasal pressure and the rate of airflow per second during respiration using rhinometry with a RhinoStream SRE2000 rhinomanometer (RhinoMetrics).

The respiratory function was examined by forced expiratory spirography using a Schiller SP-10 spirograph. Normal values of the main parameters of nasal airway patency were calculated by the equipment software taking into account patient's age, sex, weight and height. The degree of bronchial patency impairment was assessed by two indicators - forced expiratory volume in 1 second (FEV1) and peak expiratory flow rate (PEF) - by comparing the relative parameters at the flow-volume curve (the percent from the normal values) with the existing gradations to assess airway conductance (MP Anokhin, 2003).

The mathematical processing of the data was performed using special statistical software – Statistica 6.0.

We examined a total of 180 children aged 3 to 7 years with allergic rhinitis (J30.3) and hypertrophy of the palatine and nasopharyngeal tonsils (J35.0 and J35.2) (44.9% are girls, 55.1% are boys), who were residing in areas with high levels of ambient air pollution by particulate matter (PM_{10}) and chemicals such as nitrogen dioxide, hydrogen chloride and ammonia (a study group).

A control group consisted of 100 children with similar pathology, residing in relatively unpolluted areas. The age and sex distributions were similar in both groups.

The laboratory testing and the diagnostic examinations of the children were carried out in accordance with the ethical principles stated by the 2nd revision (1983) of the Declaration of Helsinki. The consent was obtained in accordance with Article 9 of the Declaration of Helsinki (1964) and GCP (Good Clinical Practice) guidelines.

Results and Discussion

The area of residence of the study group children was characterized by the levels of suspended matter and fine dust (PM_{10}) exceeding the maximum concentrations by 5.53 and 4.13 times and average annual concentrations by up to 1.56 and 2.69 times, respectively, the levels of nitrogen dioxide and hydrogen chloride exceeding the maximum concentrations by up to 2.3 and 6.2 times and average daily MPC by 1.78 and 1.27 times, respectively, and the concentrations of ammonia exceeding the maximum concentrations by up to 3.1 times. Epidemiological studies have proven a true cause-and-effect relationship between exposure to suspended matter, PM_{10}, nitrogen dioxide, ammonia and hydrogen chloride and the onset of respiratory diseases (OR=4.27), including allergic rhinitis (OR=4.05) and chronic diseases of tonsils and adenoids (OR=3.72).

The children living in environmentally polluted areas (the study group) more often, in comparison with the control group, complained about frequent colds (more than 5 times per year) (89.0% vs 71.0%, p=0.05), nasal congestion and itching (92.0% vs 77.0%, p=0.05, 39.0% vs 21.0%, p=0.05), bouts of sneezing in the morning (81.05% vs 69.0%, p=0.04), itchy red eyes (58.4% vs 33.1%, p=0.05), lacrimation (42.0% vs 28.0%, p=0.03), tickling throat and choking (38.0% vs 19.0%, p=0.04). Due to the significant nasal breathing problems, the children complained about rapid fatigability (48.0% vs 16.0%, p=0.01), headaches (45.0% vs 21.0%, p=0.02), impaired nocturnal sleep (29.0% vs 12.0%, p=0.05).

According to the anamnesis, more than two thirds of the study group children showed no seasonality of exacerbations, which usually lasted for more than 2 weeks (in 57.0% of the children), and mild manifestations of respiratory symptoms were observed in all year round (62.0%). The ineffectiveness of the standard antiviral therapy in disease exacerbation was observed in 38.0% of the study group children vs 69.0% in the control group (p=0.02). Among the latter ones, the seasonality of exacerbations in the spring and summer was observed in the majority of the patients (89.0%, p=0.03).

An objective examination showed that the children of the study group, in comparison with the control group, demonstrated symptoms of chronic intoxication: pale skin, dark circles around the eyes (37% vs 11%, p=0.04), lymphadenopathy (82% vs 22%, p=0.001).

A rhinoscopy more often detected mucosal swelling (57.0% vs 27.0%, p=0.03), pallor or hyperemia with a slight bluish tint (72.0% vs 61 , 0%, p=0.05), mucosal hypertrophy of the nasal conchae (38.0% vs 17.0%, p=0.04), mucus discharge (44.0% vs 19.0%, p=0.02) in the study group children, compared to the control group. A postnasal rhinoscopy identified adenoids, occupying from one half to two thirds of the nasopharynx in 59.0% of the study group children (vs 36.0% of the control group children, p=0.05).

A throat examination revealed that, compared to the control group, the study group more often showed enlarged porous tonsils (72.0% vs 49.0%, p=0.02), wide lacunae (51.0% vs 22.0%, p=0.03), adhesions between tonsils and the anterior pillars of the fauces (49.0% vs 33.0%, p=0.02), follicular cysts (31.0% vs 19.0%, p=0.05), pus in the lacunae, degree 1 hypertrophy (48% vs 38 %, p =0.09), degree II hypertrophy (14% vs 7%, p=0.05), degree III hypertrophy (10% vs 4%, p=0.05).

A comparative analysis of the clinical and laboratory testing revealed statistically significant differences between the study group and the control group, indicating the features of pathogenic mechanisms of the development of respiratory diseases depending on the industrial pollution of the area of residence.

The analysis of blood biochemical indicators in the study group children showed the activation of lipid peroxidation (LPO) and, as a result, the accumulation of lipid peroxidation products. The levels of lipid hydroperoxide – a primary LPO product – in the serum of the children averaged at 348.3 ± 9.4 μmol/cm^3, which was significantly higher than the physiological levels and the values in the control group by 1.1 to 1.2 times, respectively ($p \leq 0.005$). The plasma levels of MDA – an ultimate metabolite of lipid peroxidation – reached 3.08 ± 0.12 μmol/cm^3, which was 1.3 times higher than the physiological limit and the control group values (p=0.0001). The percentage of samples with elevated levels of lipid hydroperoxide and MDA was 52% and 56% in the study group, respectively, and 23% and 25% in the control group, respectively. We have identified a true relationship between the probability of an increase in MDA and lipid hydroperoxide levels and an increase in average daily levels of suspended particles in ambient air (R^2=0.23 to 0.45, $23.15 \leq F \leq 172.17$, p=0.000). The study group demonstrated lower levels of nitric oxide in the blood serum (31.36 ± 2.32 μmol/cm^3) in comparison with the physiological levels and the control group values (1.2 and 2.7 times, respectively, p=0.0001). We revealed a significant probability of a decrease in the levels of nitric oxide in the blood serum when the daily average levels of suspended matter in ambient air increased (R^2=0.49, F=196.88, p=0.0001).

An evaluation of antioxidant processes revealed the depletion of the antioxidant system in the study group (in 51% of the children). The average value of the total AOA in the blood plasma in the study group was 35.89 ± 1.05% (p=0.0001), which was 1.2 times less than that in control group. We reveled a significant probability of a decrease in total AOA levels in the blood plasma when the daily average levels of suspended matter in ambient air increased (R^2=0.42, F=158.89,

p=0.0001). We observed a statistically significant decrease in the activity of superoxide dismutase, which is responsible for the inhibition of reactive oxygen species (in 93% of the cases, the average study group value of 30.25 ± 1.31 ng/cm^3), compared to the physiological levels and the control group values (by 1.5 and 2.4 times, respectively, p=0.0001). We identified a true relationship between the elevated average daily levels of PM_{10} particles in ambient air and the probability of a decrease in superoxide dismutase levels in the blood serum (R^2=0.58, F=208.71, p=0.0001).

The mean value of the ASAT activity in 28% of the study group children amounted to 47.84 ± 4.45 U/dm^3, which was 1.2 and 1.3 times higher than the normal levels and the control group values (p=0.0001).

In the children with long-term exposure to nitric oxide, 16.4% of the blood samples were found to contain methemoglobin while in the control group it was not detected.

The study group patients, in comparison with the control group, demonstrated inflammatory changes in the complete blood count which manifested through moderate leukocytosis (7.18 ± 0.18 x 10^9/L, p=0.05), and 55.0% of the study group children showed elevated neutrophil count up to 52.5%. Furthermore, relative lymphopenia (in 45% of the children up to 35.7 ± 3.12%) and an increase in eosinophil count (in 44.5% of the patients up to 8.25 ± 1.91%, p=0.03) led to a significant increase in eosinophil to lymphocyte ratio (97.2% of the study group samples vs 61.4% of the control group samples) suggesting the severity of the immune inflammatory processes. The average value in the study group was 0.11 ± 0.016 U, which was 5.5 times higher than the physiological level (p=0.0001). We revealed a true relationship between the average daily levels of suspended matter in ambient air and an increase in the blood levels of leukocytes (R^2=0.25, F=73.72, p=0.0001), eosinophils (R^2=0.20, F=51.30, p=0.000), and eosinophil to leukocyte ratio (R^2=0,67, F=104.74, p=0.000).

Long-term irritating impact of suspended matter and the chemical compounds on the upper respiratory tract mucosa led to innate immune stress (non-specific immune defense), which manifested through phagocytosis activation, i.e. a statistically significant (p=0.02 to 0.05) increase in phagocytic index (1.43 ± 0.13 U) and the percentage of cells having performed phagocytosis (2.35 ± 0.41 U) compared to the physiological levels (1.1 ± 0.25 U and 1.75 ± 0.15 U) and the control group (1.1 ± 0.06 U and 1.85 ± 0.05 U), and to humoral immune dysfunction, i.e. increased IgA levels up to 1.57 ± 0.24 g/dm^3 in 50% of the children (p=0.02 to 0.04), a reduced IgG (8.69 ± 0.23 g/dm^3, p=0.05 to 0.01) and IgM levels (1.19 ± 0.08 g/dm^3, p=0.03 to 0.01) compared to the normal levels (1.24 ± 0.11 g/dm^3, 10.85 ± 0.84 and 1.51 ± 0.11 g/dm^3) and the control group value (1.34 ± 0.14 g/dm^3, 10.22 ± 0.25 g/dm^3, 1.24 ± 0.03 g/dm^3).

We observed pronounced changes in the cellular immunity in the study group children in comparison with the physiological levels and the control group values, i.e. a statistically significant increase in the absolute CD3 (2.2 ± 0.12 x10^9/L vs 1.62 ± 0.09 x10^9/L and 1.84 ± 0.11 x10^9/L, p=0.02 to 0.05), CD4+ (1.3 ± 0.12 x10^9/L vs 1.0 ± 0.09 x10^9/L and 1.2 ± 0.07 x10^9/L, p=0.01 to 0.07), CD8+ (0.91 ± 0.02 x10^9/L vs 0.67 ± 0.12 x10^9/L and 0.67 ± 0.06 x10^9/L, p=0.05 to 0.09) and CD19+ count (0.46 ± 0.06 x10^9/L vs 0.38 ± 0.03 x10^9/L and 0.36 ± 0.03 x10^9/L, p=0.05 to 0.01), with a decrease in the percentage of CD56+ cells (8.46 ± 1.15% vs 16.0 ±

2.75% and 11.25 ± 1.3%, $p<0.05$). This findings suggest the existence of excessive or chronic antigenic activation in the study group patients, which leads to the restructuring of the receptors of immunocompetent cells, when the expression of CD56+ receptors typical of natural killer cells, which are responsible for antiviral and anti-tumor immunity.

A spirography test detected slight changes in the respiration function such as moderate restrictive (21.8%), and obstructive (29.1%) disorders. The average airflow rate in the secondary bronchi was 89.30 ± 19.97% from the normal sex- and age-related levels and were significantly lower than those in the control group ($p<0.05$).

A radiographic examination of the sinuses in the frontal projection showed more pronounced changes in the study group than in the control group, i.e. total or partial swelling of the mucous membrane of the sinuses (82.0% vs 62.0%, $p=0.03$) and radiographic signs of exudative processes which manifested through subtotal or total opacity (38.0% vs 19.0%, $p=0.02$), bands of the fibrous tissue, indicating a lingering inflammatory process (52.0% vs 21.0%, $p = 0.02$).

According to the rhinomanometry, almost all the study group children aged 3-7 years had disorders of nasal airway patency or intra-nasal pressure lower than the age-related normal value. In the control group, such changes were observed 1.5 times less often (69%). The evaluation of the function of the upper respiratory tract using rhinomanometry revealed significant differences between the indicators of the total nasal airflow – 221.35 ± 42.56 cm^3/sec in the study group vs 255.65 ± 53.84 cm^3/sec in the control group, $p<0.05$.

Conclusions

1. In areas with high levels of ambient air pollution by fine dust and irritating chemicals (nitrogen dioxide, hydrogen chloride and ammonia), the prevalence of the upper respiratory tract diseases is higher than that in relatively unpolluted areas. A cause-and-effect relationship between the levels of ambient air pollution by these pollutants and the onset of respiratory diseases (OR=4.27), including allergic rhinitis (OR=4.05) and chronic diseases of tonsils and adenoids (OR=3.72) has been proven to exist.

2. We have determined the features of the clinical course of the upper respiratory tract pathologies. These features include a combination of respiratory symptoms with signs of asthenic and neurotic syndrome, the absence of seasonality of the exacerbations, resistance to standard treatment methods, clinical signs of hypoxia and intoxication, lymphadenopathy.

3. We have revealed characteristic changes in clinical laboratory parameters - increased lipid peroxidation, decreased AOA in the blood and superoxide dismutase activity, increased MDA and methaemoglobin levels, mild inflammatory changes on the complete blood count with no clinical signs of disease exacerbation, reduced non-specific resistance, the imbalance of cellular and humoral immunity, suggesting a long-term antigenic stimulation, restructuring of the receptors of immunocompetent cells, the inhibition of the receptor CD56+ expression, which reduces the antiviral and anti-tumor immunity.

4. We have identified the features of changes in the parameters of instrumental and functional examination methods – a reduction in the total nasal airflow rate in the absence of disease exacerbation, the presence of mild restrictive and obstructive signs of impaired respiration function with no clinical signs of respiratory failure, the presence of inflammatory changes in the mucous membranes of the paranasal sinuses such as swelling, exudation, fibrous changes.

5. The determined features of the clinical course of respiratory diseases indicate a more severe course of respiratory pathologies and the necessity to use a comprehensive approach when providing treatment and prevention.

Conflict of Interest: None declared.

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