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RESEARCH ARTICLE

Treatment for Patients with Primary Immunodeficiency Diseases

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Abstract

Primary immunodeficiency diseases occur with a frequency of 1: 10,000 pp. among population. The purpose of this study is to evaluate the most common forms of primary immunodeficiency among patients in Moscow based on the Russian registry for primary immunodeficiency, as well as to analyse the treatment tactics of three patients. The studies were conducted in 2016-2018 among 73 patients aged 5-12 from Russian Children's Clinical Hospital (RCCH), all diagnosed with primary immunodeficiency. The classification of patients was carried out according to the Russian registry by type of primary immunodeficiency. Lethal cases, gender and age distribution were considered. The treatment tactics of three patients were analysed. The number of boys exceeds the number of girls by 7.2 times ($p \leq 0.001$) for defects in antibody production, by 6.0 times ($p \leq 0.001$) for combined immunodeficiency, by 1.4 times ($p \leq 0.05$) for phagocytic defects, and by 2.5 times ($p \leq 0.01$) for other types of immunodeficiency. The patients with defects in antibody production predominated, namely by 1.5 times - patients with combined immunodeficiency ($p \leq 0.05$), by 2.8 times - patients with phagocyte defects ($p \leq 0.01$), by 4.7 times - patients with other types of immunodeficiency ($p \leq 0.001$). 73 patient patients under the age of 12 years with primary immunodeficiency had their anamnesis analysed that helped to identify 4 main forms. Boys prevailed in gender composition (80.8%), and there were no significant differences between boys and girls in age. The lethality prevailed among patients with combined type immunodeficiency. Thus, there were 1.3 times less lethal cases among patients with phagocyte defects comparing to the combined type ($p \leq 0.05$), but 2.4 times more compering to the other types of immunodeficiency ($p \leq 0.01$).

Keywords: *Primary immunodeficiency diseases, Patient registry, Combined immunodeficiency, Defects in antibody production.*

Introduction

Despite growing production and consumption of pharmaceutical products, the primary immunodeficiency states remain an unresolved and very complex problem of modern medicine [1]. There are two leading methods of immunodeficiency treatment - gene therapy and stem cell transplantation. Other types of treatment are not so effective and can only correct deterioration of the immune system based on the drugs that patient can take and the type of primary immunodeficiency [2]. Nevertheless, the most important is time when the diagnosis was made along with the manifested symptoms and the therapy corresponding to it. The immune system is influenced by environmental, and it displays the internal processes that occur in the body. Accordingly, the immune system disorders are usually divided into two categories - primary and secondary [3]. Secondary disorders, generally, reflect strong external effects as high doses of ionizing radiation, or the elimination of protein associated with kidney disease, or the infections like HIV. The immunodeficiency commonly is of a long-term and pathological nature. Primary disorders are rather difficult to diagnose and are less common than secondary ones [4]. Moreover, in some cases, patients with primary immunodeficiency may simply not see out the diagnosis. However, therapy for primary and secondary immunodeficiency is similar, as it is usually associated with infections [5].

Since the immune recognition is affected, patients may experience a high frequency of autoimmune diseases, and significant increase of the tumour formation or severe allergies. The inflammatory processes are activated, as well as lymphoproliferative disorders. Primary immunodeficiency is usually caused by a genetic factor; their development is associated with defects in immune cells, in particular phagocytes and complement elements [6].

Through, there is a violation of the cellular immune mechanisms. Generally, primary immunodeficiency appear in early childhood, i.e., at the age of 1-3 years, caused by an increased tendency to infectious diseases. Modern medicine describes more than a hundred varieties of primary immunodeficiency diseases. Their frequency is 1 to 10 thousand among the population [2].

Patients with immunodeficiency become more susceptible to infections. For instance, pyogenic infections, when more pus is produced, are caused by bacteria such as Haemophilus influenza, Streptococcus pneumonia, Staphylococcus aureus [7]. A severe infection is observed in case of T cell deficiency that may lead to death without proper treatment. The causative agents of these infections commonly found widely in the environment. Normally, people quickly develop immunity to these microorganisms and viruses, including chickenpox, as well as various yeast fungi.

The widespread infections that are not dangerous for health are called opportunistic infections [8]. The modern classification of primary immunodeficiency is associated with the mechanisms of their development. It is customary to distinguish the following 5 groups of primary immunodeficiency: a) associated with functional damage of humoral immunity; b) a complex immunodeficiency, when both humoral and cellular immunity are defected; c) defect or dysfunction of phagocytes; d) defect or dysfunction of complement elements; e) other types of primary immunodeficiency [9].

Thus, for proper therapy, it is necessary to establish which part was defected, depending on the type of affected immunity. A genetic factor may also have a specific influence, namely having relatives with immunity disorders [10].

Particularly, frequent cases of URTI among children may not be sufficient for diagnosing primary immunodeficiency, while for adults, frequent URTI, especially with persistent pneumonia, sepsis and meningitis increases the probability of the diagnosis. However, the primary immunodeficiency generally occurs in childhood [11]. Therefore, it is very important to diagnose primary immunodeficiency in children, so that it is possible to choose a correct and time-saving treatment tactic.

Thus, a number of primary immunodeficiency types can occur in adolescence, and even in people aged 20. Firstly, this is due, to the course of the disease hidden by diagnostic signs [12]. An unambiguous diagnosis of primary immunodeficiency can be established by examination in special immunological laboratories. Meanwhile, some types of immunodeficiency may be detected using simple tests. Thus, immunodeficiency associated with damage to cellular immunity can be detected with persistent lymphopenia observed since childhood [13].

The views on the frequency of primary immunodeficiency among the population have changed over the past three decades. Today, 1 out of 10,000 people is diagnosed with this disease [14]. Thus, primary immunodeficiency is a fairly common disease that requires monitoring of its frequency. The study attempts to analyse the frequency of primary immunodeficiency among the population of Moscow (Russian Federation), as well as the results of the used therapy on the example of three clinical cases.

The purpose of this study is to establish the most common forms of primary immunodeficiency among the sample of patients included in the Russian registry, as well as to analyse the treatment tactics of three patients. Registry data from around the world can be combined and compared according to the frequency of different types of primary immunodeficiency, as well as the treatment strategy and its effectiveness.

Material and Methods

Material

The data of clinical case has been entering to the registry of RCCH (Moscow, Russian Federation) since 1996. Moreover, the data come from various regions of Russia, including Moscow.

Therefore, it is possible to compare data on the frequency of various types of primary immunodeficiency generally in Russia, as well as in its individual parts. The registry contains information on 73 children who suffer from 16 forms of primary immunodeficiency of four types.

These children were admitted for treatment at the RCCH in 2016-2018. An agreement was signed with the parents of three patients, who underwent therapy at the RCCH, on observance of the anonymity of anamnesis information, as well as on observance of moral and ethical standards. The study included only childhood (4-12 years old, average age 8.1 ± 1.1 years), with a confirmed diagnosis of primary immunodeficiency. The study did not include patients with a diagnosis of primary immunodeficiency older than 12 years, or with diagnoses of other diseases (secondary immunodeficiency) of the immune system.

Research Methods

The registry data was processed, with the patients divided into groups according to the type of primary immunodeficiency. Thereafter, the number of patients was put in percentages and correlated with data on similar types of primary immunity. The gender and age ratio of patients was also considered. The classification of patients by type of primary immunodeficiency was carried out according to that in the Russian registry. Lethal cases and the cause of death were considered as well.

The number of patients who successfully underwent treatment and socially adapted was revealed. An analysis of the anamnesis and the therapy used were performed for three patients. We analysed the drugs, their dosage, frequency of use, as well as effectiveness during therapy. Past v. 3.0 was used for statistical analysis. The significant difference was observed at $p \leq 0.05$, with the help of two-sample t-test for independent samples.

Results

The distribution of patients by age, gender and mortality is presented in Table. 1.

Table 1: Age, gender mortality rates among patients with various forms of primary immunodeficiency observed during 2016-2018, in Moscow

Diagnosis	Number of patients	Gender, average age		Mortality, number of patients
		Male, number of patients, age	Female, number of parents, age	
Defects in antibody production	33 (45 %)	29 (88 %), 10.0 ± 0.5	4 (12 %), 8.0 ± 1.0	0 (0 %)
Combined immunodeficiency	21 (29 %)	18 (86 %), 6.0 ± 3.0	3 (14 %), 6.5 ± 2.5	7 (34 %)
Phagocytic defects	12 (16 %)	7 (58 %), 9.3 ± 0.7	5 (42 %), 8.5 ± 0.5	3 (25 %)
Other types of immunodeficiency	7 (10 %)	5 (71 %), 5.0 ± 2.0	2 (29 %), 6.5 ± 3.5	1 (14 %)

Among the patients, male children predominate. The number of boys exceeds the number of girls by 7.2 times ($p \leq 0.001$) for defects in antibody production, by 6.0 times ($p \leq 0.001$) for combined immunodeficiency, by 1.4 times ($p \leq 0.05$) for phagocytic defects, and by 2.5 times ($p \leq 0.01$) for other types of immunodeficiency. Thus, the number of boys predominates for all types of immunodeficiency. There were no significant differences between boys and girls in age within each type; however, it was noted between different types of immunodeficiency. Thus, children with defects in antibody production were usually 1.5 to 2.0 times older than children with other types of immunodeficiency ($p \leq 0.05$). However, these differences may be associated with a later diagnosis made to children upon admission to the clinic. The patients with defects in antibody production predominated, namely by 1.5 times - patients with combined immunodeficiency ($p \leq 0.05$), by 2.8 times - patients with phagocyte defects ($p \leq 0.01$), by 4.7 times - patients with other types of immunodeficiency ($p \leq 0.001$). Finally, the most significant (and most disappointing) of the parameters considered is mortality. According to Table 1, there were no cases of mortality in the group of patients with defects in antibody production (the largest in amount). Meanwhile, the second largest group of patients with combined immunodeficiency is the leading one for

mortality rates and patients on record. The mortality is 1.3 times less ($p \leq 0.05$) in the group of patients with phagocyte defects, and 2.4 times ($p \leq 0.01$) in the group of patients with other types of immunodeficiency compering to the group with combined immunodeficiency. Thus, combined immunodeficiency may be the most dangerous among the four types considered. The frequency of primary immunodeficiency in Moscow and generally in Russia showed similar trends (Table 2).

Table 2: The frequency of primary immunodeficiency in Moscow and generally in Russia for 2018

The form of primary immunodeficiency	In Moscow, patients (%)	In Russia, patients (%)*
Defects in antibody production	45	50
Combined immunodeficiency	29	27
Phagocytic defects	16	13
Other types of immunodeficiency	10	10

* - data from the Russian registry

According to the Table 2, there were found no significant differences between Moscow and Russia. All 4 forms of primary immunodeficiency are recorded with approximately the same frequency

Treatment for Three Patients with Primary Immunodeficiency

Case I. Patient F., 11 years old, initially had diagnosis of acute glomerulonephritis, with features of nephrotic syndrome. The disease occurred at the age of 8, since then patient F. has constantly had coughing attacks, chronic bronchitis and sinusitis, and also herpes infection with time. A subsequent examination by a pulmonologist revealed a chronic deforming bronchitis with bronchiectasis.

An immunological study, performed at the Department of Clinical Immunology of the RCCH, showed the presence of common variable immunodeficiency, which is under defect in antibody production. The second patient, L., 9 years old, has been suffering from chronic pneumonia, infections of the nasal cavity and ear since early childhood (4 years).

Subsequently, it led to pneumonia, complicated by bronchial obstruction with bronchiectasis. The 2nd patient was also diagnosed with common variable immunodeficiency. Both patients had complications of the ENT-organs that led to bronchiectasis, as well as the presence of chronic bronchitis, sinusitis over time. That happened due to inadequate therapy caused by the initially incorrect diagnosis. The common variable immunodeficiency is characterized by a decrease of IgA, IgC, IgM immunoglobulins in blood plasma up to less than 3 g per 1 litter.

Both patients are currently alive, aged 16 and 14, respectively. They both go to school, and are socially adapted. They have to visit the clinic monthly to get immunoglobulin replacement therapy (i.e., IVIG) at a dosage of 0.4 g per 1 kg of body weight, as well as antibiotic therapy for prevention. The antibiotic BISEPTOL is prescribed considering age-related characteristics. Both parents had no exacerbation of bacterial infections for the last three years. The third patient, K., diagnosed with agammaglobulinemia, has been monitored since earlier age, from 3 years. The disease is characterized by a decrease in IgG globulins less than 2 g per 1 litter, as well as the complete absence of IgA, IgM globulins.

The course of this disease is characterized by infections not only of ENT-organs, but also of gastrointestinal tract, and skin. Patients are especially susceptible to viral infections, in particular enteroviruses, which can cause severe meningocephalitis. Agammaglobulinemia therapy includes a combination of IVIG and immunotherapy. Immediately after diagnosis, IVIG therapy begins, every 21-28 days, throughout the patient's life. IVIG therapy is intensified to 1.0-1.5 g per 1 kg of body weight, in the case of infectious exacerbations. Then, during the period of remission, the dosage is reduced to 0.4-0.5 g per 1 kg of body weight.

The main goal of such therapy is to achieve sufficiently high (500 mg per 1 dl (decilitre or 1-10 part of one litter) concentrations of immunoglobulins, as it eliminates severe bacterial infections. The administration set of 20 DPM is the most effective during remission. The patient K. was diagnosed with agammaglobulinemia, in the form of rheumatoid arthritis, at the age of 2 years. Subsequently, bronchitis, otitis media and meningoencephalitis occurred along with arthritis, which led to a coma for 7 days.

The treatment helped to save the child's life. Today, patient K., aged 9, is in need of constant care, since he has contractures of almost all joints, disorientation due to hearing loss of both ears, which led to a sharp decrease in social adaptation. Thus, the primary immunodeficiency diseases are characterized by high mortality or disability subject to continuous treatment. However, the favourable treatment outcome can be achieved with the timely diagnosis, often in early/during childhood.

Discussion

The greater amount of boys over girls is due to the tendency of the X-linked forms inherited with primary immunodeficiency [15, 17]. These include a number of primary immunodeficiency forms such as agammaglobulinemia, chronic granulomatous disease (CGD), Wiskott-Aldrich syndrome (WAS), combined immunodeficiency, and lymphoproliferative disorders [18, 20].

According to the study and a number of other works [21, 23], modern medicine provides a number of effective therapies that can significantly improve the patients' condition, and even return them to a full social life, despite the high mortality of some forms of primary immunodeficiency. Due to modern means of communication, it became possible to quickly exchange DNA material and consult of leading experts. The importance of timely diagnosis of primary immunodeficiency is also worth noting, since many patients die from concomitant oncological, septic, autoimmune or neurological diseases mostly due to late diagnosis. Is possible to establish the form of primary immunodeficiency with the help of 1) monitoring maintains, 2) by following the methodological recommendations and 3) immunological support at the level of republican and regional centres of Russia. For instance, further patients with a particularly severe diagnosis can be transferred to specialized centres for undergoing transplant surgery. Thus, such centres promote the possibility of adequate and conservative therapy at the place of patient residence.

Conclusion

73 patient patients under the age of 12 years with primary immunodeficiency had their anamnesis analysed that helped to identify 4 main forms. Boys prevailed in gender composition (80.8%), and there were no significant differences between boys and girls in age.

The patients with defects in antibody production predominated, namely by 1.5 times - patients with combined immunodeficiency ($p \leq 0.05$), by 2.8 times - patients with phagocyte defects ($p \leq 0.01$), by 4.7 times - patients with other types of immunodeficiency ($p \leq 0.001$). The lethality prevailed among patients with combined type immunodeficiency. Thus, there were 1.3 times less lethal cases among patients with phagocyte defects comparing to the combined type ($p \leq 0.05$), but 2.4 times more compering to the other types of immunodeficiency ($p \leq 0.01$).

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