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ORIGINAL PAPER

Evaluation of warning signs of primary immunodeficiencies

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ABSTRACT

Introduction: Primary immunodeficiencies (PID) are a group of more than 350 rare diseases, which are characterised by a variety of clinical symptoms and are difficult to diagnose. Early diagnosis is very important for improvement of quality of life of the children with PID. The aim of the study was to evaluate the warning signs of PID, taking into account the regional features of PID prevalence to improve early verification of these disorders.
Material and methods: Overall, 107 children aged between two months and 18 years with warning signs of PID, developed by the Jeffrey Modell Foundation Medical Advisory Board, as well as with other warning signs of PID, developed by the Ukrainian Association of Pediatric Immunology, were enrolled in the study. The patients were referred to immunologists by primary care physicians or hospital specialists during the implementation of physician education and a public awareness program of early diagnosis and management of PID.
Results: Among 107 children with warning signs, PID was diagnosed in 19 (17.8%) patients. Chronic diarrhoea with malabsorption was present more frequently in the patients with definable PID ($p = 0.0048$). Dysmorphic features and/or microcephaly were also more common in the patients with PID ($p = 0.0456$). More significant differences were found when microcephaly was combined with dysmorphic features ($p = 0.0004$). Congenital heart disease occurred only in the patients with PID ($p = 0.0437$), in particular with DiGeorge (22q11.2 deletion) syndrome.
Conclusions: For early detection of PID, it is necessary to take into account regional features of the prevalence of certain PID. Our study has established that such warning signs as chronic diarrhoea with malabsorption, dysmorphic features and microcephaly, and congenital heart disease with/or without seizures with underlying hypocalcaemia were important for PID diagnosis in the studied region.

KEY WORDS:
early diagnosis, primary immunodeficiencies, warning signs.

INTRODUCTION

Primary immunodeficiencies (PID) are a group of more than 350 rare diseases, which are characterised by a variety of clinical symptoms and are difficult to diagnose [1]. The delay from initial symptoms to PID diagnosis is more than four years [2, 3]. There are differences between the PID types (i.e. severe combined immunodeficiency – SCID, antibody deficiency, complement deficiency, etc.) [2, 3]. The study reported that in cases of SCID the delay was one month; therefore, in the patients with complement deficiency the average delay was longer – 56 months [3].

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Early diagnosis is very important because timely treatment increases patients' life expectancy and improves the quality of life of children with PID significantly [4]. Newborn screening for PID using T-cell receptor excision circle (TREC) and kappa recombining excision circles (KREC) analysis is implemented in many countries worldwide [5]. It allows early detection of infants with SCID manifested by T-cell and B-cell lymphopaenia, and use of effective treatment that can prevent serious sequelae.

Due to the rapid development of genetic research, the number of newly discovered PIDs is increasing every year [6, 7]. However, primary care physicians and hospital specialists often are unaware of the variability of clinical signs of PID [8].

The Jeffrey Model Foundation (JMF) Medical Advisory Board developed warning signs of PID based on expert opinion [3, 9]. These signs are still relevant today, although they are associated mainly with the clinical signs of the infectious syndrome, which is the most significant in the clinic manifestation of PID. Although, besides the infectious syndrome, PID is characterised by autoimmune, autoinflammatory, allergic, and neoplasm manifestations [10, 11]. Immunologists in many countries have developed other features that need consideration for early PID diagnostics. They often take into account the ethnic and regional features of PID prevalence.

The Ukrainian Association of Pediatric Immunology has also established signs, the revealing of which needs in-depth immunological testing or referral to an immunologist.

The aim of our study was to evaluate the warning signs of PID, developed by JMF Medical Advisory Board, as well as other warning signs of PID, developed by the Ukrainian Association of Pediatric Immunology, taking into account the regional features of PID prevalence in order to facilitate early detection of these disorders.

MATERIAL AND METHODS

In total, 107 children aged two months – 18 years, with warning signs of PID, developed by the JMF Medical Advisory Board, and with other warning signs of PID, developed by the Ukrainian Association of Pediatric Immunology, were enrolled in the study.

The study was conducted in 2017–2018.

TABLE 1. Main characteristic features of patients with definable and no definable primary immunodeficiencies (PID)

Parameter	Definable PID (*n*, %)	No definable PID (*n*, %)
Male	11 (57.9)	45 (51.1)
Female	8 (42.1)	43 (48.9)
Age (years), mean (range)	6.3 (0.2–16)	6.2 (0.5–18)

The patients were referred to immunologists by primary care physicians (34) or hospital specialists (68) during the implementation of the program of physician education and public awareness of early diagnosis and management of PID. Five patients referred to a specialist after acknowledging public information.

Clinical manifestation, history, and physical examination were studied in all children.

Screening tests for PID were performed for all children: CBC and differential, immunoglobulin levels of IgG, IgM, and IgA. For in-depth study, IgG subclass analysis, lymphocyte surface markers CD3/CD4/CD8/CD19/CD56, neutrophil oxidation burst, complement levels were used. More profound analyses were performed for 72 patients.

Written informed consent was obtained from each participant of the study. The study protocol was carried out following the guidelines of the Declaration of Helsinki 1975, as revised in 2000.

STATISTICAL ANALYSIS

The statistical processing of the results of the studies was carried out using statistical package STATISTICA 10.0 and the spreadsheet application Microsoft Excel 2003. The comparison of frequency indices in the study groups was performed using χ^2 criterion. The differences of the indices were statistically significant at $p < 0.05$.

RESULTS

Among 107 children with warning signs of PID, according to the JMF Medical Advisory Board, as well as with other warning signs of PID, in relation to the Ukrainian Association of Pediatric Immunology, PID was diagnosed in 19 (17.8%) patients.

The baseline characteristics of the patients are listed in Table 1. There was no significant statistical difference between patients with definable PID and no definable PID regarding gender and age. In the patients with definable PID males (57.9%) slightly dominated, but the difference was not significant.

The warning signs that predetermined the patients' referral are presented in Table 2.

Significant differences in warning signs, developed by the JMF Medical Advisory Board, between patients with definable PID and no definable PID were not found. Among other warning signs of PID, developed by the Ukrainian Association of Pediatric Immunology, chronic diarrhoea with malabsorption occurred more frequently in the patients with definable PID ($p = 0.0048$). Dysmorphic features or microcephaly were also more common in the patients with PID ($p = 0.0456$). More significant differences were evident in cases of microcephaly combined with dysmorphic features ($p = 0.0004$). Congenital heart disease was present only in the patients with PID

TABLE 2. Percentage of warning signs in the patients with definable and no definable primary immunodeficiencies (PID)

No.	Signs	Definable PID $n = 19$		No definable PID $n = 88$	
		n	%	*n*	%
Warning signs (according to the JMF Medical Advisory Board)					
1.	Four or more new ear infections within 1 year	1	5.2	4	4.5
2.	Two or more serious sinus infections within 1 year	3	15.8	8	9.1
3.	Two or more pneumonias within 1 year	5	26.3	16	18.2
4.	Failure of an infant to gain weight or grow normally	4	21.1	22	25.0
5.	Recurrent, deep skin or organ abscesses	1	5.2	5	5.7
6.	Persistent thrush in mouth or fungal infection on skin	1	5.2	8	9.1
7.	Need for intravenous antibiotics to clear infections	3	15.8	16	18.2
8.	Two or more months on antibiotics with little effect	1	5.2	5	5.7
9.	Two or more deep-seated infections including septicaemia	1	5.2	4	4.5
10.	A family history of PID	0	–	7	8.0
Other signs					
1.	Bronchiectasis	0	–	0	–
2.	Delayed umbilical cord separation	0	–	0	–
3.	Complicated course of BCG vaccination	0	–	0	–
4.	Chronic diarrhoea (over 1 month) with malabsorption	3	15.8**	1	1.1
5.	Thrombocytopaenia and/or of small their size	1	5.2	2	2.3
6.	Neutropenia	2	10.5	7	8.0
7.	Lymphopenia	3	15.8	6	6.8
8.	Recurrent unexplained high-grade fevers with CBC inflammatory markers	0	0	12	13.6
9.	Recurrent, non-causative, non-inflammatory oedema of the skin or mucous membranes	0	–	0	–
10.	Ataxia	1	5.2	0	–
11.	Telangiectasia	1	5.2	0	–
12.	Microcephaly or dysmorphic features	6	31.6*	9	10.2
	Microcephaly with dysmorphic features	3	15.8***	0	0
	Dysmorphic features	3	15.8	9	10.2
13.	Congenital heart disease with/or without seizures with underlying hypocalcaemia	2	10.5*	0	0
14.	Arthritis in early age	0	–	0	–
15.	Late teeth eruption	2	10.5	4	4.5
16.	Difficulties in the treatment of respiratory tract obstruction	2	10.5	12	13.6
17.	Unusual autoimmunity and/or lymphoproliferative disorders	1	5.2	4	4.5
18.	Partial albinism, abnormal hair structure	0	–	0	–
19.	Gingivitis, aphthous stomatitis	1	5.2	7	8.0
20.	Lymphadenopathy or absence of lymphoid organs	3	15.8	8	9.1
21.	Hyperplasia of the organs	2	10.5	5	5.7
22.	Vasculitis	1	5.2	1	1.1
23.	Infections causes by atypical pathogens or of atypical localisation	1	5.2	3	3.4
24.	Recurrent infections caused by the same pathogens	1	5.2	4	4.5
25.	Family child death due to infections or oncological diseases	2	10.5	11	12.5

Note: significant difference of the values compared to the no definable PID group ($p < 0.05$, ** $p < 0.01$, *** $p < 0.001$)*

TABLE 3. Diagnoses in children with no definable primary immunodeficiencies (PID)

Diagnosis	*n*	%
Recurrent infection		
Recurrent otitis	4	4.5
Recurrent sinusitis	8	9.1
Recurrent tonsillitis	2	2.3
Recurrent pharyngomycosis	1	1.1
Recurrent viral respiratory infections	21	23.8
Recurrent pneumonia	7	7.9
Recurrent urinary tract infection	1	1.1
Recurrent furunculosis	2	2.3
Atypical phlegmon	1	1.1
Recurrent lymphadenitis	2	2.3
Recurrent meningitis	1	1.1
Epstein-Barr virus infection	1	1.1
Recurrent herpes simplex infections	3	3.4
Recurrent aphthous stomatitis	7	7.9
Herpes zoster infection	1	1.1
Cytomegalovirus hepatitis	1	1.1
Allergies		
Atopic dermatitis	8	9.1
Asthma	3	3.4
Allergic rhinitis	2	2.3
Autoimmune diseases		
Juvenile idiopathic arthritis	2	2.3
Immunoglobulin-A vasculitis	1	1.1
Ulcerative colitis	1	1.1
Congenital diseases		
Congenital lung defects	4	4.5
Neurofibromatosis	2	2.3
Neurodegenerative disease	1	1.1
Congenital haemolytic anaemia	1	1.1
Other diseases		
Human immunodeficiency virus infection	1	1.1
Transient neutropaenia	2	2.3
Transient lymphopaenia	2	2.3
Lymphadenopathy	3	3.4
Multiple warts	2	2.3

($p = 0.0437$), in particular in the patients with DiGeorge (22q11.2 deletion) syndrome.

Among those diagnosed with PID, combined immunodeficiency (CID) with associated or syndromic features were found in eight patients (Nijmegen breakage syndrome – three, 22q11.2 deletion syndrome – three, ataxia-telangiectasia – one, cartilage-hair hypoplasia – one); antibody deficiencies were present in seven patients (common variable immunodeficiency – two, selective IgA deficiency – three, IgG subclasses deficiency – two); congenital defects of phagocyte number, function, or both were evidenced in three patients (congenital neutropaenia, unspecified – two, chronic granulomatous disease – one); new unclassified disease was revealed in one patient (FINCA syndrome).

The main diagnosis in the children with no definable PID is presented in Table 3.

Recurrent infection occurred in 63 (71.6%) cases. In the patients with no definable PID viral respiratory infections (23.8%) were the most common. Allergies were evidenced in 13 (14.8%) cases. Of these allergies, atopic dermatitis (9.1%) was the most frequent. Autoimmune diseases were present in four (4.5%) cases of unusual cause of autoimmunity. Congenital disorders were revealed in eight (9.1%) patients.

Among patients with no definable PID, 12 patients were followed-up. They required monitoring of their disorders and continual examinations to finalise the diagnosis.

DISCUSSION

Despite no significant difference in the warning signs of the groups found, according to the JMF Medical Advisory Board, in the patients with definable PID and no definable PID, these signs are crucial in early diagnosis of PID, in particular for diagnostics of antibody deficiencies and combined immunodeficiencies [3, 12]. A retrospective study of 563 children (430 patients with defined PID and 133 patients with undefined PID) was carried out in England to evaluate the effectiveness of the warning signs by the JMF in predicting defined PID [3]. The study points out three warning signs (family history of immunodeficiency disease, intravenous antibiotics, and failure to thrive), which were the most important for PID diagnostics. Some studies outline that 10 warning signs are insufficient for early PID diagnosis because they do not include sporadic infections, autoimmunity, autoinflammation, and malignancy, which can also be signs of PID [13]. The European Society for Immunodeficiencies also developed clinical diagnostic criteria for the most common PID [14].

In our study, we found that other signs of PID are also important for their early diagnosis. In particular, it was established that chronic diarrhoea with malabsorption is also important, as well as dysmorphic features and microcephaly, especially when microcephaly is associated with dysmorphic features, and congenital heart disease with/or without seizures with underlying hypocalcaemia. Another study also established some specific signs, such as lower respiratory tract infections, persistent fungal infections, and lymphopaenia for early diagnosis of PID in neonates and infants [12]. The significant warning signs

of PID evaluated in our study were predetermined by regional features of PID. We revealed Nijmegen breakage syndrome and 22q11.2 deletion syndrome the most often; consequently, microcephaly with dysmorphic features and congenital heart disease were the most common. The population of our region (Western Ukraine) has a high carrier frequency of the 657del5 mutation (1/177) that is the cause of Nijmegen breakage syndrome [15]. 22q11.2 deletion syndrome is also very common in our region [16], first of all due to its better recognition [17]. In our region its higher prevalence can also be associated with the available genetic testing. In populations with high percentages of births from consanguineous parents, combined immunodeficiencies predominate, especially severe combined immunodeficiencies [3, 12].

In the patients with no definable PID, recurrent infections predominated, and viral respiratory infections (23.8%) occurred the most often. Allergies and autoimmune disorders were revealed less often. Another study reported that most patients referring with suspected PID were diagnosed with allergies (47.7%) [17].

Raising physicians' awareness would facilitate PID detection; previous studies have proven that physicians, students, and interns are not sufficiently aware of PID diagnosis and management [8, 18, 19]. The lowest awareness was established on the specific signs of PID, especially those concerning verification and management of Nijmegen breakage syndrome, ataxia-telangiectasia, and DiGeorge syndrome [8, 18].

Therefore, to identify children with suspected PID, it is necessary to take into account the regional prevalence of these diseases.

Antibody deficiencies were detected in 36.8%, which is less than reported in other studies [2, 20]. Severe CID was also not revealed. Our study proved the prevalence of CID with associated or syndromic features (42.1%), which could be the reason for the establishment of the greater diagnostic value of specific features than the general signs of recurrent infectious syndrome. Some studies have also reported a predominance of PID with syndromic features [17].

The limitation of this study was predetermined by the inclusion of one regional centre and a two-year period.

CONCLUSIONS

For early detection of PID, it is necessary to take into account regional features of the prevalence of certain PID. Our study has established that such warning signs as chronic diarrhoea with malabsorption, dysmorphic features and microcephaly, and congenital heart disease with/or without seizures with underlying hypocalcaemia are very important for PID diagnostics in our region.

DISCLOSURE

The authors declare no conflict of interest.

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