Physicians’ awareness concerning primary immunodeficiencies in the Ternopil Region of Ukraine

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ABSTRACT

Introduction: Primary immunodeficiencies (PID) are genetic defects of the immune system that result in chronic, serious, and often life-threatening infections if they are not diagnosed and treated. Worldwide, from 70 to 90% of PID sufferers remain undiagnosed because of poor awareness. Early diagnosis is very important for adequate prevention and management of PID infectious complications and may improve the life quality of patients with PID.

Aim of the study: The aim of this study was to assess the awareness of physicians of different specialties about the signs of primary immunodeficiency in children and adults.

Material and methods: A survey among physicians of different specialties on awareness of PID was conducted. The study involved physicians of the Ternopil region of Ukraine. Of 103 participants 42 were paediatricians, 25 general practitioners/family physicians, eight internists, 13 paediatric surgical specialists, and 15 physicians of paediatric sub-specialties. The survey consisted of a questionnaire containing 25 questions.

Results: Sixty-one (59.2%) physicians gave more than 50% of correct answers. The percentage of correct answers to the questions about warning signs of PID in children was 66.1% among paediatricians and 64% among general practitioners, in adults – 66.7% and 72%, respectively. The lowest knowledge of PID was about the specific signs of PID, more often concerning verification of Nijmegen breakage syndrome, ataxia-telangiectasia, and DiGeorge syndrome.

Conclusions: This study has revealed poor awareness about PID among physicians in the Ternopil region of Ukraine. There was no significant difference in the percentages of correct answers among the first-contact physicians (paediatricians, general practitioners/family physicians) and paediatric sub-specialists. There is a significant need for educational programs to improve physicians’ knowledge on PID. Implementation of the model of combined physician education and public awareness may improve detection of PID in children in the early stages.

KEY WORDS: primary immunodeficiencies, physicians’ awareness, Ukraine medical education.

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INTRODUCTION

Primary immunodeficiencies (PID) are genetic defects of the immune system, which result in chronic, serious, and often life-threatening infections if they are not diagnosed and treated [1]. Previously classified as “rare diseases”, PID are no longer as rare as was previously believed: today, it is estimated that PID affects more than six million people worldwide, with no gender, age, or geographical differences. Recent studies have proven that 1-2% of the population may be affected with PID when all types and varieties are considered [1, 2].

Because PID can present in the form of “common” infections, 70 to 90% of PID sufferers are still undiagnosed because of poor awareness, their healthcare practitioners manage PID-related infections as some other “common infection”. Patients with PID require ready access to antimicrobial and antifungal and prophylactic antibiotics and continuous access to immunoglobulin replacement therapies. Some patients also need haematopoietic stem cell transplantation (HSCT) or even gene therapy (GT), and emergency medicine, according to their needs and following their specialists’ advice [3]. Due to the urgent need to increase awareness of this issue, numerous educational campaigns and activities have been developed all over the world, aimed at physicians and the general public, to improve early diagnosis, appropriate treatment, and management of PID, with a view to reducing morbidity and mortality related to PID [4].

Over the past 10 years, the number of diagnosed PID cases in Ukraine has increased threefold; however, a significant number of cases remain undetected. According to the data of Ukrainian registry of patients with PID, in 2015 the prevalence of PID in Ukraine was 1.23 living patients per 100,000; in the Ternopil region – 1.03 per 100,000 [5]. The majority of PID cases in the Ternopil region (44.4%) were diagnosed in patients older than 2-4 years because prior to this age children were usually examined and treated by a variety of medical specialists [6]. 77.8% of diagnosed PIDs were of characteristic phenotypic features (e.g. Nijmegen breakage syndrome [NBS], Di-George syndrome [DGS], ataxia-telangiectasia syndrome [AT]) [6]. At the same time, PID prevalence in Europe and North America is much higher [2, 7]. Thus, there is insufficient detection of patients with PID in Ukraine, especially in Ternopil region.

Taking this into consideration, the aim of the study was to assess the awareness of physicians of different specialties about the signs of primary immunodeficiency in children and adults.

MATERIAL AND METHODS

We conducted a survey among physicians of different specialties on the awareness of PID. The study involved physicians of Ternopil region, Ukraine, and was conducted between October 1 and December 30, 2016. The questionnaires were offered to 171 doctors; only 103 (60.2%) of them agreed to answer the questions. Of 103 participants, 42 were paediatricians, 25 general practitioners/family (GP/F) physicians, 8 internists, 13 paediatric surgical specialists (7 surgeons and 6 otorhinolaryngologists) and 15 physicians of paediatric sub-specialties (3 endocrinologists, 3 infectious diseases specialists, 3 pulmonologists, and 6 neurologists). Among the participants 67 were physicians of the first contact (primary care physicians – paediatricians, family physicians), and 28 were specialists working at a tertiary care hospital. All physicians-internists worked at a secondary care hospital. The questionnaires were distributed on-site during work hours.

The survey included a questionnaire with 25 questions (Table 1). The questionnaire can be divided into four sections: warning signs in children (four questions) and adults (two questions); general signs of PID (five questions); specific signs of PID (nine questions); and treatment strategies and immunisation of patients with PID (five questions). The questionnaire was drawn up by immunologists. Most questions were of “true” or “false” type. Two questions had two possible answers, and two questions had three. In total, the physicians had to give 31 answers.

Verbal consent was obtained before conducting the questionnaire survey; the participants were informed of the reasons why the information was collected and how it would be used. Prior to handling the questionnaire, a statement was read to participants informing them that their participation was voluntary and assuring them that their answers were anonymous and confidential.

Ethical approval for the study was provided by the scientific Ethics Committee of I. Horbachevsky Ternopil State Medical University. The study conformed to the principles outlined in the WMA Declaration of Helsinki.

The results were analysed using standard procedures with the Statistica StatSoft 6.0 software package. The distribution of variables was assessed by χ² test and the Fisher’s exact test. The significance level of the tests was set at α = 0.05.

RESULTS

The ages of the respondents ranged from 22 to 69 years. Women made up the majority of the surveyed physicians (67%). The list of the questions and percentage of correct answers of all the respondents are presented in Table 1.

Analysis of the data demonstrated that all physicians knew quite well the treatment methods of PIDs with antibody deficiency and contraindications for administration of live vaccines. The doctors gave more than 80% of correct answers to the questions about certain warning signs of PID, in particular about recurrent otitis (82.5%) or infections with atypical localisation or caused by atypical pathogen as signs of PID (82.5%). However, most
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Physicians (80.6%) did not know that common variable immunodeficiency (CVID) is often diagnosed in adults. Insufficient knowledge was demonstrated about the specific features of NBS. Thus, only 29.1% of physicians indicated that children with microcephaly should be directed to genetic testing. Specific signs of NBS, such as dysmorphic facial features and numerous (six or more) “coffee-with-milk” coloured spots were recognised by, respectively, only 29.1% and 36.9% of the physicians. Only 9.7% of physicians indicated that chest X-ray examination is contraindicated for children with NBS.

Poor knowledge was demonstrated about specific features of other PIDs, in particular about ataxia-telangiectasia syndrome (ranging from 18.4% to 49.5% of correct answers) and DGS (ranging from 38.8% to 56.3% of correct answers). The number of correct answers given by the physicians depending on their specialties is presented in Table 2.
Sixty-one (59.2%) physicians had answered more than 50% of the questions correctly. Table 3 presents the breakdown of the number and percentage of physicians who gave more than 50% of correct answers according to their specialty.

There was no significant difference in the percentage of correct answers between physicians of different specialties. There was no significant difference the level of knowledge of the first contact physicians (pediatricians and general practitioners) and doctors who work in the institutions of tertiary level (medical specialists of regional hospitals), 58.1% and 60.1% of the correct answers, respectively.

Sixty-one (59.2%) physicians had answered more than 50% of the questions correctly. Table 3 presents the breakdown of the number and percentage of physicians who gave more than 50% of correct answers according to their medical specialty.

Only 40% of GP/F physicians gave above 50% of correct answers, while among the sub-specialists of both surgical and therapeutic specialties the percentage of such physicians exceeded 66.7%.

Analysis of the answers were conducted in the context of questions and medical specialties. The number of correct answers was analyzed according to the specialty of the surveyed physicians (Table 2).

### Table 2. Number and percentage of correct answers given by the surveyed physicians depending on medical specialty

| Physicians specialty                      | Physicians (n) | Answers (n) | Correct answers |
|-------------------------------------------|----------------|-------------|-----------------|
| Paediatricians                            | 42             | 1302        | 785             | 60.3 |
| General practitioners/family physicians   | 25             | 775         | 422             | 54.5 |
| Internists                                | 8              | 248         | 168             | 67.7 |
| Physicians of surgical specialties         | 13             | 403         | 249             | 61.8 |
| General paediatric surgeons               | 7              | 217         | 133             | 61.3 |
| Paediatric otolaryngologists              | 6              | 186         | 116             | 62.4 |
| Paediatric sub-specialists                | 15             | 465         | 273             | 58.7 |
| Paediatric endocrinologists               | 3              | 93          | 64              | 68.8 |
| Children’s infectious diseases specialist  | 3              | 93          | 57              | 61.3 |
| Paediatric pulmonologists                 | 3              | 93          | 56              | 60.2 |
| Paediatric neurologists                   | 6              | 186         | 96              | 51.6 |

### Table 3. Number and percentage of the surveyed physicians who gave more than 50% of correct answers according to their specialty

| Physician specialty                      | n  | %    |
|-------------------------------------------|----|------|
| Paediatricians                            | 26 | 61.9 |
| General practitioners/family physicians   | 10 | 40   |
| Internists                                | 6  | 75   |
| Physicians of surgical specialties         | 9  | 69.2 |
| Paediatric sub-specialists                | 10 | 66.7 |

### Table 4. Percentages of correct answers to the questions about warning signs in children and adults

| Question                                                                 | Paediatricians | GP/F physicians | Internists | Surgical specialists | Paediatric sub-specialists |
|--------------------------------------------------------------------------|----------------|-----------------|------------|----------------------|----------------------------|
| **Warning signs in children**                                            | n = 42         | n = 25          | n = 8      | n = 13               | n = 15                     |
| 1. Four or more new ear infections within one year may be warning signs of PID | 111            | 66.1            | 64         | 64                   | 27                         | 84.4            | 43  | 82.7 | 37 | 61.7 |
| 2. Failure of a child to gain weight normally may be a sign of PID       | 38             | 90.5            | 17         | 68                   | 7                          | 87.5            | 13  | 100  | 12 | 80  |
| 3. Two or more cases of pneumonia in a year may be the only clinical manifestation of PID | 25             | 59.5            | 13         | 52                   | 6                          | 75              | 12  | 92.3 | 9  | 60  |
| 4. Repeated abscesses of skin and organs (without damage to the tissue integrity caused by trauma) may be a sign of PID | 19             | 45.2            | 15         | 60                   | 6                          | 75              | 6   | 46.2 | 4  | 26.7 |
| **Warning signs in adults**                                              | n = 56         | n = 36          | n = 72     | n = 11               | n = 68                     | n = 6            | n = 10 | n = 38.5 | n = 22 | n = 73.3 |
| 1. Four or more episodes of infection (otitis, bronchitis, pneumonia) in an adult patient may be a sign of PID | 26             | 61.9            | 22         | 88                   | 6                          | 75              | 6   | 46.2 | 8  | 53.3 |
| 2. In adults, two or more cases of pneumonia (radiographically confirmed) within three years may be a sign of PID | 30             | 71.4            | 14         | 56                   | 5                          | 62.5            | 4   | 30.8 | 14 | 93.3 |
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Physicians of the first contact such as paediatricians and general practitioners demonstrated average knowledge of the warning signs of PID in children. The average percentage of correct answers was 65.3%; it ranged from 45.2% to 90.5% among paediatricians and from 52 to 76% among general practitioners. Medical specialists appeared to be slightly more aware of the signs of PID with an average 74.3% of correct answers (ranging from

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**TABLE 5. Percentages of correct answers to the questions about general signs of PID**

| Question                                                                 | Paediatricians | GP/F physicians | Internists | Surgical specialists | Paediatric sub-specialists |
|--------------------------------------------------------------------------|----------------|-----------------|------------|----------------------|---------------------------|
| 1. PID occur only in children                                           | 15 (35.5%)     | 10 (40%)        | 2 (25%)    | 10 (76.9%)           | 3 (20%)                   |
| 2. Common variable immunodeficiency (CVID) is most often diagnosed in children | 7 (16.7%)     | 8 (32%)         | 3 (37.5%)  | 2 (15.4%)            | 0 (0%)                    |
| 3. Oncological diseases can be a sign of PID                             | 25 (59.5%)     | 14 (56%)        | 8 (100%)   | 6 (46.2%)            | 11 (73.3%)                |
| 4. Autoimmune diseases are much more common in patients with PID         | 35 (83.3%)     | 15 (60%)        | 6 (75%)    | 10 (76.9%)           | 14 (93.3%)                |
| 5. Infections with atypical localisation or caused by atypical pathogens may be a sign of PID | 33 (78.6%) | 23 (92%) | 8 (100%) | 12 (92.3%) | 11 (73.3%) |
| Total                                                                   | 115 (54.8%)    | 70 (56%)        | 27 (67.5%) | 40 (61.5%)           | 39 (52%)                  |

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**TABLE 6. Numbers and percentages of correct answers to the questions about specific signs of PID**

| Question                                                                 | Paediatricians | GP/F physicians | Internists | Surgical specialists | Paediatric sub-specialists |
|--------------------------------------------------------------------------|----------------|-----------------|------------|----------------------|---------------------------|
| 1. Telangiectasia may be specific to:                                     |                |                 |            |                      |                           |
| a) hepatic insufficiency,                                                | 28 (67.7%)     | 16 (64%)        | 8 (100%)   | 10 (76.9%)           | 6 (40%)                   |
| b) ataxia-telangiectasia syndrome (Louis-Bar syndrome)                   | 25 (59.5%)     | 8 (32%)         | 3 (37.5%)  | 4 (30.8%)            | 11 (73.3%)                |
| 2. The absence of thymus confirms DiGeorge syndrome                      | 18 (42.9%)     | 13 (52%)        | 6 (75%)    | 11 (84.6%)           | 10 (66.7%)                |
| 3. Numerous (6 or more) “coffee-with-milk” coloured spots are particularly specific to: |                |                 |            |                      |                           |
| a) Nijmegen breakage syndrome (NBS)                                      | 19 (45.2%)     | 5 (20%)         | 6 (75%)    | 6 (46.2%)            | 4 (26.7%)                 |
| b) Louis-Bar syndrome                                                    | 4 (9.5%)       | 7 (28%)         | 2 (25%)    | 4 (30.8%)            | 4 (26.7%)                 |
| c) Bruton’s agammaglobulinemia                                           | 25 (59.5%)     | 17 (68%)        | 6 (75%)    | 11 (84.6%)           | 10 (66.7%)                |
| 4. Dysmorphic facial features are specific to:                           |                |                 |            |                      |                           |
| a) common variable immunodeficiency (CVID)                               | 33 (78.6%)     | 17 (68%)        | 4 (50%)    | 5 (38.5%)            | 2 (13.3%)                 |
| b) DiGeorge syndrome                                                     | 19 (45.2%)     | 10 (40%)        | 6 (75%)    | 5 (38.5%)            | 2 (13.3%)                 |
| c) Nijmegen breakage syndrome                                            | 13 (30.9%)     | 2 (8%)          | 2 (25%)    | 3 (23.1%)            | 12 (80%)                  |
| 5. Inflammation + thrombocytopenia + eczema                               |                |                 |            |                      |                           |
| a) Wiskott-Aldrich syndrome                                              | 36 (85.7%)     | 10 (40%)        | 7 (87.5%)  | 11 (84.6%)           | 9 (60%)                   |
| b) atopic dermatitis                                                     | 36 (85.7%)     | 13 (52%)        | 7 (87.5%)  | 11 (84.6%)           | 9 (60%)                   |
| 6. AFP (α-fetoprotein) appears in high concentrations in A-T syndrome   | 14 (33.3%)     | 17 (68%)        | 7 (87.5%)  | 9 (69.2%)            | 8 (53.3%)                 |
| 7. Normal levels of leukocytes (WBC), haemoglobin, platelets, HCT are sufficient to exclude neutropaenia | 36 (85.7%) | 16 (64%) | 5 (62.5%) | 10 (76.9%) | 14 (93.3%) |
| 8. In cases of NBS chest X-ray examination is allowed                    | 8 (19.1%)      | 0 (0%)          | 0 (0%)     | 1 (7.7%)             | 1 (7.7%)                  |
| 9. Children diagnosed with microcephaly should undergo genetic testing  | 21 (50%)       | 4 (16%)         | 0 (0%)     | 3 (23.1%)            | 5 (33.3%)                 |
| Total                                                                   | 335 (53.2%)    | 155 (41.3%)     | 69 (57.5%) | 106 (54.4%)          | 119 (52.9%)               |
was 40% among general practitioners and significantly lower in general practitioners (41.3% of correct answers).

Regarding the manifestations of Wiskott-Aldrich syndrome, the percentage of correct answers was higher in paediatricians (85.7%). But the most difficult question for physicians was to determine the correct signs and appropriate management of NBS.

The analyses of the answers to the questions about treatment and immunisation of children with PID and with reference to the specialties is presented in Table 7.

The average percentage of correct answers to the questions about vaccination was more than 75% in all groups of physicians.

**DISCUSSION**

Early diagnosis of PID is very important for adequate prevention and management of infectious complications and may improve life quality of children with PID. Unfortunately, a delay in diagnosis is common and causes increased morbidity [7].

According to our research, the percentage of correct answers to the questions about warning signs in children was 66.1% among paediatricians and 64% among GP/F physicians, in adults – 66.7% and 72%, respectively.

Brazilian studies showed that 77% of physicians did not know the 10 warning signs for primary immunodeficiency and only 40.3% had further examined patients who frequently use antibiotics for PID [8, 9]. The indicator for knowledge obtained in this study had a mean of 48.08% ±16.06. These studies also demonstrated that paediatricians had more substantial knowledge of PID than clinicians and surgeons. Similar results were reported in a study in Iran, where the reported mean total score was 55.9% ±14.3 [10]. Total scores significantly differed between physician groups. Paediatric sub-specialties ranked the highest, and their knowledge was significantly higher than that of other participants (p < 0.05). In our study we found no significant difference in awareness on PID between paediatricians, GP/F physicians, and surgeon and paediatric specialists.
Al-Hammadi S. et al. evaluated PID knowledge and experience among paediatricians of the United Arab Emirates [11]. The study showed that the majority of paediatricians recognised the common signs and symptoms of PID. 76% of them answered correctly to 60-79% of the questions, and 4% answered correctly to ≥ 80% of the questions. Although the theoretical knowledge was reasonably good, the data revealed limitations in practical care for children suspected to suffer from PID.

The percentage of correct answers among Turkish physicians ranged from 38.7% to 91.2% [12]. The authors concluded that physicians in Turkey may be in need of more comprehensive pre/postgraduate education in PID.

The results similar to ours were reported in a USA study of paediatricians [13]. More than one third (35%) of them were uncomfortable with the recognition and diagnosis of PID; however, 95% prescribed screening tests or referred patients to specialists to be examined for PID, and 77% followed up at least one patient with PID.

The evaluation of PID knowledge among paediatric residents was conducted in the State of Qatar [14]. Paediatric residents answered correctly to 58.6% of all questions, and 67.5% of the questions about clinical features of PID. The poor knowledge and hesitancy to diagnose and properly manage patients with PID could be due to the lack of immunology training during the residency.

Evaluation of attitudes and practices related to diagnosis and management of PID among family practice physicians and pulmonologists was conducted among the members of the American Medical Association and the American Osteopathic Association [15, 16]. During the survey, information was collected on primary patient care settings, number of PID diagnoses being followed, awareness of PID identification testing and treatment strategies, use of Ig replacement therapy, hygiene-based interventions, and vaccination recommendations. These studies underscore the areas in which improved educational and training initiatives may benefit patient care.

Lewandowicz-Uszynska et al. developed an educational program for doctors and nurses caring for PID patients being treated with subcutaneous immunoglobulins [17]. They provided practical guidelines for identifying the patients in need of referral for examination for possible immunodeficiency, and gave practical instructions on how to start and follow-up a subcutaneous therapy in all immunology centres in Poland for those who are engaged in this kind of treatment.

In 2003 the Jeffrey Modell Foundation (JMF) established a program of medical education and public knowledge: PEPAC – the Physician Education and Public Awareness Campaign [4]. The result of the program was evaluated in 39 countries and there was a significant increase in referrals, diagnoses, and treatments of PID [7].

Subbarayan et al. reported that 95% of children with PID are referred by hospital paediatricians [18]; therefore, it is more important to focus on educating physicians rather than the general public to ensure that children with PID are diagnosed in a timely fashion [19]. Implementation of a physician-focused awareness program in Central and Eastern Europe (J-Project) demonstrated an increase in the number of patients with PID being followed up between 2004 and 2007 from tens to thousands of patients [20].

CONCLUSIONS

This study has revealed a poor awareness of PID of physicians in Ternopil region, Ukraine. The lowest knowledge was demonstrated about the specific signs of PID, in particular verification of Nijmegen breakage syndrome, ataxia-telangiectasia and DiGeorge syndrome. There was no significant difference in the percentages of correct answers between the first-contact physicians (paediatricians, general practitioners/family physicians) and paediatric sub-specialists.

There is a significant need in educational programs to improve physicians’ knowledge about PID. Implementation of the model of combining physician education and public awareness may improve detection of PID in children in the early stages.

DISCLOSURE

The authors declare no conflict of interest.

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