L.P. Sizyakina, I.I. Andreeva
Rostov State Medical University of the Ministry of Health of the Russian Federation

Register of patients as an effective method of diagnosing primary immunodeficiencies

Author affiliation:
Lyudmila Petrovna Sizyakina, PhD, Professor, head of the clinical immunology research institute at the SBEI HPO "Rostov State Medical University" of the RF MH
Address: Rostov-on-Don, Nakhichevanskiy Ln. 29, 344022, **tel.:** +7 (8632) 63-44-41, **e-mail:** msiziakina@mail.ru
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It has been traditionally considered that primary immunodeficiency states (PID) are rare diseases. However, the incidence rate of PID in Europe is significantly higher than in Russia: our statistics on innate immunodeficiency morbidity is far from reality. Experience of establishing a register of PID patients in the Rostov Region proved that the combination of organizational and educational activities contributes to timely diagnostics, rational therapy and life quality improvement in patients with primary immunodeficiencies.
Keywords: *primary immunodeficiency, register of patients.*

A clear tendency to the change of attitude to the problem of primary immunodeficiencies (PID) has recently been observed. These diseases are no longer considered fatal, although the international experience shows that the main condition of a relatively favorable diagnosis is timely diagnostics [1-3]. The reason why the incidence rate of PID is Europe is much higher than the number of registered cases in Russia is the lack of registration of patients [4, 5]. In order to resolve this problem in the Rostov Region, the research institute of clinical immunology RostSMU has used capabilities of the methodology of establishing registers of patients.

The register is a system of accumulation, registration and storage of unified information on patients with a certain disease receiving certain treatment. Establishment of a register in the Rostov Region, i.e. systematic measures aimed at the registration of patients with established genetic immune system's defects and primary detection of such patients, has been in process for 2 years. This is primarily a complex of organizational measures, which started with the preparation of the order of the regional Ministry of Health aimed at managers of all the medical establishments. The order proclaims not only the need in improving PID diagnostics, but also presents the main alarming symptoms of PID (tb. 1, 2) and the algorithm of doctor's actions when clinical confirmation of the clinical diagnosis is required in the patient's information card attached to the document. In order to attract attention to the problem of primary immunodeficiencies and the possibility of feedback from medical establishments, the annual report on medical work of the regional territories includes the clause reflecting description of patients with PID.

It has been clear from the first steps of realization of the project on register establishment that the organizational measures may only be successful if there is active public awareness campaign. It primarily concerns awareness of the issues of primary immunodeficiencies both of the highly specialized doctors and the primary healthcare specialists. We have encountered "total hyperdiagnostics" of primary immunodeficiency states (IDS), based on such conceptions as "PID is an extremely rare disease, pediatricians do not have such patients in outpatient practice" and "primary immunodeficiency in adults is impossible". Doctors often equate PID with AIDS. The role of history taking remains underestimated. Thus, registering patients with the previously established diagnosis "X-linked agammaglobulinemia (XLA), we have for the first time revealed patient with agammaglobulinemia among their relatives on the basis of detailed analysis of the family history data only.

Lack of alertness of the primary healthcare specialists to PID results in untimely diagnostics and, therefore, inadequate therapy. This may be illustrated by the following clinical cases from our practice.

Patient O., 51 years of age; admitted to the therapeutic unit with complaints of fever up to 39^{o}C, chest pains, general weakness, pains along intestines. The patient had been subject to unmotivated fevers since childhood. The patient had been subject to inpatient treatment numerous times with no lasting positive effect. Diagnosis “Chronic pyelonephritis” was established at the age of 31 years; had purulent meningitis at the age of 42 years, exacerbation of chronic enterocolitis – at 45; body weight loss was up to 10 kg within 3 months. Results of laboratory examination at the RostSMU clinic: IgG – traces, IgM – traces, IgA – traces. Thus, diagnosis “common variable immunodeficiency (CVID), agammaglobulinemia” was first established in the patient at the age of 51 years. The patient was prescribed replacement therapy.

Another clinical case (pic. 1) is a convincing proof of the need in regular replacement therapy. Agammaglobulinemia (Bruton type) was revealed in 2 boys of 7 years of age. Patient B. has been receiving therapy including intravenous immunoglobulins on a monthly basis for 15 years; at present he has no complaints and leads an active lifestyle. Relatives of patient D. refused a full-scale replacement therapy. As a result, multiple organ failure formed in the patient after 15 years of pneumonias, purulent encephalitis, sepsis and osteomyelitis.

Therefore, training doctors is an important measure of improving PID diagnostics in the framework of register establishment. It involves not only obligatory introduction of lectures on PID in the curriculum of internship and clinical studies, but also organization of the specialized thematic advanced training cycles on immunodeficiencies for doctors of all clinical specialties. We believe that it is important to enhance training by including information on PID in the program of theoretical-and-practical conferences not only of allergists-immunologists, pediatricians and therapists, but also of ENT-doctors, surgeons, dermatologists, general practitioners, neurologists, hematologists, dentists, and to cooperate with the regional theoretical-and-practical societies of all clinical specialties. Along with information on the main clinical symptoms of immunodeficiencies, it is also important to dwell on the information value of the laboratory methods of immune diagnostics for universal training of doctors. Doctors must be aware that results of the immune-enzyme analysis – a widespread diagnostic method of infectious pathologies – are not informative in case of agammaglobulinemia, while a routine biochemical analysis of protein fractions of blood may serve as the first laboratory test in absence of an immunological laboratory when humoral PID is suspected.

Before the register had been established, there were 11 people registered with primary IDS in the Rostov Region. At present, this list includes 165 patients. Among the patients with the established diagnosis “Primary immunodeficiency”, the dominant diseases are the ones mediated by disturbed antibody production – 95% of all the revealed cases: 43% - selective IgA-insufficiency; up to 30% - transient hypogammaglobulinemia; 11% - X-linked agammaglobulinemia; 16% - common variable immunodeficiency. Dominant symptoms in the patients with agammaglobulinemia are bronchopulmonary and ENT-infections (90% at XLA and 100% at CVID). Purulent infections of soft tissues are observed in both groups of patients with the same frequency: 25% at XLA and 27% at CVID; gastroenterocolitis and allergic diseases are more often observed in the patients with XLA than in the patients with CVID – 38 and 28% of patients, respectively. Moreover, the range of clinical manifestations is wider in the patients with X-linked agammaglobulinemia: unlike in patients with CVID, reactive arthritis is registered in 50% of cases in such patients, meningoencephalitis – in 38%, osteomyelitis and sepsis – in 12%. At the same time, the rate of recurrent herpetic infection (43 and 22%) is higher at CVID; hemocytopenia was revealed in 12% of cases. The first symptoms of the disease in the patients with XLA were registered in the first year of life in 50% of cases, at the age of 2-9 years – in 50%. The average age of diagnosis establishment is 9 years; duration of the period from the first occurrence of clinical symptoms to diagnosis establishment is 4 years. The first occurrence of symptoms in the patients with CVID was observed at the age of 10-20 years (80%); clinical

symptoms manifested themselves at the age of 0-10 and 30-40 years in 10% of cases. Diagnosis "Primary immunodeficiency, common variable immunodeficiency" was established at the age of 35 years on the average, while duration of the period from the first occurrence of clinical symptoms to clinical diagnosis was 19 years.

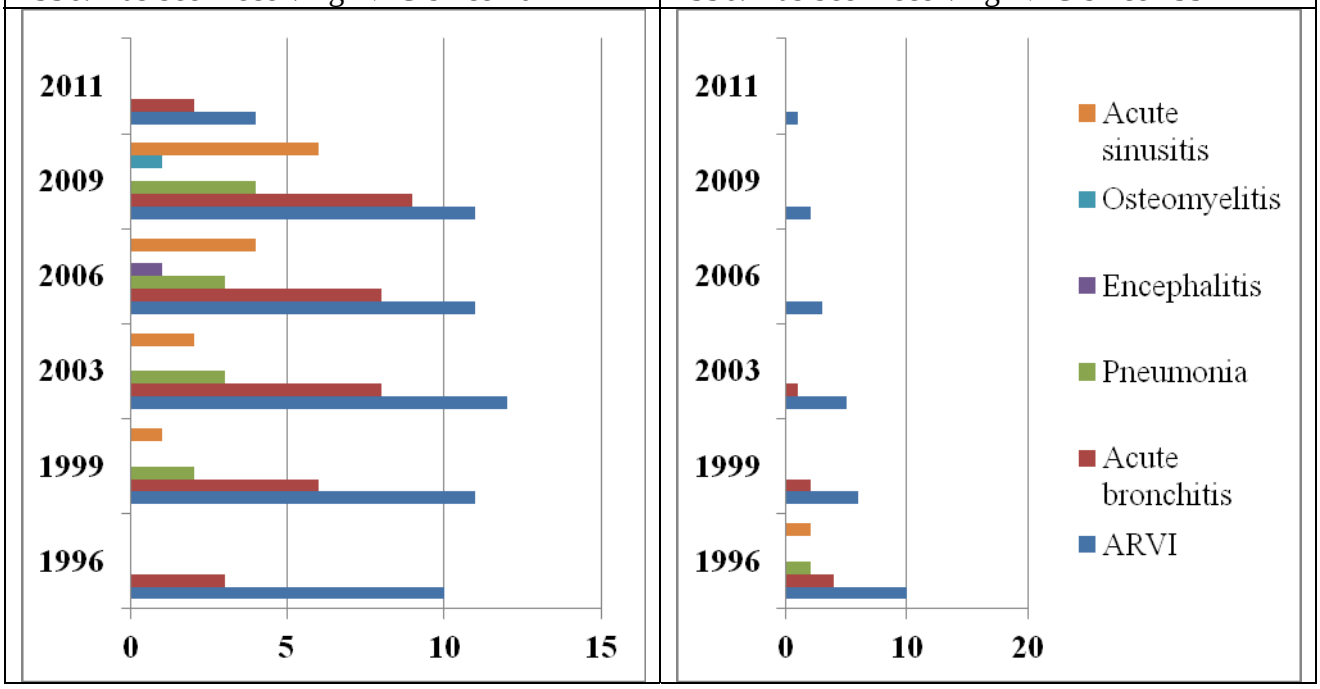
Medical reports' analytic data indicating the fact that duration of the period from diagnosis establishment to the beginning of regular therapy in patients with XLA was 2 years are of high interest. Duration of such a period in patients with CVID was 1 year, while the other 50% of patients have not been receiving regular replacement therapy, despite the presence of clinical symptoms and diagnosis.

Thus, the following important task was dictated by the work on PID register establishment – provision of replacement therapy. Against this background, the problem of taking intravenous immunoglobulins (IVIG) by adult patients without incapacitation who must not become incapacitated due to the diagnosis of primary immunodeficiency is insurmountable using resources of our competence. Moreover, the IVIG drugs offered to patients as additional medicinal provision do not always comply with requirements of the replacement therapy, which is why we regularly address a request to the governing body for health in the Rostov Region of a possibility of overcoming these problems on the local level and take part in events of the All-Russian Patient's organizations and charity foundations.

Another sphere of our work, the need in which arose in the process of register establishment, is activities for patients, such as school for PID patients, which has considerable positive effect on psychological status of the patients, and awareness communication about the importance of accurate fulfilment of doctor's recommendations on the individual level.

Thus, the methodology of establishing a register of patients based on the combination of organizational and professional measures promotes timely diagnostics and, therefore, rational therapy and improvement of life quality of the patients with primary immunodeficiencies.

Patient D. Diagnosis "XLA"; established in 1996. Has been receiving IVIG since 2011	Patient B. Diagnosis "XLA"; established in 1996. Has been receiving IVIG since 1997



Pic. Rate of clinical manifestations

Table 1. Alarming symptoms of primary immunodeficiency in children

4 or more exacerbations of otitis within a year	Recurrent profound skin and organ abscesses
2 or more severe sinusites within a year	Persistent oral candidiasis or fungal skin infections
Need in antibacterial therapy for 2 or more months with minimal effect	Recurrent need in intravenous antibacterial therapy for treating infections
2 or more pneumonias within a year	2 or more generalized infections, including sepsis
Low weight and height gain of infants	Primary immunodeficiencies in family anamnesis

Table 2. Alarming symptoms of primary immunodeficiency in adults

2 or more exacerbations of otitis within a year	Recurrent profound skin and organ abscesses
2 or more exacerbations of sinusitis within a year (no allergy)	Persistent candidiasis or fungal skin infections
Pneumonia once a year for several years in a row	Recurrent need in intravenous antibacterial therapy for treating infections
Chronic diarrhea, weight loss	Infection caused by atypical mycobacteria
Recurrent viral infections (ARD, herpes, warts, condylomae)	Primary immunodeficiencies in family anamnesis

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