The relevance of primary immunodeficiency registries on a global perspective

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Primary immunodeficiencies or inborn errors of immunity (IEIs), are a group of more than 400 monogenic diseases that present with recurrent infections, immune dysregulation, atopic disorders, autoinflammation, and susceptibility to cancer or in association with complex syndromes. The estimated overall incidence of these diseases is 1:10,000, but it varies worldwide depending on genetic background, environmental factors, social habits, and access to health services.1-2

In the article by Thalhammer et al3 that appears in this issue of the Journal of Allergy and Clinical Immunology and was written on behalf of the European Society of Primary Immunodeficiencies (ESID) Registry, the authors focused on the initial manifestations of IEIs, which is indeed an important angle because knowledge about these clinical manifestations should prompt pediatricians and clinicians to suspect and start the diagnostic investigation of a particular IEI. The study by Thalhammer et al1 shows that 68% of patients initially presented with infections only, 9% presented with immune dysregulation only, and 9% presented with a combination of both. Symptomatic features were the presenting feature in 12% of cases, 4% of patients had laboratory abnormalities only, 1.5% were diagnosed because of family history only, and 0.8% presented with malignancy. It is noteworthy that 19% of patients initially presented with more than 1 manifestation, most frequently a combination of immune dysregulation and infection (45%). Immune dysregulation was an initial manifestation in some patients with chronic granulomatous disease and severe combined immunodeficiency in a subgroup analysis. Two-thirds of patients with IEIs presented before the age of 6 years, but a quarter of patients developed initial symptoms only as adults. A key message is that the presentation varied according to age, although infection was the most common presentation at all ages (Fig 1). In a subset analysis, the authors defined the presenting manifestations according to the classification designed by the IEI committee of the International Union of Immunological Societies. Immune dysregulation has been diagnosed in all categories, and it was most frequently recognized as an initial IEI manifestation between the ages of 6 and 25 years, with male predominance until age 10 years, shifting to female predominance after age 40 years. Infections were most prevalent as a first manifestation in patients presenting after age 30 years. This study highlights the fact that an exclusive focus on infection-centered warning signs would have missed around 25% of patients with IEIs who initially presented with other manifestations, and it suggests an update of the IEI warning signs originally proposed by the Jeffrey Modell Foundation.

In 1994, the ESID became the first medical society to start an IEI registry. Currently, the ESID database includes more than 28,000 cases, most of which involve antibody defects. The Latin American Society of Immunodeficiencies (LASID) started its own registry in 2009; the registry currently includes more than 8500 cases, most of which also involve antibody defects.5 The USIDNET Registry, representing the United States and Canada, was started in 1992 as a registry of patients with chronic granulomatous disease and currently includes more than 6000 patients with diverse diagnoses, with patient quality of life entries for a subset.6 In a recent global systematic review of IEI registries, Abolhassani et al1 compiled more than 104,614 patients worldwide, with only 13% of them having a definitive molecular diagnosis, and they suggest that these patients represent just half of the cases, with most of the missed cases being in Africa and Asia. They clearly show the different distribution of the diseases and inheritance patterns according to the particular regions of the world (Fig 2). These registries provide critical insights into geographic differences in clinical presentations, infectious organisms, the impact of consanguinity, and our recognition of IEIs. The current ESID publication shows the relevance of registries with large numbers of patients to improving our awareness of patient subsets that might otherwise be missed. Another important aspect of registries is to bring groups together for clinical trials of best practices and new treatments. The growing appreciation of immune dysregulation as a manifestation of IEIs was revealed dramatically through this data analysis of more than 16,000 patients. No single center could have identified the age and sex effects noted by the authors, nor would it identify the pervasive nature of immune dysregulation across all categories of patients.

The field of IEI is rapidly expanding with increasing heterogeneity of genotypes and phenotypes. Registries are a strategic instrument to adjust educational programs regionally to prompt physicians from other specialties to suspect a diagnosis of an...
immunodeficiency and refer to the clinical immunologist. Registries provide foundational data to tailor this educational content according to particular regions of the world. In addition, registries are instrumental for public health planning and patient advocacy, helping to uncover unmet needs. The progressive implementation of newborn screening for IEIs has also been changing the landscape of IEI epidemiology in a positive way, decreasing morbidity, sequelae, and mortality. It became universal in the United States in 2018; in Brazil in 2021; and in Sweden, Switzerland, and The Netherlands beginning in 2019, and was partly adopted by Canada and some other European countries. 8

In conclusion, the further implementation and expansion of IEI registries worldwide will potentially facilitate advancing the clinical knowledge on primary immunodeficiency and help in developing new diagnostic procedures and treatments. The article by Thalhammer et al 3 on behalf of the ESID has advanced clinical care for clinicians everywhere and serves as a model for future registry efforts.

REFERENCES