Implementation of a Reference Center for Inborn Errors of Immunity in Latin America

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Short Report

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Abstract

We would like to report our experience in the deployment of an Immunology outpatient clinic that over 14 years became a Reference Center for Inborn Errors of Immunity (IEI) in Brazil, which is located in the city of Taubaté, in the region of Vale do Paraíba, state of São Paulo, responsible for serving a region of approximately 2.5 million inhabitants. During this period, we participated in the pilot project to implement neonatal screening for severe combined immunodeficiency and initiated courses for physicians from basic health units, implementation of classes on clinical immunology in the undergraduate program of medicine, implementation of an outpatient clinic at the city's Faculty of Medicine, in addition to the assessment of patients hospitalized in emergency and intensive care units. Thus, the implementation of a Reference Center for IEI in Latin America proved to be viable and can serve as a model for other services to be initiated. Based on our experience, we suggest some itens for additional IEI centers to emerge.

Full Text

We would like to report our experience in the deployment of an Immunology outpatient clinic that over 14 years became a Reference Center for Inborn Errors of Immunity (IEI) in Brazil, which is located in the city of Taubaté, in the region of Vale do Paraíba, state of São Paulo, responsible for serving a region of approximately 2.5 million inhabitants.

During this period, we participated in the pilot project to implement neonatal screening for severe combined immunodeficiency and initiated courses for physicians from basic health units, implementation of classes on clinical immunology in the undergraduate program of medicine, implementation of an outpatient clinic at the city's Faculty of Medicine, in addition to the assessment of patients hospitalized in emergency and intensive care units.

IEIs are a group of genetic diseases that cause immunological abnormalities with an increase in infections, autoimmunity, hyperinflammation and neoplasms (1), with an estimated incidence of 1:1000–2000 live births, being considered rare diseases according to WHO (1.3:2000 people) (2).

In Brazil, the pilot neonatal screening project started in 2010 in the city of São Paulo. In 2014, it expanded to other states and in 2016 it encompassed our department. The quantification of TREC (T-cell Receptor Excision Circles) by polymerase chain reaction is used for neonatal screening of IEI with T lymphocyte deficiency, mainly SCID (Severe Combined Immunodeficiency). The KREC (kappa deleting recombination excision circles) which is a circular DNA segment, generated during the maturation of B lymphocytes in the bone marrow, evidences the production of B lymphocyte by the patient (3). In addition to screening, some studies suggest that TREC and KREC can be used in the diagnosis of patients with IEI mainly in countries with limited resources due to the lower cost of this test compared to immunophenotyping (4).

We carried out a cross-sectional, retrospective and unicentric study by collecting data from the medical records of patients being followed up at the HMUT (Hospital Municipal Universitário de Taubaté [Municipal University Hospital of Taubaté]) with the objective of describing the clinical profile of patients

with IEI and those who had ENSTIEI (extended neonatal screening test for inborn errors of immunity), abnormal TREC and/or KREC performed in our department.

Over 14 years, more than 1,050 children were evaluated and 112 probable diagnoses of IEI were made which were distributed into predominant antibody deficiencies (41.1%), immunodeficiency combined with associated or syndromic features (10.7%), congenital defects of phagocytes (3.6%), immunodeficiency affecting cellular and humoral immunity (1.8%), immune dysregulation diseases (0.9%), probable diagnosis of IEI (42.0%). There was a prevalence of males (62.5%), presence of allergies, hospitalization (79.5%), admission to neonatal ICU (40.2%) and pediatric ICU of 22.3% ($p < 0.001$). The use of intravenous immunoglobulin was 49.1% and mortality was 6.3%.

Between 2016 and 2020, we started a pilot project to collect TREC and KREC as neonatal screening for newborn patients at HMUT and for patients up to 1 year of age who had recurrent infections.

In total, 2,679 ENSTIEI were performed and 33 abnormal results were found, with cases of severe combined immunodeficiency (SCID), agammaglobulinemia, actinopathy, trisomy 21 and hypogammaglobulinemia. Twelve patients remain under investigation and in nine patients IEI was ruled out later. Among these patients with abnormal ENSTIEI, it was possible to observe a prevalence of males (54.5%), presence of allergies, hospitalization (75.8%), admission to neonatal ICU (45.5%) and pediatric ICU (30.3%). The use of intravenous immunoglobulin was 39.4% and mortality was 18.2%. If we compare the 21 patients who underwent collection of TREC and KREC in the neonatal period with the 14 patients who underwent collection of TREC and KREC in the post-neonatal period, the latter group showed greater use of immunoglobulin (21.1% vs. 64.3%) and mortality (10.5% vs. 28.6%), respectively.

Taking into account our results and the reports of other authors, such as Alvarez-Cardona *et al.* 2016, about their experience in Mexico with an educational program on IEI for physicians and the general population, it became evident that continuing education and training of physicians is critical to increasing the diagnosis and care of these diseases. (5) In addition, an efficient reference network with molecular diagnostic capabilities should be developed. Our experience demonstrated the importance of this informative work, involving the entire pediatric team (specialists, residents and medical students), taking into account the number of and reasons for referrals to the immunology department in Taubaté.

Thus, the implementation of a Reference Center for IEI in Latin America proved to be viable and can serve as a model for other services to be initiated. Based on our experience, we suggest that, for additional IEI centers to emerge, it is necessary to:

- Stimulate teaching of Rare Diseases such as IEI in medical schools.
- Perform neonatal screening test for IEI (TREC and KREC).
- Conduct continuing medical education programs on IEIs involving the entire pediatric team, for the correct interpretation of screening tests, avoid the use of BCG and live virus vaccines in these patients,

know the protocol for the initial treatment of IEIs with doses of prophylactic antibiotics and immunoglobulin and referral of the patient to a reference center in immunology as soon as possible.

- Add screening tests for IEI to the list of procedures of the public health system (immunoglobulins, TREC and KREC, lymphocyte immunophenotyping, complement, post-vaccination serology, etc.)
- Define the reference ranges of serum immunoglobulins and lymphocytes for the Brazilian population of different age groups, seeking uniformity in the data.
- Create reference centers for sending more specific laboratory tests such as genetic testing.
- Define the procedure code for evaluation by the immunologist of patients hospitalized by face-to-face care or telemedicine, avoiding the delay in the diagnosis of IEI.
- Ensure supply of human immunoglobulin to patients.
- Define the location for outpatient care of patients with IEI and for immunoglobulin infusion throughout the patient's life, until adulthood.
- Define public policies for patients to receive bone marrow transplants.
- Register the cases in the existing database, to define the prevalence and incidence of IEI.

Thus, with the increase in physicians' knowledge on the subject and greater possibility of diagnostic tests, more patients will be diagnosed earlier with IEI, improving the quality of life of these patients and their families, reducing sequelae, morbidity and mortality.

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Declarations

All the authors declare no competing interests at the article "Implementation of a Reference Center for Inborn Errors of Immunity in Latin America". Ethics: All the authors declare that had approval for the study "Implementation of a Reference Center for Inborn Errors of Immunity in Latin America" by UNIFESP - Federal University of São Paulo.