Jornal de Pediatria 97 (2021) S34–S38

Jornal de Pediatria

www.jped.com.br

REVIEW ARTICLE

Failure of immunological competence: when to suspect?

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Received 5 October 2020; accepted 6 October 2020
Available online 8 November 2020

KEYWORDS
Primary immunodeficiency diseases;
Clinical manifestations;
Diagnosis

Abstract
Objectives: To draw physicians' attention to the different warning signs of diseases of inborn errors of immunity.
Data sources: A non-systematic review of the literature was carried out in the PubMed, LILACS, and SciELO databases, in addition to consultation of reference textbooks.
Summary of the findings: It is known that the lack of immunological competence observed in patients with inborn errors of immunity diseases causes particularly serious and/or recurrent infections. However, manifestations related to autoimmunity, inflammation, allergies, and malignancy can also occur. Aiming at the early identification of these patients, a list of warning signs for inborn errors of immunity was created, in which the need for intravenous antibiotics or prolonged antibiotics use to control infection, failure to thrive, and positive family history for this group of diseases are considered the most sensitive. Regarding non-infectious manifestations, early onset, difficulty in controlling with the usual treatments, atypical presentations or association with other warning signs are noteworthy, and investigation for inborn errors of immunity in these situations is recommended.
Conclusions: This article highlights the importance of considering this group of diseases even in the face of patients with non-infectious manifestations. Disclosure of inborn errors of immunity diseases, especially to non-specialists, is essential for early diagnosis and, consequently, for the reduction of these patients' morbidity and mortality.

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https://doi.org/10.1016/j.jped.2020.10.007

Introduction

Historically, the immune system is associated with the defense of the organism against various pathogens; therefore, individuals with a ''competence gap'' are expected to present with recurrent and/or serious infections. This concept is supported by observations in patients with diseases of inborn errors of immunity (IEI; previously called primary immunodeficiencies [PID]), whose main clinical manifestations are severe and/or repeated infections.[1]

It is known that several factors can contribute to recurrent infectious conditions such as prematurity, physiological immaturity of the immune system, living with siblings, especially those younger than 5 years, attending day care, exposure to smoke, and incomplete vaccination.[2]

There is no consensus regarding the number that defines the concept of repetition. Some definitions have been proposed in relation to the respiratory tract, the most accepted of which are described in Table 1.[3]

In addition to IEI, other conditions, such as secondary immunodeficiencies (*e.g.*, medication use, AIDS), atopy, gastroesophageal reflux disease, anatomical or mechanical changes (*e.g.*, adenoid hypertrophy, malformations), and chronic diseases (*e.g.*, cystic fibrosis, dyskinesia ciliary, alpha1-antitrypsin deficiency) are also risk factors for recurrent infections.[2]

Although anatomical or mechanical changes are risk factors, in these cases infections always occur in the same place, which is usually not observed in patients with IEI diseases.[4]

According to the literature, approximately 50% of patients with recurrent respiratory infection are healthy, 30% are atopic, 10% have IEI, and 10% have a chronic disease.[5]

The early identification of IEI patients improves quality of life and reduces morbidity and mortality. In this study, the authors will address the so-called ''ten warning signs of primary immunodeficiency'' in addition to other manifestations, especially non-infectious, which should draw attention to IEI diseases.

Data sources

Non-systematic literature review in the last ten years in the PubMed, LILACS, and SciELO databases. The following terms and their synonyms (MeSH terms) were used for the search: ''*Primary immunodeficiency disorders*'' OR ''*inborn errors of immunity*'' AND ''*warning signs*'' OR ''*recurrent infections*'' OR ''*dysregulatory disorders*'' *OR* ''*allergy*'' OR ''*atopy*'' OR ''*autoinflammatory diseases*'' OR ''*autoimmunity*'' OR ''*câncer*'' OR ''*clinical manifestations*'' OR ''*diagnosis*''.

Articles in Portuguese, English, French, and Spanish were carefully selected using the checklist proposed by the User's Guide to Medical Literature (JAMA Evidence) as an inclusion criterion.[6]

Textbooks considered references on the subject were also consulted.

Table 1 Definition of recurrent infections.

Acute otitis media: more than three episodes in six months or four in 12 months
Infectious rhinitis: more than five episodes in 12 months
Pharyngitis/tonsillitis: more than three episodes in 12 months
Pneumonia: more than two episodes in 12 months
OR
Six or more respiratory infections in 12 months
One or more upper respiratory tract infections per month
Three or more lower airway infections in 12 months

Summary of the data

The ten warning signs of primary immunodeficiency

Aiming at the early identification of patients with IEI diseases, the ''10 warning signs'' for IEI in children were created in the 1990s and recently modified (Table 2).[7] It is recommended that individuals with two or more warning signs be investigated for these diseases.

Patients who have infections with unusual pathogens, severe infections with common pathogens, persistent infections, family members with the same susceptibility pattern, or infections associated with other clinical manifestations related to the dysregulation of the immune system should also be investigated.[8]

In addition to infections, severe or atypical vaccine reactions should draw attention to the possibility of primary or secondary immunodeficiencies.[9] Considering the importance of bacillus Calmette-Guérin (BCG) in Brazil, an adverse reaction to that vaccine was included as one of the warning signs proposed for children under 1 year old (Table 3).[10]

In this context, Mazzucchelli et al. described that 65% of patients with severe combined immunodeficiencies (SCID) who inadvertently received BCG presented local or disseminated complications; in 20%, this was the first clinical manifestation of the disease.[11]

Fever, pneumonia, abscess and ulcer at the vaccination site, subcutaneous nodule, lymphadenomegaly, hepatosplenomegaly, and osteomyelitis are examples of manifestations related to BCG in patients with SCID.[11]

In another study, it was reported that 65% of patients with SCIDs vaccinated with BCG developed widespread skin reactions, most of them between 4 and 6 months of life. However, it is noteworthy that in some patients, such manifestations occurred only after 1 year of age.[12]

The warning signs of IEI in children younger than one year are shown in Table 3.

Several studies have evaluated the sensitivity and specificity of the so-called ''ten warning signs of primary immunodeficiency in children.'' Among the proposed signs, the most important for the identification of these patients are those related to the use of antibiotics, difficulty in gaining weight and/or growing properly and, mainly, a positive or suspicious family history for some IEI, which can increase the chance of such a child being diagnosed with one of these diseases by 18 times.[13]

In a study involving 563 children, it was observed that 96% of those with defects of phagocytes or complement and

Table 2 The new ''ten warning signs for primary immunodeficiency''(currently called inborn errors of immunity), in children.

Four or more otitis in one year	Recurrent, deep skin or organ abscesses
Two or more severe sinus infection within a year	Persistent thrush in mouth or fungal infection on skin
Antibiotic use for two months or more with little effect	Need for intravenous antibiotics to clear infections
Two or more pneumonia in one year	Two or more deep-seated infections including septicemia
Failure to gain weight or grow normally	Family history of primary immunodeficiency (inborn errors of immunity)

Table 3 Warning signs in children under 1 year old.

Persistent or severe fungal, viral, and/or bacterial infections	Congenital heart disease (mainly from the base vessels)
Adverse reactions to bacillus Calmette-Guérin (BCG)	Delay in the fall of the umbilical stump (over 30 days)
Autoimmune and/or inflammatory disease	Family history of inborn errors of immunity or early death from infection
Febrile sepsis-like condition, without identification of infectious focus	Lymphocytopenia (less than 2500 cells/mm^3), or other cytopenia, or persistent leukocytosis without infection
Extensive skin lesions	Hypocalcemia, with or without seizure
Persistent or chronic diarrhea	Absence of thymic image on chest X-ray.

89% of those with defects of T lymphocytes were identified using these three warning signs.[13]

However, in general, the sensitivity of the ten warning signs for the diagnosis of IEI is low, around 60%–70%, being even lower for less serious diseases.[14] In the study carried out by MacGuinnitie et al., among the 141 children evaluated, more than one-third of those whose diagnosis was confirmed did not show any warning signs.[15] In addition, in another study, waiting for two warning signs led to a delay in diagnosis in 38% of patients.[13]

Although this list was created to draw attention and allow early diagnosis of patients with IEI, this group of diseases is still underdiagnosed. In children, the time between the first consultation and the diagnosis ranges from nine months to almost five years.[16] In adults, the mean time between the first clinical manifestation and the diagnosis is four years.[17]

The lack of medical awareness regarding IEI diseases[18] and the predominant focus on infectious manifestations as warning signs can contribute to this scenario.

Non-infectious clinical manifestations: when to suspect IEI?

It is known that the immune system also plays a fundamental role in maintaining the body's homeostasis and that some changes in the innate and/or adaptive immune response can lead to clinical manifestations related to autoinflammation, lymphoproliferation, autoimmunity, allergies, and neoplasms, which are increasingly described in patients with IEI diseases.[1]

Therefore, research is also recommended for this group of diseases in patients with multiple autoimmune diseases or disease of early onset, difficult to treat, or associated with other warning signs;[19] early or recurrent malignant diseases, rare for the age group (childhood: extranodal lymphoma, T-cell lymphoma), unusual histopathological and cytogenetic changes, unusual location for the age group (*e.g.*, CNS–childhood) or malignancy associated with recurrent infections or family history suggestive of IEI;[20] severe allergies, refractory to usual treatments, associated with autoimmune manifestations or serious or unusual infections;[21] inflammatory process, recurrent or persistent, with or without fever, with or without severity and without evidence of infection or autoimmunity as the main mechanism involved.[22]

Table 4 illustrates some non-infectious manifestations, in addition to those included in the ''warning signs'', which may be present in this group of patients. It is important to highlight that some IEI diseases can precede serious and/or recurrent infections, or even not be accompanied by infectious manifestations.[23]

Although some of these manifestations are also observed in individuals who do not lack immunological competence, they should draw attention to the diagnosis of IEI, especially when associated with other warning signs, very early onset, or disease refractory to the usual treatments.

It is worth mentioning that some phenotypes are characteristic, such as eczema, thrombocytopenia with small platelets (Wiskott–Aldrich syndrome), partial oculocutaneous albinism (Chédiak–Higashi syndrome), cerebellar ataxia with oculo-cutaneous telangiectasia (ataxia-telangiectasia syndrome) and extensive erythroderma, lymphoproliferation, autoimmune cytopenia, eosinophilia, and increased levels of IgE (Omenn syndrome).[5]

Omenn syndrome, as it is a severe combined immunodeficiency, is considered a medical emergency that must be promptly recognized and referred to a specialized service.

Conclusions

Although IEI diseases are considered rare, the underdiagnosis of these patients is still a problem. In this sense, the

Table 4 Some non-infectious manifestations of diseases of inborn errors of immunity.

Gastrointestinal	Celiac disease and ''celiac-like disease,'' IBD and IBD-like, atrophic gastritis, pernicious anemia, autoimmune enteropathy, sclerosing cholangitis, autoimmune hepatitis, granulomatous hepatitis, granulomatous colitis and enteritis, ulcers, exocrine pancreatic insufficiency.[23–26]
Cutaneous/hair and nail	Extensive and severe eczema, erythroderma, alopecia, eyebrow loss, pachydermia, trichorrhexis invaginata (bamboo hair), granulomas, ectodermal dysplasia (skin, nail, hair, and teeth), delayed wound healing, vasculitis, vitiligo, ocular-cutaneous albinism, telangiectasias (ocular-cutaneous), angioedema without urticaria, urticaria (especially neutrophilic), generalized pustular psoriasis, congenital livedo, severe acne associated with gangrenous pyoderma.[23,24,27]
Respiratory	Interstitial lung disease, granulomatous lymphocytic interstitial lung disease, bronchiolitis obliterans, alveolar proteinosis, bronchiectasis.[23,24,28]
Neurological	Ataxia, delayed neuropsychomotor development, microcephaly, mental retardation, neurosensory deafness, transient or early onset ischemic stroke, nystagmus, aseptic meningitis, autoimmune encephalitis, early onset encephalopathy.[23,24,29]
Hematologic	Immune thrombocytopenic purpura, autoimmune hemolytic anemia, Evans syndrome, small platelet thrombocytopenia, neutropenia, neutrophilia, eosinophilia, hemophagocytic lymphohistiocytosis, lymphomas, myelodysplasia.[23,24,30]
Rheumatologic	Arthritis, systemic lupus erythematosus, juvenile idiopathic arthritis.[23,24,31]
Others	Thymic aplasia, lymphoproliferative syndromes, absence of tonsils or ganglia, malnutrition, recurrent serositis, dysmorphisms, malformations, TORCH-like syndrome, type I diabetes mellitus, thyroiditis, hypoparathyroidism, adrenal insufficiency.[23,24]

IBD, inflammatory bowel disease; TORCH, *Toxoplasma gondii*, rubella, cytomegalovirus, or herpes simplex.
*The manifestations related to the dysregulation of the immune system are discussed in detail in another study.
*The clinical manifestations and some of the laboratory alterations related to the different diseases of the IEI can be easily consulted in the phenotypic classification tables.[23]

dissemination of the clinical manifestations of this group of diseases, especially among non-immunologists, is essential for the early recognition and treatment of these patients.

Conflicts of interest

The authors declares no conflicts of interest.

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