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Inborn Errors of Immunity: What to Look for Beyond Infections

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ABSTRACT

Inborn errors of immunity (IEI) are a heterogeneous group of more than 400 diseases, mostly genetically determined, whose main clinical manifestations are severe and / or recurrent infections. Despite the efforts of immunology societies worldwide, this group of diseases remains underdiagnosed. The present review attempts to describe, and call the attention of the physicians, for the infectious and non-infectious manifestations related to IEI. The main clinical manifestations, as well as others that are not so frequent, have been reported in this manuscript. In order to facilitate clinical reasoning, we created a table to illustrated some of them and subdivided the main manifestations into infectious, infectious associated with immune dysregulation, only related to dysregulation and others. The dissemination of knowledge about clinical manifestations, especially non-infectious ones, can contribute to early diagnosis of IEI and, consequently, to the reduction of their morbidity and mortality.

Keywords: primary immunodeficiency diseases, inborn errors of immunity, diagnosis, clinical manifestations, infections, immune dysregulation, allergy, autoimmunity, autoinflammation, cancer.

Introduction

Primary immunodeficiencies are a heterogeneous group of diseases with compromise of immune system, mostly genetically determined, first described in the 1950s in patients with severe and / or recurrent infections. Since then, with advances in science, especially genetics, new genes and diseases have been identified, and other clinical manifestations, especially non-infectious ones related to autoimmunity, neoplasia, inflammation, allergy and lymphoproliferation have been described[1,2]. The identification of manifestations of dysregulation of the immune system in these patients has now led this group of diseases to be called inborn errors of immunity (IEI).

Currently, more than 400 diseases are described, and 430 genetic defects have been identified[3], and it is estimated that, together, the prevalence of these diseases is from 1: 1000 to 1: 5000. Predominantly antibody deficiencies are the most frequent, corresponding to approximately 50% of cases[4].

In order to facilitate the diagnosis and research of these diseases, the IEI were divided into 10 tables3, according to the classification by the International Union of Immunological Societies (IUIS): 1- Immunodeficiencies affecting cellular and humoral immunity (severe combined immunodeficiency – SCID and combined immunodeficiency - CID), 2- Combined immunodeficiencies with associated or syndromic features, 3- Predominantly antibody deficiencies, 4- Diseases of immune dysregulation, 5- Congenital

defects of phagocyte number or function, 6- Defects in intrinsic and innate immunity, 7- Autoinflammatory disorders, 8- Complement deficiencies, 9- Bone marrow failure, 10- Phenocopies of inborn errors of immunity.

Severe and/or recurrent infections by common and/or opportunistic microorganisms that require intravenous antibiotics to resolve are the most common manifestations of IEI diseases[5]. Despite infections being the most frequent clinical manifestations of this group of diseases and being part the clinical picture of most of them, they are not necessarily the main manifestations. Autoinflammatory disorders, for example, rarely develop infectious conditions and are characterized by persistent or recurrent multisystemic inflammation[5].

Some IEI diseases are characterized by well-defined clinical phenotypes such as Wiskott-Aldrich Syndrome, Ataxia telangiectasia, Comèl-Netherton Syndrome, Autosomal dominant HyperIgE Syndrome, among others[5].

Warning Signs for Inborn Errors of Immunity

The suspicion of an IEI must start from non-immunologists, that's why many lists of warning signs have been created. However, the warning signs in use are not able to identify many of the IEI[6-8]. and studies have shown that family history, need for intravenous antibiotic therapy and failure to thrive are the most efficient signs[9].

Warning signs by medical specialties were proposed, focusing on pulmonary, gastrointestinal, cutaneous and other manifestations[10, 11], but their greater efficacy in the identification of patients was not demonstrated.

Table I describes the warning signs which, even though we know that they are not sensitive, are the most used in the world.

IEI: Other Manifestations Beyond Infections

In general, the sensitivity of the 10 warning signs for the diagnosis of IEI is low, around 60 to 70%, being even lower for less severe diseases[6]. The medical lack of knowledge about the diseases[13] and the predominant focus on infectious manifestations as warning signs can contribute to this scenario.

Currently, it is recommended that patients with autoimmune manifestations of early onset and/or refractory to conventional treatments[14], severe and difficult to control allergic conditions[15], recurrent or persistent inflammatory processes associated or not with fever[16] and malignant diseases with early onset and/or unusual presentation[17] should be investigated for IEI.

The diagnosis of patients with IEI requires a high degree of suspicion, and knowledge of other manifestations besides the infectious ones is essential.

Identifying the disease also represents a great challenge.

Table I – Warning signs for inborn errors of immunity in newborns, children and adults

NEWBORNS
Severe and/or persistent fungal, viral, or bacterial infections
Adverse reaction to Live vaccine specially BCG
Persistent diabetes mellitus or other autoimmune and/or inflammatory manifestation
Sepsis-like clinical picture without microbial isolation
Extensive skin lesions
Persistent diarrhea
Congenital heart defects (mainly conotruncal anomalies)
Delayed umbilical cord detachment (>30 days)
Familial history of PID or early deaths caused by infection
Persistent lymphocytopenia 2,500 cells/mm3 or other cytopenia, or leukocytosis without infection
Hypocalcemia with or without seizures
Absence of thymic shadow at X-Ray
CHILDREN
Four or more new ear infections within 1 year
Two or more serious sinus infections within 1 year
Two or more months on antibiotics with little effect
Two or more pneumonias within 1 year
Failure of an infant to gain weight or grow normally
Recurrent, deep skin or organ abscesses
Persistent thrush in mouth or fungal skin infection
Need for intravenous antibiotics to clear infections
Two or more deep-seated infections including septicemia
A family history of an inborn error of immunity
ADULTS
Two or more new ear infections within 1 year
Two or more serious sinus infections within 1 year, in the absence of allergy
One pneumonia per year for more than 1 year
Chronic diarrhea with weight loss
Recurrent viral infections (colds, herpes, warts, condyloma)
Recurrent need for intravenous antibiotics to clear infections
Recurrent, deep abscesses of the skin or internal organs
Persistent thrush or fungal infection on skin or elsewhere
Infection with normally harmless tuberculosis-like bacteria
A family history of an inborn error of immunity

Sources: [3,11]

In this sense, the reasoning guided by the main clinical manifestations, pathogens preferentially involved, the main affected sites, and other manifestations that may also be present, facilitate the clinical diagnosis of IEI diseases.

Aiming to draw attention to non-infectious manifestations, as well as to facilitate clinical reasoning for the diagnosis of this group of diseases, we created a table that illustrates some of the IEI diseases, highlighting the main clinical manifestations and those that may be associated (Table II). Furthermore, we believe that the division by groups of clinical manifestations (infectious or not), type of pathogen and affected sites is useful for a bedside consultation and could facilitate the diagnosis of IEI diseases.

Table II - Main clinical presentation and associated manifestations of some of the inborn errors of immunity.

Main Manifestations/ Characteristics		
Infections	**IUIS Classification**	**Other manifestations/Disease**
Early onset of severe/recurrent bacterial, fungal and víral infections; severe reactions with live microorganism vaccines	**Severe combined immunodeficiency** (SCID)	Cytopenias, chondroesternal dysplasia, deafness, dysmorphisms, congenital alopecia + nail dystrophy, lymphoproliferation, failure to thrive granuloma, autoimmunity
Late onset (>1 year of age) Recurrent bacterial, fungal and viral infections, especially EBV Less severe than SCID	**Combined immunodeficiency** (CID)	Hepatosplenomegaly, lymph node swelling, eczema, eosinophilia, elevated IgE: ***Omenn syndrome*** Severe eczema, cutaneous infections, severe atopy, câncer, high IgE, eosinophilia: ***DOCK8 deficiency*** Autoimmunity, immune dysregulation, granuloma, biliary tract and liver disease
Recurrent/severe bacterial infections (extracellular) Mainly sinopulmonary infections	**Predominantly antibody deficiencies** B cells: decreased or absent, severe reduction in all serum Ig isotypes (Agammaglobulinemia: XL, AD, AR)	IBD (***p110δ deficiency)***, cytopenias (***p85 deficiency***), blistering, dermatosis, failure to thrive (***ZIP7 deficiency)***, thrombocytopenia, facial dysmorphism, limb anomalies (***Hoffman Sd***)
	Predominantly antibody deficiencies B cells: decreased or N, severe reduction in at least 2 serum Ig isotypes (IgG and IgA) (CVID phenotype)	Polyclonal, lymphoproliferation, autoimmune cytopenias, granulomatous disease, lymphadenopathy, splenomegaly, lymphoma EBV ±CMV viremia: ***APDS1*** Developmental delay: ***APDS2***, ***PTEN deficiency*** Glomerulonephritis: ***CD19 and CD81 deficiencies*** Congenital sideroblastic anemia, deafness, developmental delay: ***TRNT1 deficiency***
Bacterial respiratory tract infections + Enlarged lymph nodes (***AID and UNG deficiency***)	**Predominantly antibody deficiencies** B cells: N IgG and IgA: severe reduction IgM: N or elevated (Hyper IgM)	Café-au-lait skin spots, hypopigmented skin áreas, family or personal history of câncer (***MSH6 deficiency***) Autoimmunity (***AID and UNG deficiency)***
Recurrent or severe bacterial infection, mainly respiratory (***specific antibody deficiency***) Mild bacterial respiratory and gastrointestinal tract infections or asymptomatic (***selective IgA deficiency***) Usually not associated with significant infections, resolution around 4 years old (***transient hypogammaglobulinemia of infancy***)	**Predominantly antibody deficiencies** Isotype, Light Chain, or Functional Deficiencies B cells: N in general	Atopic dermatitis, asthma (***specific antibody deficiency***) Autoimmunity (***selective IgA deficiency***)
Omphalitis Recurrent and severe infections Skin infections evolve to large ulcers; *S. aureus* and Gram-negative organisms; fungal infections (some patients) Absence of pus Leukocytosis with neutrophilia	**Congenital defects of phagocyte** (function) Leukocyte adhesion deficiency (LAD1)	Delayed separation of the umbilical cord Severe gingivitis, periodontitis Impaired wound healing Failure to thrive Malnourishment Colitis
Recurrent bacterial infections – pneumonia, otitis media, cellulitis, periodontitis Skin infections without pus Milder infections than in LAD1	**Congenital defects of phagocyte** (function) LAD2	Bombay blood phenotype, mental retardation, short stature, distinctive facial appearance
Omphalitis Recurrent and severe bacterial and fungal infections – similarly to LAD1 Absence of pus Leukocytosis with neutrophilia	**Congenital defects of phagocyte** (function) LAD3	Delayed separation of the umbilical cord, impaired wound healing, bleeding tendency Osteopetrosis-like state (some patients)

Recurrent bacterial infections (skin, oropharynx and lung) Aphthous stomatitis and gingivitis Gram positive and Gram negative bacterial infections Absence of pus Severe congenital neutropenia	**Congenital defects of phagocyte** (number)	MDS/leucemia (***Elastase deficiency****) Mental retardation and seizures (***Kostmann disease***) MDS (***X-linked neutropenia***) Intestinal inflammation
Ear sinopulmonary, skin and soft tissue bacterial infections HPV (warts) Hypogammaglobulinemia, Neutropenia (myelokathexis)	**Defects in intrinsic and innate immunity** CXCR4 GOF	Tetralogia of Fallot, urogenital abnormalities HPV-induced cancers Tooth loss Mycobacterial, fungal and candida infections
Predisposition to invasive bacterial infections (pyogens), mainly meningitis *S. pneumoniae* > *S. aureus* and *P. aeruginosa* *Pus formation, little/no increase in body temperature* *Low CRP levels, normal levels of total leukocytes and neutrophils during infections* Improves with age	**Defects in intrinsic and innate immunity** IRAK4/MyD88 deficiencies	Delayed separation of the umbilical cord Omphalitis Non invasive bacterial infections (skin and upper respiratory tract infections) usually necrotizing; *S. aureus* > *P. aeruginosa* > *S. pneumoniae*
Recurrent pyogenic infections	**Complement deficiencies** C3LOF	Glomerulonephritis
	MASP2 deficiency	Inflammatory lung disease, autoimmunity
	Ficolin 3 deficiency	Necrotizing enterocolitis in infancy; selective antibody defect to Pneumococcal polysaccharides; infections with encapsulated organisms
Disseminated Neisserial infections	**Complement deficiencies** C5-C9 Properdin and Factor D deficiency	–
Fungal, bacterial, and parasitic infections Systemic adverse effects to BCG Most severe in XL disease	**Congenital defects of phagocyte** (function) Chronic Granulomatous Disease (AR e XL)	Autoinflammatory phenotype, IBD
BCG disease (localized or disseminated) Mycobacteria, Salmonellae or other intracellular pathogens	**Defects in intrinsic and innate immunity** Mendelian susceptibility to mycobacterial disease (MSMD)	Viral infections Mucocutaneous candidiasis
Severe viral or mycobacterial [NTM] infections Myelodysplasia	**Congenital defects of phagocyte** (function) GATA2 deficiency	Alveolar proteinosis, lymphedema, invasive fungal infections, acute myeloid leukemia
Invasive fungal diseases (mainly Candida and Trichophyton species)	**Defects in intrinsic and innate immunity** CARD-9 deficiency	–
Chronic Mucocutaneous Candidiasis without ectodermal dysplasia	**Defects in intrinsic and innate immunity** STAT1 GOF	Fungal, bacterial and viral (HSV) infections, auto-immunity (thyroiditis, diabetes, cytopenias), enteropathy
Susceptibility to viral infections: Severe viral infections	**Defects in intrinsic and innate immunity** STAT1 deficiency	Mycobacteria infection
Disseminated vaccine strain measles	STAT2 deficiency	
Severe influenza disease	IRF7 and IRF9 deficiencies	
Severe rhinovirus and other RNA viruses	MDA5 deficiency	
Herpes simplex encephalitis	UNC93B1 deficiencies	
	TLR3 deficiencies	Severe pulmonary influenza and VZV
Epidermodysplasia verruciformis (HPV)	EVER1 and EVER2 deficiencies	Cancer of the skin

Main Manifestations/Characteristics		
Infections and Immune dysregulation	**IUIS Classification**	**Other manifestations/Disease**
Bacterial respiratory tract infection, autoimmunity (cytopenias), enteropathy, splenomegaly	**Diseases of immune dysregulation** LRBA deficiency CTLA-4 haploinsufficiency	Autoimmunity (others than cytopenias), failure to thrive; non-respiratory tract infection, lymphadenopathy, interstitial lung disease, hepatomegaly
Ear/sinopulmonary infections, EBV associated lymphoproliferative disease/lymphoma, lymphadenopathy, splenomegaly	**Diseases of immune dysregulation** X-linked magnesium EBV and neoplasia (XMEN)	Viral infections, gastrointestinal infections, autoimune cytopenias.
Chronic mucocutaneous candidiasis Hypoparathyroidism Addison disease	**Diseases of immune dysregulation** Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED)	Other autoimmunity endocrinopathies Ectodermal dystrophy Enteropathy Pernicious anemia
Hemophagocytic lymphohistiocytosis (HLH) Oculocutaneous albinism Recurrent infections	**Diseases of immune dysregulation** (HLH with hypopigmentation) Chediak-Higashi	Bleeding tendency, progressive neurological dysfunction, neutropenia
	Griscelli type 2 Hermansky-Pudlak type 2	Pulmonary fibrosis, increased bleeding, neutropenia
	Hermansky-Pudlak type 10	Severe neutropenia, seizures, hearing loss and neurodevelopmental delay
Main Manifestations/Characteristics		
Immune dysregulation	**IUIS Classification**	**Other manifestations/Disease**
Familial hemophagocytic lymphohistiocytosis (FHL)	**Diseases of immune dysregulation** (FHL without hypopigmentation) Perforin, UNC13D/Munc13-4, Syntaxin 11 and STXBP2/Munc18-2 deficiencies	
	FAAP24 deficiency	EBV-driven lymphoproliferative disease
	SLC7A7 deficiency	Lysinuric protein intolerance, bleeding tendency, alveolar proteinosis
Severe and protracted enteropathy with villous atrophy, eczema, severe, often multiple endocrinopathies (mainly diabetes and thyroiditis)	**Diseases of immune dysregulation** IPEX (FOXP3 deficiency)	Hemolytic anemia, thrombocytopenia
IBD and folliculitis	**Diseases of immune dysregulation** IL-10 deficiency	Recurrent respiratory diseases, arthritis
	IL-10 receptor deficiency	Recurrent respiratory diseases, arthritis, lymphoma
EBV associated HLH, lymphoma, non-malignant lymphoproliferation	**Diseases of immune dysregulation** SAP deficiency (XLP1)	Aplastic anemia, vasculitis, colitis
EBV associated HLH, colitis, lymphoproliferation	XIAP deficiency (XLP2)	Recurrent HLH, hepatitis, IBD
Chronic adenopathy Splenomegaly Autoimmune cytopenias	**Diseases of immune dysregulation** ALPS-FAS	Lymphoma
	ALPS-FASLG	SLE
	ALPS-Caspase 10	Bacterial and viral infections
Chronic adenopathy Splenomegaly	ALPS-Caspase 8	Bacterial and viral infections
	FADD deficiency	Recurrent episodes of encephalopathy and liver dysfunction

Main Manifestations/Characteristics		
SLE-like Syndrome	**IUIS Classification**	**Other manifestations/Disease**
SLE	**Complement deificency**	Infections with encapsulated organisms
	C1q	
	C1 r	Ehlers Danlos phenotype
	C1s	Ehlers Danlos phenotype, multiple autoimmune diseases
	C2	Vasculitis, polymyositis, atherosclerosis
	C4	
Main Manifestations/Characteristics		
Angioedema	**IUIS Classification**	**Other manifestations/Disease**
Angioedema without urticaria	**Complement deficiency** C1inhibitor	Serpiginous rash

AD: autosomal dominant inheritance, AID: activation-induced cytidine deaminase, ALPS: Autoimmune lymphoproliferative syndrome, APDS: Activated p110δ syndrome, AR: autosomal recessive inheritance, BCG: Bacillus Calmette–Guérin, CID: Combined immunodeficiency, CRP: C-reactive protein, CTLA-4: cytotoxic T lymphocyte antigen 4, CVID: Common variable immunodeficiency, EBV: Epstein-Barr virus, GOF: gain-of-function, HIES: Hyper IgE syndrome; HPV: Human papilloma virus, HSV: Herpes simplex virus, IBD: inflammatory bowel disease, ID: immunodeficiency, Ig: immunoglobulin, IL: interleukin, IPEX: Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome, IRF: interferon regulatory factor, IUIS: International Union of Immunological Societies, LOF: loss-of-function, LRBA: lipopolysaccharide responsive beige-like anchor protein, MASP: MBL associated serine proteases, MBL: mannose-binding lectin, MDS: Myelodysplastic syndrome, MTHFD1: methylene-tetrahydrofolate dehydrogenase1, N: normal, NTB: non-tuberculous mycobacteria, Sd: syndrome, SLE: Systemic lupus erythematosus, TLR: Toll-like receptor, UNG: uracil-DNA glycosylase, VZV: Varicella zoster virus, XL: X-linked inheritance, XLP: X-linked lymphoproliferative.
* Some patients with elastase deficiency can present with cyclic neutropenia.

Conclusion

Early diagnosis is essential to reduce morbidity and mortality related to this group of diseases[4, 18]. Suspicion should be made by general practitioners, pediatricians or other medical specialties, so that early referral is made to the clinical immunologist. Therefore, warning signs should be known by all medical specialties and other clinical manifestations, especially non-infectious, cannot be forgotten.

In addition, the incorporation of TREC and KREC count in neonatal screening programs is essential to ensure early identification of severe and fatal forms of IEI[19].

Conflict of Interest

All authors declare no conflict of interest related to this manuscript.

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