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Diagnosis of Immunodeficiency Disease in Pediatric Patients with Recurrent Respiratory Infection

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Abstract

Respiratory pathology represents a great challenge for health institutions, due to its frequency, its diagnostic and therapeutic complexity and the burden it represents in economic and vital costs. For the most part, these infections only affect the upper respiratory tract and can be considered mild in immunocompetent individuals, with a benign and self-limiting course. It is difficult to establish the limit between normal and pathological in terms of the number of infections presented by a child in a given time. The body´s defense against infections is carried out by the immune system. Due to its possibility of presentation between one and five years and its association with pulmonary pathology, we must focus our attention on: immunodeficiency related to malnutrition, immunodeficiency due to infections, immunodeficiency due to the use of drugs, prematurity and inborn errors of immunity, such as antibodies defects. Therefore, whenever the diagnostic possibility of the child who presents with recurrent respiratory infections disease, whether primary (inborn errors of immunity) or secondary, we propose and algorithm, with which we have more than 15 years of experience in our Pediatric Immunology Services, where children with recurrent respiratory infections are treated.

Keywords: Respiratory tract infections; Immune system; Primary immunodeficiency Diseases; Haemophilus influenzae; Psychomotor development

Introduction

Respiratory pathology represents a great challenge for health institutions, due to its frequency, its diagnostic and therapeutic complexity and the burden it represents in economic and vital costs. These concepts extend to all age groups and their characteristics have been changing over time due to the advances made in immunizations, diagnostic methods and treatments [1,2].

In the year 2000, the WHO mentioned that almost 11 million children had died worldwide due to malnutrition and respiratory infections, considering that currently a third of mortality from acute respiratory infections occurs in children under five years of age, of these, the 90 % are due to pneumonia. In Latin America, upper respiratory infections also constitute a major health problem in this age, being the main cause of hospitalization (30 - 60 %), antibiotic therapy and death; more frequent in cold and rainy months; in addition, upper respiratory infections represent between 50 - 70 % of all pediatric consultations in Latin America. In Cuba, influenza and pneumonia represents fourth place in the causes of infant mortality, and are also the first cause of death of infectious origin [3-6].

For the most part, these infections only affect the upper respiratory tract and can be considered mild in immunocompetent individuals, with a benign and self-limiting course (common cold, rinitis and pharyngotonsillitis). Around 53 % involve the lower or lower respiratory tract (bronchiolitis, bronchopneumonia and pneumonia) and constitute potentially more serious infections, especially in patients with underlying diseases, immunosuppressed or at the extreme ages of life, and may require hospital care. In the United States, it is estimated that more than 400,000 children under 18 years of age are hospitalized annually for viral respiratory infections [7].

It is difficult to establish the limit between normal and pathological in terms of the number of infections presented by a child in a given time. Factor such as ethnicity and socioeconomic and hygienic conditions influence. Most authors, rather than the num-

ber, give value to the type of infections and their characteristics: organs and systems affected, severity, germ responsible, as well as the response to usual treatment. In our environment, it has been estimated that healthy children in the first years of life have an average of 6 to 8 upper respiratory infections each tear, up to 6 annual episodes of acute otitis and two of acute gastroenteritis. The frequency of upper respiratory infections is higher in those children who attend daycare or when their siblings do so. In 90 % of cases, we can find 2 to 7 days for the resolution of a throat inflammation and up to a period of 15 to 16 days to resolve a nonspecific respiratory infection. This, together with the fact that many of these conditions are grouped together seasonally, can give the impression that the child is always sick [7]. The body´s defense against infections is carried out by the immune system, a set of complex interrelated mechanisms that include the integrity of the skin-mucous barriers, innate immunity and adaptive immunity. A failure in any of these mechanisms can result in an increase in infections [8].

It can be considered that childhood, with its temporary immaturity of the immune system, is the primary cause of recurrent respiratory infections in the pediatric population. However, there are other modifiable and non-modifiable risk factors that may also contribute to the risk of recurrence. Modifiable risk factors associated with the development of recurrent respiratory infection include preschool age, male sex, ineffective breastfeeding, low birth weight, attendance at day care centers, overcrowding, and environmental tobacco smoke [9,10], while non-modifiable risk factors include prematurity, genetic predisposition and atopy [10,11].

When faced with a child with recurrent respiratory infections, we must think about the following possibilities:

i. Normal child.

ii. Child with atopic profile.

iii. Child with a chronic illness.

iv. Child with an immunodeficiency disease.

Infections caused by primary immunodeficiencies or inborn errors of immunity are almost always accompanied by other clinical manifestations due to the involvement of various organs and systems. Inborn errors of immunity are the paradigm of diseases that cause recurrent infections and should be suspected whenever some of the warning signs exist [12]. They are rare, of genetic origin and hereditary [12]. 10 % of children who have recurrent infections will have an immunodeficiency with one or more components of the immune system affected. Immunodeficiencies are entities in which there is quantitative or qualitative impairment of any component of the immune system: adaptive immune system: adaptive immunity (B cells, humoral immunity or antibody response and T cells or cellular immunity) and innate immunity (phagocytic and complement systems, among others) [13].

The infections that occur in this type of disorders are characterized by being:

i. More serious infections or infections with a poor response to adequate treatment, sometimes in unusual or non-characteristic locations, but with an unusual evolution.

ii. Infections due to atypical or opportunistic germs.

Immunodeficiencies can be primary (inborn errors of immunity) or secondary. Both groups of immunodeficiencies may present a greater susceptibility to suffering from oncoproliferative processes, autoimmune and allergic diseases [13]. The panorama of immunodeficiency diseases becomes more serious if we consider their polymorphism or clinical variability, the different laboratory tests necessary for diagnosis which are not available in less developed countries due to lack of technology, the insufficient training of different clinical specialties for its detection and study as well as for the adequate and timely referral to the specialist in Clinical Immunology [14]. The classification currently used by the International Societies of Immunology divides them into inborn errors of immunity (previously primary immunodeficiencies) and secondary immunodeficiencies. Among the immunodeficiency diseases that are characterized from a clinical point of view by recurrent respiratory infections, both primary antibody defects (inborn errors of immunity) and secondary defects standout [14].

Among the predominant primary antibody deficiencies, the following stand out: hyper-IgM syndrome, transient hypogammaglobulinemia of childhood, deficiencies of specific antibodies with normal immunoglobulins, deficiencies of IgG sub classes, selective IgA deficiency and Bruton´s X-linked agammaglobulinemia. Among the predominant secondary antibody deficiencies, protein-energy malnutrition by default, prematurity and the chronic use of immunosuppressants such as glucocorticoids stand out [14]. The hiper-IgM syndrome is characterized by opportunistic infections, lymphadenopathy and autoimmunity, otitis, sinusitis, bronchitis, pneumonia. Transient hypogammaglobulinemia of childhood is characterized as an immunodeficiency that occurs in infants, otitis, sinusitis, bronchitis, pneumonia. This condition normalizes around 2-4 years of age. Deficiency of specific antibodies with normal immunoglobulins occurs after 2 years of age.

It is characterized by otitis, sinusitis, bronchitis and pneumonia. IgG subclass deficiencies in young children may by transient. They generally occur in children over 7 years of age. It is characterized by respiratory infections, otitis, recurrent or chronic lung disease, recurrent meningitis, sinusitis, bronchitis, pneumonia. The selective IgA deficiency mostly occurs asymptomatically. It is characterized in symptomatic patients by recurrent respiratory infections, otitis, sinusitis, bronchitis, pneumonia, chronic diarrhea, allergies or autoimmune diseases such as celiac disease. It usually occurs in children over four years of age. For its part, Bruton´s X-linked agammaglobulinemia occurs in males under 5 years of age. It is characterized by recurrent pyogenic infections

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of the respiratory tract, otitis, sinusitis, bronchitis, pneumonia, osteomyelitis, bronchiectasis and chronic respiratory infections, invasive bacterial infections of the digestive system and skin [14].

In the case of secondary immunodeficiencies, they develop secondary to other conditions that indirectly affect response. If this condition is controlled or eliminated, immunocompetence is recovered [15]. In pediatric clinical practice, the following causes of secondary immunodeficiencies stand out: prematurity, protein-energy-malnutrition, metabolic disease (diabetes mellitus), autoimmune disease, hemato-oncological diseases (lymphoma, leukemia, myeloma, infections (Human Immunodeficiency Virus 1 and 2 -HIV 1 and 2- , Herpesviruses such as Cytomegalovirus and Epstein-Barr Virus - CMV and EBV- , Chickenpox, Measles, Rubella, Mycobacterium tuberculosis, Plasmodium spp., Strongyloides stercoralis), chromosomal abnormalities (Down syndrome, 18q Syndrome), immunosuppressive drugs, other drugs (Phenytoin, Carbamazepine), radiation, entities with protein loss, anatomical or functional asplenia, injury, trauma, burns [15].

Due to its possibility of presentation between one and five years and its association with pulmonary pathology, we must focus our attention on: immunodeficiency related to malnutrition, immunodeficiency due to infections, immunodeficiency due to the use of drugs and prematurity [15]. The algorithm that we define for the diagnosis in children with recurrent, severe or invasive respiratory infection, with suspected immunodeficiency disease, is the following:

Interrogation

Family and personal pathological history, allergic manifestations, drug allergy, food allergy, parents alive or dead, consanguinity, causes of death, number of siblings, deceased, causes, sex of siblings, clinical alterations similar to those of the patient, toxic habits during pregnancy, normal or pathological pregnancy, abortions, gestational age at birth, conditions of delivery, weight and size at birth, use of breastfeeding, duration, psychomotor development, compliance with the vaccination schedule, post-vaccination reaction, eating habits, conditions of housing, number of people who live in the house, number of rooms where people sleep, overcrowding, smoking in the home, age of the mother, education of the mother, home hygiene, attendance at daycare, perinatal history, history of infections, location and etiology, associated diseases, location, habitual use of drugs.

Physical Examination

i. Weight, height and nutritional evaluation.

ii. Exhaustive general, regional and organ systems physical examination emphasizing the exposure of the respiratory system.

iii. Look for lymphadenopathy and hepatosplenomegaly.

iv. Comprehensive examination of the mucous membranes.

v. Comprehensive skin examination.

Laboratory Exams

First Stage

i. Hemogram.

ii. Quantification of major classes of immunoglobulins (IgG, IgA, IgM).

iii. IgG subclass quantification.

iv. Quantification of specific antibodies to tetanus toxoid and Haemophilus influenzae.

v. Thymus sonography.

vi. Delayed hypersensitivity skin test.

Second stage

i. Lymphocyte subpopulations (CD3+, CD4+, CD8+, CD19+, CD20+, CD16+, CD56+)

ii. Test for nitro blue tetrazolium and dihydrorhodamine by flow cytometry if the patient has criteria for its indication

iii. Serology for HIV and Herpesvirus if the patient has criteria for its indication

Third stage

i. Molecular biology tests to define gene mutations that define inborn errors of immunity:

ii. Microdeletion immunofluorescence in situ hybridization 22q11, RAG1/2, ADA, IL2RG, WASP, PI3K, CD 40 L, Btk, Fas, Fas L, AIRE, Foxp3, phox-91, CD 11, CD 18, LFA-1, STAT 1, IFN-ɣ R 1 y 2, IL 12 β R 1, complement genes, and others.

Respiratory Examination

i. Simple spirometry.

ii. Chest X-rays.

iii. High resolution thoracic computed tomography.

iv. Bronchoscopy (according to age and suspected disease).

Therefore, whenever the diagnostic possibility of the child who presents with recurrent respiratory infections disease, whether primary (inborn errors of immunity) or secondary, we propose that this algorithm be followed, with which we have more than 15 years of experience in our Pediatric Immunology Services, where children with recurrent respiratory infections are treated.

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