

Primary immunodeficiencies in seriously ill children: Report of 3 clinical cases

Inmunodeficiencias primarias en niños gravemente enfermos: a propósito de 3 casos clínicos

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Abstract

Primary immunodeficiency diseases (PID) are congenital disorders secondary to an impaired immune response. Infections, autoimmune disorders, atopy, and lymphoproliferative syndromes are commonly associated with this disorder. **Objective:** To present and discuss 3 infants diagnosed with PID. **Clinical cases:** The cases are presented of three patients with PID diagnosed during their first admission to a Paediatric Intensive Critical Care Unit. The first patient, a 4-month-old infant affected by a severe pneumonia, and was diagnosed as a Severe Combined Immunodeficiency Disease. The second patient was an 8-month-old infant with *Candida lusitanae* mesenteric adenitis, and diagnosed with a Chronic Granulomatous Disease. The last patient, a 6-month-old infant presented with ecthyma gangrenosum and X-linked agammaglobulinaemia. **Conclusion:** PID should be suspected when an infectious disease does not respond to the appropriate therapy within the expected period. An update of each disease is presented.

Keywords:

Primary immunodeficiencies; Children; Critical care; Immune response.

Introducción

Cellular immunity is significantly compromised in the critically ill patients. Increased lymphocyte depletion and apoptosis, a severe suppression of innate immunity system in children with severe influenza and low immunoglobulin levels have been observed in deceased patients from multiple organ failure¹⁻³. At the same time there is a group of patients without immu-

nosuppression history that in whom an immunodeficiency is suspected in the course of a serious illness. The 3 most frequent forms of presentation are severe infections, infections by atypical or opportunistic germs, and poor response to the usual therapies. The interpretation of these phenomena is rather complex including the challenge for the physician to suspect a primary immunodeficiency (PID), which may influence the short-term evolution, presenting a greater risk

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of morbidity and mortality, time in the ICU, as well as greater medical costs. In the long term, the lack of diagnosis of a PID will contribute to the progressive deterioration of each compromised system.

PIDs are genetic diseases that cause quantitative and/or functional alterations in different immune response processes. They are characterized by predisposition to infections, prone to autoimmune diseases, allergies and lymphoproliferative disorders. Since the discovery of agammaglobulinemia by Odgeon Bruton, 50 years ago, more than 200 IDPs have been described and the molecular basis of half of them has been defined⁴, with 60% diagnosed at the pediatric age. The prevalence varies according to ethnic groups, diagnostic techniques and classifications used. In Norway, the rate reaches 6.8/100,000 inhabitants⁵, while in Australia, which does not have an IgA or complement deficiency, this rate decreases to 2.8/100,000 inhabitants⁶.

PIDs vary according to the different series, the most frequent are humoral immunodeficiency (50-60%), combined deficiencies (15%), phagocyte deficiencies (10%) and cellular and complement deficiencies (5%).^{7,8} The Latin American Society for Immunodeficiencies (LASID) reported 4,765 patients with PID by October 2013, the most frequent being antibody deficiency (53.2%) (www.lasid.org). The current classification was carried out by an international committee of experts, the International Union of Immunological Societies, who grouped the PIDs into 9 groups⁹ (table 1).

In our Unit, the majority of patients admitted with severe or unusual infections are required to test levels of immunoglobulins G, A and M which, in case to be diminished or if there is persistent lymphopenia, they are supplemented with CD4, CD8, CD19 lymphocytic subpopulations and natural killer (NK). Our objective was to report cases of cellular PID identified between January 2011 and February 2015. During this period, 2,371 patients were admitted to our Unit.

Clinical Case 1

A 4-month male patient with a history of cow's milk protein allergy (CMPA) and fungal dermatitis of the scalp. Doctor's visit due to cough and fever. Severe multifocal pneumonia was diagnosed and the patient was hospitalized. He developed acute respiratory failure and was connected to mechanical ventilation (MV) after 72 h. IgM tests regarding cytomegalovirus (CMV), Mycoplasma and *Pneumocystis jirovecii* are negative. The patient was transferred to the ICU. Tests showed leukocytosis of 49,000/mm³, lymphopenia of 1,000/mm³ and low levels of C3 and C4 supplements and IgG. In lymphocyte subpopulations, the absence of T lymphocytes (LT) and absolute lymphopenia are

described. PCR test for *P. jirovecii* from bronchoalveolar lavage was positive. It evolved into severe ARDS, requiring 10 days of MV. Computed tomography of the chest revealed multiple foci of alveolar filling, some in frosted glass. Severe combined immunodeficiency is confirmed with absence of the interleukin 2 gamma (IL 2 RG) receptor, an X-linked severe X-SCID. Intravenous gammaglobulin (IVGG) with doses every 3 weeks, antifungal and *P. jirovecii* prophylaxis, and periodic surveillance of Epstein Barr virus (EBV), CMV and adenovirus are initiated. A month after evolution, a treatment with the Calmette-Guérin bacillus (CGB) vaccine is started. A study for possible allogeneic bone marrow transplantation identified no compatibility. Patient is enrolled into a gene therapy protocol at Children's Hospital in Boston, which was done after the BCG treatment. Favorable evolution. Periodic lymphocyte controls were within normal/low ranges. He required monthly GGEV and presented no infectious complications, he is currently 4 years old.

Clinical Case 2

An 8-month old male patient with a history of neonatal pustular hypermelanosis, small ventricular septal defect and CMPA. Consultation due to 5 days of high fever and abdominal distension. Hemogram showed: leukocytes 5,800/mm³, 9 mm/h ESR, C-reactive protein of 20 mg/l and normal complete urine. Examination showed erythematous BGC scar with left axillary adenopathy of 1 cm in diameter. PCR for herpes virus 6 was positive, and the rest of the bacteriological and virological studies were negative. Abdominal ultrasound showed mild hepatomegaly. Liver tests and bone scintigraphy were normal. G, A and M Immunoglobulin counts were low. Patients developed fever, showing a

Table 1.

Immunodeficiencias combinadas de células T y B
Déficit predominante de anticuerpos
Otros síndromes de inmunodeficiencias bien definidas
Enfermedades de disregulación inmune
Defectos del número y/o función fagocítica
Defectos en la inmunidad innata
Deficiencias del complemento
Desórdenes autoinflamatorios
Fenocopias de IDP

Fuente: Al-Herz et al⁹.

urinary infection caused by *Proteus* and *Enterococcus*, which is treated with cefotaxime. He was transferred to the ICU to receive IVGG. He developed abdominal distension and control ultrasound showed ascitic fluid and enlarged lymph nodes. Due to suspected immunodeficiency and disseminated BCG, it was decided to perform a mesenteric adenopathy study, identifying *Candida Cusitaniae* and treated with antifungals for 3 weeks. Due to the impossibility of ruling out disseminated BCG, antituberculosis treatment was started. He developed severe sepsis and abdominal compartment syndrome and needed MV and vasoactive drugs. Low lymphocytic subpopulations is complemented by a study of lymphoproliferation and lymphocyte activation that is abnormal. He presented diminished respiratory burst, typical anatomical pathological study, concluding chronic granulomatous disease (CGE). The respiratory burst test performed on the mother, clinically healthy, is abnormal. He is treated serially with IVGG and interferon gamma. Subsequently, umbilical cord blood transplantation was performed, complicated by autoimmune hemolytic anemia that responded to rituximab. He remains in periodic control until the current age of 3 years.

Clinical Case 3

A 6-month old male patient vaccinated until 4 months, with fever and labial lesions 24 h after onset. Hemogram showed 5,200 leukocytes/mm³ (1% segmented), severe neutropenia, 227 mg/l PCR, 77 ug/ml procalcitonin, and culture of labial lesions (+) to *Pseudomonas aeruginosa*. He started treatment with ceftazidime, amikacin and cloxacillin. IgG, IgA and IgM Immunoglobulin levels are decreased, receiving 400 mg/kg IVGG. Neutrophils returned to normal at 48 h. Lymphocyte subpopulations presented absence of B lymphocytes suggesting agammaglobulinemia. A maternal uncle's history presented agammaglobulinemia and the X-linked frame was configured. Favorable evolution, reversing sepsis. He required monthly administration of IVGG. There has been no recurrence of infection.

Discusión

Our cases presented clinical and laboratory evidence that made us to suspect a PID. In all cases, there was a severe infection that does not respond to the usual treatment and which demands a search for opportunistic germs. Initial measurement of immunoglobulins was important as a screening method. In case 1, it is important to emphasize that the symptoms related to

PID could wrongly lead to the diagnosis of CMPA. In case 2, immunoglobulin level should have been normal or high, but it is likely that, because he was an infant with severe infection, his level was decreased. Case 3 is an example of the importance of directed anamnesis, which found an older male relative recently diagnosed with X-linked agammaglobulinemia. The medium and long-term evolution was satisfactory. Next, we review the PID characteristics diagnosed in this series of cases.

Severe Combined Immunodeficiency Syndrome (SCID)

Group of disorders caused by mutations of genes that are critical for the development and function of T and B lymphocytes. In some cases molecular defects affect only the T lymphocyte, but because B lymphocytes require signals from T cells to produce antibodies, a severe cellular immunity dysfunction will affect the humoral immunity. NKs are present in 50% of severe combined immunodeficiency syndromes (SCID) providing defenses against viral and bacterial infections. Some types of SCIDs have been defined, based on immunological, genetic and mutation criteria, in 39 distinct genes. The most common defects are mutations of the interleukin 2 receptor gamma (IL2RG) gene, Janus kinase 3 gene (JAK3), among others.

It is the most common form of cellular PID and is fatal unless the immune system is replaced through an allogeneic hematopoietic transplantation¹⁰. According to neonatal screening data, its incidence, higher than expected, is estimated at 1/58,000 live births. Most are of the autosomal recessive type, except for IL2RG that is associated to the X chromosome and has a greater incidence in zones of greater consanguinity¹⁰⁻¹². Early symptoms are pneumonitis, chronic diarrhea, pondostatural delay, and difficulty eradicating infections. Some infants may present graft versus host manifestations by maternal T lymphocytes, such as erythroderma or chronic hepatitis. A compromise by disseminated or localized BCG or persistent candidiasis is observed. A common characteristic is the progressive respiratory compromise with radiological evidence of interstitial pneumonitis or hyperinflation. The isolation of respiratory viruses and *P. jirovecii* is common. Atypical features such as cutaneous or pulmonary autoimmunity, lymphadenopathy, hepatomegaly, autoimmune blood cytopenias and lymphoproliferative disease are also observed^{13,14}.

The detection of lymphopenia is extremely important despite a normal count does not exclude SCID. The measurement of IgG, A, M and E should be interpreted according to the child's age. In case of normal levels, the antibody response against the administered vaccines should be evaluated. Before the suspicion of SCID, a measurement of lymphocyte

subpopulations and an evaluation by immunologist should be performed. The absence or severe decrease of T lymphocytes is consistent with the diagnosis. The presence or absence of B and NK lymphocytes are useful in decreasing possible genetic causes of SCID. Since 2008 neonates have been screened in the United States through polymerase chain reaction techniques and T lymphocyte receptor excision circles (TREC) that are pieces of DNA released during the maturation process. This technique has shown high sensitivity in its detection¹⁰.

SCID is a medical emergency whose early diagnosis is fundamental to implement measures to reduce the risk of early mortality and improve long-term quality of life. These precautions include prophylaxis of *P. jirovecii* infection, regular administration of immunoglobulin G and avoid vaccination with living organisms. Negative and irradiated CMV red blood cell and platelet transfusions avoid the risk of graft versus host disease. The final survival depends on the reconstitution of the immune function, which is achieved with BMT and/or gene therapy in the case of X-linked SCID, due to the deficiency of the common gamma chain and adenosine deaminase deficiency^{15,16}. Results with BMT are better if performed early¹⁷.

Chronic Granulomatous Disease

Disorder characterized by the early establishment of severe intercurrent respiratory infections that start in lungs, lymph nodes and skin and eventually move to liver, spleen, bones and brain. Hepatic abscess is the hallmark of CGD. Its estimated incidence is 1/250,000 live births per year¹⁸. The immunopathological mechanism is a defect of bactericidal activity of the phagocytes due to a defective NADPH oxidase; therefore it does not generate superoxide radicals, failing to produce the respiratory burst that kills the phagocytic germ. There are the X-linked and autosomal recessive forms, the most frequent being the first (60%). The pathogens found in CGD are generally catalase negative bacteria such as *Staphylococcus aureus*, gram-negative bacilli, and fungi such as *Candida* and *Aspergillus*. The BCG of the vaccine generates adverse effects in 20% of the CGD patients. Microscopic examination of lesions shows granulomas. Inflammatory complications of the intestine and perianal area are frequent (30%) and pulmonary granulomas can lead to respiratory failure in older patients.

Several mutations and affected genes explain the clinical and genetic heterogeneity of CGD. Its severity is related to the defective function of NADPH oxidase. It is evaluated through a neutrophil count and respiratory burst test using dihydrorhodamine (DHR) as a fluorescent detector of hydrogen peroxide. DHR is highly sensitive to detect CGD carriers linked to the X

chromosome or the autosomal recessive form¹⁹. The count of immunoglobulins may be elevated due to chronic infections.

Management includes prophylaxis of bacterial and fungal infections with cotrimoxazole and itraconazole and early recognition and aggressive management of severe infections. These latter could be prevented through immunomodulation with interferon gamma, with up to 70% efficacy, although other studies do not prove to be effective in the long term²⁰⁻²³.

BMT is the only proven therapy that provides definitive cure for CGD. Gene therapy has been used with diverse results. Liposomal reconstitution of oxygen intermediates has only shown to be useful in vitro. The average survival of patients is 40 years, although an early diagnosis avoids complications in the long term²⁴⁻²⁷.

X-linked Agammaglobulinemia

It is a humoral immunodeficiency characterized by severe hypogammaglobulinaemia and high susceptibility to infections. The United States registry estimates a frequency of about 1 in 379,000 live births and 1 in 190,000 newborn males²⁸. It is caused by a tyrosine kinase (TK) domain mutation, whose gene is located on the long arm of the X chromosome, and it is responsible for promoting preB cell development and their maturation, causing B lymphocytes and immunoglobulins deficiencies. Most patients present recurrent respiratory infections between 6 months and 5 years old, although some are detected earlier due to family history. Newborns are protected by transfer of maternal IgG, which explains the onset of infections after 3 months.

The germs involved are capsulated bacteria and certain blood-borne viruses, hence the importance of antibodies in bacterial opsonization and virus neutralization. An alteration in memory T-cell response to mucosal colonizing bacteria (*Neisseria meningitidis*) is observed. The most common germs are *Streptococcus pneumoniae*, *Haemophilus influenzae* type B, *Streptococcus pyogenes*, *Pseudomonas* sp. Infections such as *P. jirovecii*, *Mycoplasma* and *Ureaplasma* are observed. Patients may present chronic infections by Coxsackievirus and ECHOvirus and develop polio related to attenuated virus vaccine, presented as chronic encephalomyelitis.

The hallmark of X-linked agammaglobulinemia (ALX) is hypo or agammaglobulinemia; 25-50% of cases present neutropenia in relation to severe infections, which are solved with infection management and gamma globulin administration. A meticulous diagnosis is important not only for the patient but also for the women in the family who may be carriers, and whose children will have a 50% chance of being affected.

Neonatal Screening: A drop of blood analyzed by polymerase chain reaction may detect a decrease in the kappa-deleting recombination excision cycles of IgG (KREC), formed during B cell maturation and which would not form in patients with TK mutation²⁹. The detection of TK mutation, linkage analysis and the detection of altered X inactivation are techniques available to determine the ALX carriage.

The management of ALX consists of the administration of immunoglobulin, which reduces morbidity and mortality. Levels of IgG <400 mg/dl are associated to a higher frequency of pneumonias³⁰. The use of vaccines with attenuated germs is contraindicated. Despite the lack of antibody production, vaccines from dead organisms are indicated as the B lymphocyte-mediated response may generate some degree of protection.

It is important to educate parents about avoiding contact with contagious infections, washing their hands and drinking only safe water. Also, it is necessary to monitor pulmonary function to avoid evolution to chronic lung damage.

In summary, we believe that the PID frequency may be greater and it should be kept in mind due to

its potential of influencing survival and quality of life in the long term by preventing the deterioration of the compromised organs that affect morbidity and mortality.

Ethical Responsibilities

Protection of people and animals: The authors reported that no experiments on either people or animals have been performed.

Confidentiality of personal data: The authors reported that patient data publication is in accordance with protocols.

Privacy rights and informed consent: The authors reported that no patient data is contained in this article.

Conflict of interests

The authors declare no conflict of interest.

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