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ORIGINAL ARTICLE

Humoral deficiency in three paediatric patients with genetic diseases

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Abstract
Background: Primary immunodeficiencies (PID) represent a heterogeneous group of genetic disorders characterised by poor or absent function in one or more components of the immune system. Humoral or antibody immunodeficiencies are the most common form of PID, of which common variable immunodeficiency (CVID) is the most frequent symptomatic form. CVID is usually characterised by hypogammaglobulinaemia with poor antibody specificity, and an increased susceptibility to infections, autoimmunity and lymphoproliferation. Fewer than 10% of CVID patients have a known monogenic basis. Several chromosomal abnormalities (chromosome 18q-syndrome, monosomy 22, trisomy 8 and trisomy 21) are currently identified as causes of hypogammaglobulinaemia, and can manifest with recurrent infections and mimic CVID.
Methods: Review of clinical charts and laboratory results of paediatric patients followed in the outpatient clinic of PID with a diagnosis of genetic disease and humoral immunodeficiency.
Results: Three patients with different genetic diseases (19p13.3 deletion, a ring 18 chromosome and Kabuki syndrome), were identified. During follow-up, they developed signs and symptoms suggestive of humoral deficiency mimicking CVID, despite which immunoglobulin levels were quantified with considerable delay with respect to symptoms onset, and specific management was subsequently delayed.
Conclusions: Patients with genetic abnormalities and recurrent infections should be evaluated for hypogammaglobulinaemia. An early diagnosis of humoral deficiency can allow treatment optimisation to prevent complications and sequelae.

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Introduction

Primary immunodeficiencies (PID) represent a heterogeneous group of genetic disorders characterised by poor or absent function in one or more components of the immune system. Currently there are at least 250 genetically defined inborn errors of immunity, which are classified into nine categories by the International Union of Immunology Societies (IUIS), according to the part of the immune system that is most dysfunctional.

Humoral immunodeficiencies are the most common form of PID; they are characterised by alterations in the development and function of B lymphocytes resulting in a defect in the synthesis of antibodies, manifested by reduced or absent serum immunoglobulin levels with poor specificity, and an increased susceptibility to infections (mainly of the respiratory and gastrointestinal tract).[1] Common variable immunodeficiency (CVID) is the most frequent from of symptomatic humoral deficiency and, besides infections, can also involve other manifestations such as autoimmunity and lymphoproliferation. The CVID diagnostic criteria comprise: hypogammaglobulinaemia with IgG levels two standard deviations below the mean for age and a marked decrease in at least one of the isotypes IgM or IgA; impaired vaccine responses or absent isohaemagglutinins; and exclusion of other causes of hypogammaglobulinaemia.[2,3] There are several causes of hypogammaglobulinaemia, which should be considered in the differential, which include chromosomal abnormalities of which chromosome 18q-syndrome, monosomy 22, trisomy 8 and trisomy 21 are currently included in the guidelines.[2,3] These patients can present with recurrent infections that are often ascribed to the chromosomal abnormality, and hypogammaglobulinaemia is usually not ruled out. The aim of this study was to describe three cases with different genetic diseases that during follow-up developed signs and symptoms suggestive of humoral deficiency, despite which immunoglobulin levels were quantified with considerable delay with respect to symptoms onset.

Materials and methods

Of the 18 paediatric patients followed in the Immunodeficiency Outpatient Clinic at Sant Joan de Déu Hospital in Barcelona with a diagnosis of CVID-like humoral deficiency (based on hypogammaglobulinaemia with IgG levels two standard deviations below the mean for age and a marked decrease in at least one of the isotypes IgM or IgA; impaired vaccine responses or absent isohaemagglutinins,[2,3] and symptoms (recurrent sinopulmonary infections, autoimmune and lymphoproliferative diseases)), we identified three children who were diagnosed with a genetic disease, and during follow-up had developed signs and symptoms suggestive of humoral deficiency. Immune evaluation of these patients included: immunoglobulin levels (IgG, IgA, IgM), IgG subclasses levels if >4 years old, T/B/NK lymphocytes phenotyping, antibodies against polysaccharide antigens (isohaemagglutinins and pneumococcus, post-infection), and protein antigens (diphtheria, tetanus, pneumococcus post-Prevenar vaccination), B cell subphenotyping and proliferative responses to mitogens, using standard methods.[1] No statistical methods were used in this study.

Results

The first case is a seven-year-old female born to healthy unrelated parents at 37 GA by C-section due to delayed in utero growth (birth weight 2.02 kg). Screening during pregnancy showed broad nuchal fold and enlargement of the lateral ventricles with normal foetal karyotype (46 XX). In the neonatal period, she manifested irritability, weak suction and dysmorphic features (Fig. 1). Subtelomeric analysis by FISH technique showed a 19p13.3 deletion. Further evaluation identified an hypoplasia of the corpus callosum and ventriculomegaly, with psychomotor retardation, dysphagia and refractory epilepsy, treated with different combinations of drugs (clobazam and topiramate first, followed by phenobarbital, ethosuximide and valproic acid); limb abnormalities (duplication of the distal phalanx of the right thumb and genu varum); and endocrinopathy (growth retardation, hypothyroidism and adrenal insufficiency, all under replacement since age five). At six years old, she started presenting recurrent sinopulmonary infections, including recurrent suppurative otitis media, and five episodes of bronchopneumonia, one of which required hospitalisation for respiratory distress (clinical data are summarised in Table 1). Immunological investigations (Table 2) were conducted at seven years of age, showing low IgG, IgA and IgG subclasses (IgG1, IgG2 and IgG4) with normal responses to vaccines, including Pneumovax®23, but with progressive loss of protective anti-pneumococcal levels eight months after vaccination. She is being evaluated for the dysphagia as a main trigger of respiratory infections, along with hypogammaglobulinaemia. She has not initiated immunoglobulin replacement yet, pending clinical and immunological evolution.

The second case is a nine-year-old male born at term (41 weeks GA) with adequate weight for GA, from healthy unrelated parents. From birth he had mild hypotonia and dysmorphic features with acrodermatitis in distal phalange (Fig. 1). He was diagnosed with renal tubular acidosis, congenital heart defect (membranous subaortic stenosis), gastro-oesophageal reflux disease (GERD), mild psychomotor retardation and growth hormone deficiency (under replacement). A conventional chromosome GTG-banding at a 550 band level was performed, showing a ring 18 chromosome, with no other structural or numerical anomalies; more than 50 metaphases were revised and no mosaicism was found. The genetic study was completed with subtelomeric regions analysis by FISH technique: the results showed deletion of 18ptel and 18qtel regions. During the first two years of life he presented several infections: omphalitis one month of age, three non-suppurative otitis media, recurrent bronchitis, and a multilobar pneumonia for which he was admitted to the paediatric intensive care unit. Initially, the immunological study showed only low IgA levels. Over time he developed recurrent pneumonia, recurrent diarrhoea with positive stool culture for *Giardia lamblia*, multiple autoimmune disorders (vitiligo, autoimmune hypothyroidism (on replacement therapy), hepatitis with positive anti-smooth muscle antibodies, positive parietal cells antibodies, severe panniculitis with extensive lipoatrophy, fasciitis and myositis and recurrent episodes of urticaria without trigger) (Table 1). At eight years old, his immune status was re-evaluated and low levels of IgG, IgM and IgG subclasses