

Case Report

Hyper-IgM syndrome with CHARGE association

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A girl with coloboma of the iris, sensorineural deafness, growth delay, distinctive face, and cranial nerve dysfunction was diagnosed of CHARGE association in the first year of life. She presented with repeated otitis. At 3 yr of age, the patient suffered a septicemia (*Streptococcus pneumoniae*, *Corynebacterium* sp.). The immunoglobulin G (IgG) and IgA serum levels were decreased, IgM increased and cellular immunity parameters were normal, supporting the diagnosis of hyper-IgM (HIM) syndrome. The sequence of CD40 ligand and cytidine deaminase genes were normal. From then on, she was receiving immunoglobulin intravenously with an excellent outcome. Here, we report the first case of CHARGE association and HIM syndrome in the same patient. Although the cause could not be identified, a non-random link is likely.

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The CHARGE association is an increasingly recognized non-random pattern of congenital anomalies, that may be rather a true syndrome according to Davenport et al. (1). Its estimated prevalence is 1/10,000. It was described in 1979, and the acronym CHARGE (Coloboma; Heart defect; choanal Atresia; Retarded growth and development; Genital hypoplasia; Ear abnormalities and/or deafness) was coined in 1981 (2). Some of the features are difficult to detect during the neonatal period, therefore the diagnosis must be considered in any infant with one or two major characteristics and other minor features (3).

The hyper-IgM syndrome (HIM) is a rare congenital immunodeficiency characterized by recurrent pyogenic infections mainly located on the respiratory tract (4). Symptoms usually become apparent in the first or second year of life. Immunological findings include low IgG and IgA serum levels with high IgM. Generally, it is an X-linked abnormality, although non-X-linked cases have also been reported and the pathogenesis of these forms remains unclear (5). Without treatment, the mortality rate is high, mainly as a result of infections and autoimmune disorders.

Patients with CHARGE association and HIM had not been previously reported. We describe a girl with a non-classical CHARGE association and a non-X-linked form of HIM.

Case report

The patient is a 3-yr-old girl. No significant findings in the family history were recorded and parents were not consanguineous. The delivery was vaginal and full term, with uneventful antenatal and perinatal history. The Apgar score was 9 and 10, respectively, at 1 and 5 min. At birth, an intrauterine retarded growth with single umbilical artery and iris coloboma were found. The birth weight was 2.38 kg (<third centile), the length was 45 cm (<third centile) and the head circumference was 35 cm (25–50th centile). During the first year of life, she presented bilateral sensorineural deafness (auditory evoked potentials: right ear 95 db, left ear 90 db), cranial nerve dysfunction (VIII cranial nerve and Marcus-Gunn dyscinesia), growth delay and distinctive face (high nasal bridge, hypertelorism, square face). The patient showed a combination

of clinical findings consistent with the diagnosis of CHARGE association.

Routine hematological and biochemical laboratory results were within normal limits. Skeletal survey was normal. The ultrasound (abdomen and central nervous system) and the echocardiographic study did not reveal abnormalities. The chromosomal analysis showed a normal 46 XX karyotype.

Up to 8 months of age, she presented several otitis, resistant to antibiotic treatment. Allergic pathology and cystic fibrosis were excluded. When the girl was 3 yr old, she suffered a new episode of otitis that was later complicated with a right upper lobe pneumoniae and *Streptococcus pneumoniae* sepsis. She was treated with intravenous cefotaxime, without relevant improvement. A new blood culture was positive for *Corynebacterium* sp. Laboratory studies showed leukocytosis with neutrophilia and high C-reactive protein levels. The highest reached values were 30420/ μ l leukocytes (88% neutrophils and 4.8% lymphocytes) and C-reactive protein 313.8 mg/l (normal value 0–5 mg/l).

The immunological study showed low serum levels of IgG and IgA, increased IgM, normal B- and T-cell counts, normal proliferative response to phytohemagglutinin and very reduced antibody levels against tetanus and diphtheria immunization. Immunoglobulin values were: IgG < 4.6 mg/dl (normal value 929 ± 228 mg/dl), IgA < 4.6 mg/dl (normal value 93 ± 27 mg/dl), IgM 570 mg/dl (normal value 56 ± 18 mg/dl). The sequences of CD40 ligand and cytidine deaminase genes were normal. The CD40 expression on B cells was 100%. The HIM diagnosis was carried out and the patient received regular intravenous IgG (400 mg/kg/dose).

Clinical and immunological evolution was clearly favorable and the patient was free of infections at the end of the study period. The immunoglobulin replacement resulted in a decrease of serum IgM levels and increase of IgG. To date, the patient shows a growth delay, with normal thyroid and growth hormone levels. The psychoneurological development was normal.

Discussion

The diagnosis of non-complete forms of CHARGE association may be difficult. Several criteria have been proposed for improving the diagnostic accuracy. Pagon et al. (2) proposed the presence of at least four of the six major features included in the acronym, the coloboma and/or the choanal atresia, being mandatory. In 1998, a

revised consensus was proposed defining major criteria (coloboma, choanal atresia, characteristic ear abnormalities, cranial nerve dysfunction), minor criteria (genital hypoplasia, development delay, cardiovascular malformations, growth deficiency, tracheoesophageal fistula, orofacial cleft, distinctive face), and occasional findings (3). According to these criteria, the diagnosis of CHARGE association should be considered in any infant with one or two major characteristics and several minor characteristics. The patient had three major criteria: coloboma of iris, cranial nerve dysfunction (VIII sensorineural deafness; Marcus-Gunn dyscinesia) and sensorineural hearing loss as major criteria. She had several minor characteristics: growth deficiency and distinctive face (high nasal bridge, hypertelorism, square face). She seemed to have a non-classical CHARGE association.

The HIM is an uncommon primary immunodeficiency with recurrent pyogenic infections characterized by increased serum concentrations of IgM and low IgG and IgA levels (4). In Spain, only 33 cases were registered between 1980–99, although some affected individuals may remain unreported (6). X-linked (the most frequent), autosomal recessive and sporadic forms of HIM had been reported. HIM results from defects in the CD40 ligand/CD40 signaling pathway. X-linked HIM is caused by defects in the CD40 ligand gene, while autosomal recessive is caused by defects in the cytidine deaminase enzyme, which is required for immunoglobulin isotype switching (7). The loss of interaction between CD40 and its ligand results in an impairment of T cell, monocyte function and B cell, while only B-cell differentiation appears to be affected in autosomal recessive form because of cytidine deaminase deficiency (7). Recently, a new form of HIM as a result of a mutation of CD40 gene has been published (8). These cases show a severe clinical pattern (as the X-linked HIM) and autosomal recessive inheritance (as the cytidine deaminase deficiency).

The above-dealt case presents an autosomal recessive inheritance. The sequence of cytidine deaminase and CD40 ligand genes were normal, whereas the genetic study of CD40 gene could not be carried out. As clinical manifestations, she had suffered from respiratory tract infections (otitis, pneumoniae) only, which is very common of HIM. The clinical onset was precocious, in the first year of life. The septicemia was not presented until the girl was 3 yr old. She did not show gastrointestinal, hematological or neurological problems. The treatment of HIM is based on immunoglobulin replacement, antibiotic therapy,

and bone marrow transplantation. The patient's response to immunoglobulin therapy was very good, and actually the patient was free of infections and the normality of IgM and IgG levels seemed to be consistent.

The mechanism of CHARGE association remains unclear and although most cases are sporadic, some are inherited (3). The exact genetic abnormality of the CHARGE association has not been identified. Deletion in 9p chromosome was found only in isolated choanal atresia, but not in the classical CHARGE association (9). A 14q duplication was reported in some patients, suggesting that genes causing some of the anomalies of CHARGE association may reside in the region 14q22–14q24.3 (10). Other abnormalities described are partial trisomy 19q and translocations in several chromosomes: t(9;13), t(4;6), t(2;7) or t(19;21) (11).

Some patients with features of CHARGE association and DiGeorge syndrome were previously reported (12, 13), nevertheless the microdeletion 22q11.2, common in DiGeorge syndrome, was a rare finding in these cases (14). No other immunodeficiency had been reported in CHARGE patients until now. As far as we know, this is the first published study on a patient with HIM. At present, to define a common cause for HIM and CHARGE association is cumbersome, nevertheless both entities have a genetic basis and the future finding of a mutual link seems not to be unlikely.

In summary, we describe a 3-yr-old girl with HIM and CHARGE association. Although we are unable to propose a possible genetic link, this seems to be possible.

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