Evans syndrome and antibody deficiency: an atypical presentation of chromosome 22q11.2 deletion syndrome

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Abstract

We report a case of an 8-year-old male patient with Evans syndrome and severe hypogammaglobulinemia, subsequently in whom the 22q11.2 deletion syndrome (22q11.2 DS) was diagnosed. No other clinical sign of 22q11.2 DS was present with the exception of slight facial dysmorphism. The case is of particular interest because it suggests the need to research chromosome 22q11.2 deletion in patients who present with autoimmune cytopenia and peculiar facial abnormalities, which could be an atypical presentation of an incomplete form of 22q11.2 DS.

Introduction

Chromosome 22q11.2 deletion syndrome (22q11.2 DS) is considered the most common human deletion syndrome with an estimated incidence of 1:4000 live births.[1] More than 90% of the patients are hemizygous for a 1.5-3 Mb deletion within the 22q11.2 region.[2] The clinical expressivity of the syndrome is highly variable comprising more than 100 phenotypes, the DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome being the most frequent. It is characterized mainly by facial anomalies, congenital cardiac defects, thymic and parathyroid hypoplasia or aplasia, resulting in T-cell immunodeficiency and hypocalcemia. Other common findings are velopharyngeal insufficiency, genito-urinary anomalies, learning difficulties, and psychiatric disorders. An early diagnosis of the syndrome is extremely important to assure all the necessary interventions for the different clinical aspects.

Case Report

A 12-month-old boy presented at our hospital with mucosal bleeding and diffuse skin petechiae. His previous clinical history revealed that he is the second child of healthy nonconsanguineous parents. Intrauterine growth retardation was noted during the second trimester of gestation. Neonatal seizures associated with an abnormal EEG occurred at day 2 of life. At the age of seven months, a V-grade vesicoureteral reflux was diagnosed and surgical correction was performed. The baby was examined by the geneticist who asked for conventional cytogenetic analysis: the karyotype result was normal (46, XY). At four years of age he had three episodes of afebrile seizures. Magnetic resonance imaging showed a slight alteration of the focal frontal subcortical signal, interpreted as a possible outcome of perinatal hypoxic-ischemic insult.

At the clinical examination the boy was in a severe general condition, pale with scleral icterus. His liver was palpable 5 cm below the costal margin, and the spleen was enlarged, 1 cm below the costal margin. The laboratory assessment showed leukocyte counts of 14600 cells/μL, neutrophils 3400 cells/μL, lymphocytes 11060 cells/μL, hemoglobin 4.8 g/dL, platelets 10000/μL, bilirubin 4.9 mg/dL, all unconjugated. The direct Coombs' test was positive. Serum immunoglobulin levels were normal for his age (IgG 518 mg/dL, IgA 87 mg/dL, IgM 116 mg/dL). The child was treated with prednisone and intravenous immunoglobulin (IVIg) with complete resolution of symptoms. In the following years, recurrent episodes of bleeding associated with thrombocytopenia and other episodes of acute hemolysis occurred, and a chronic treatment with corticosteroids was employed; on one occasion a further IVIg treatment was necessary to recover a good platelet level. Because of the combination of immune thrombocytopenia and autoimmune hemolytic anemia, Evans syndrome was diagnosed. A recent study has demonstrated that numerous patients with Evans syndrome may have autoimmune lymphoprolipherative syndrome.[3,4] Therefore, because of cytopenia, persistent hepatosplenomegaly, and the finding of cervical lymphadenopathy, FAS-mediated apoptosis was analyzed in our patient, despite the normal results. The number of $CD3^+CD4^-CD8^-$ cells was never tested. Moreover, since the age of one year he has suffered from recurrent respiratory infections and frequent episodes of gastroenteritis.

When he was seven years old, he was admitted to our hospital because of one episode of fever, coughing, vomiting, and abdominal pain. A chest X-ray showed bronchopneumonia. Laboratory investigations were carried out and showed low levels of γ-globulin on serum protein electrophoresis (0.35 g/dL; 5.4%, normal range: 7.7-17%) with normal serum albumin (4.5 g/dL, 65.5%). Immunoglobulin levels were tested and found to be impaired: IgG 283 mg/dL (age-related normal range: 625-1165 mg/dL), IgA undetectable, and IgM 87 mg/dL. The lymphocyte subsets (Table 1) showed slightly low $CD3^+$ and $CD4^+$ T cells, when compared to normal age values. Antibody responses to tetanus and to hemophilus B antigens were poor (tetanus IgG 0.2 IU/mL, hemophilus B IgG 2.5 mg/L). Based on the finding of hypogammaglobulinemia with normal B cell number, common variable immunodeficiency was suspected initially and replacement therapy with intravenous immunoglobulin was started. A dose of 400 mg/kg was administrated every 28 days. Because of his clinical history, a second examination by a clinical geneticist was requested in February 2009: mild but significant facial abnormalities were noticed (narrow palpebral fissures, a slightly bulbous nose with hypoplastic nares, large and low-set ears), and a 22q11 DS was clinically suspected and then confirmed by FISH analysis. Therefore a diagnosis of partial DiGeorge syndrome was made.

Consequently, a cardiological evaluation was performed and no congenital heart defect was found. The ENT evaluation showed slight velopharyngeal insufficiency that justified his nasal speech. Bone mass and metabolism were normal (ionized and total calcium, phosphate, parathyroid hormone, 25-hydroxyvitamin D,

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Table 1. Lymphocyte subsets – absolute number.

Lymphocytes	Patient (cells/μL)	Age-related normal value (cells/μL)
$CD19^+$	517	300-700
$CD3^+$	1053	1100-2800
$CD3^+CD4^+$	574	500-1800
$CD3^+CD8^+$	398	400-1200
$CD3^-CD16^+CD56^+$	149	100-600
CD4/CD8	1.4	1.4-2.7

1,25-dihydroxyvitamin D, serum osteocalcin levels, urinary deoxipyridinoline concentration, and dual energy X-ray absorptiometry were evaluated). Neonatal hypocalcemia was never detected, and titanic seizures or tremori were never shown. Besides immunological and hematological follow-up, an educational assessment was performed and the child was introduced to a neuropsychological follow-up.

Discussion

The immunodeficiency arises as a consequence of thymic hypoplasia in patients with the deletion syndrome. Patients with a complete absence of the thymus ("complete" DiGeorge syndrome) exhibit severe T-cell immunodeficiency with a severe combined immunodeficiency phenotype requiring immune reconstitution by bone marrow transplantation or thymic transplantation.[5-7] However, "complete" DiGeorge syndrome accounts for <1% of patients.[8,9] The majority of patients with 22q11.2 DS and immune defects exhibit mild to moderate deficits in T-cell numbers (so-called "partial" DiGeorge syndrome). Studies of humoral deficiencies in 22q11.2 DS patients have yielded conflicting results.[9-12] Evidence of partial antibody deficiency (IgA deficiency, IgM deficiency, IgG subclass deficiency, specific antibody deficiency, or specific antibody responses to pneumococcal polysaccharide antigen) has been reported rarely,[11,13,14] but no mention of a deficiency of almost two classes of antibodies associated with chromosome 22q11.2 DS is found in the literature.

In the 22q11.2 DS, autoimmune disease may occur in up to 30% of patients and includes autoimmune cytopenias, autoimmune endocrinopathies, and autoimmune arthritis.[15-18] Previous studies reported cases of autoimmune hemolytic anemia and immune thrombocytopenia, but only a few patients with Evans syndrome have been described.[15,16,19-21] To the best of our knowledge, the association of Evans syndrome, hypogammaglobulinemia, and 22q11.2 DS has not been reported before.

Early diagnosis of 22q11.2 DS is extremely important for early evaluation of all the clinical and functional aspects of the syndrome (endocrine, immunological, cardiac, neuropsychiatric, etc.), so as to begin a prompt therapeutic program. We concluded that hematologists should consider the possibility of the 22q11.2 DS in children of all ages who present with Evans syndrome associated with hypogammaglobulinemia and mild facial anomalies.

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