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.7 More than 90% of the patients are hemizygous for a 1.5-3 Mb deletion within the 22q11.2 region.8 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 anaemia, Evans syndrome was diagnosed. A recent study has demonstrated that numerous patients with Evans syndrome may have autoimmune lymphoproliferative syndrome.14 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 CD2+ 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 nare, 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,
autoimmune cytopenias, autoimmune endo -
occur in up to 30% of patients and includes
important for early evaluation of all the clinical
Evans syndrome have been described.15,16,19-21To
bocytopenia, but only a few patients with
some 22q11.2 DS is found in the literature.
and 22q11.2 DS has not been reported before.
classes of antibodies associated with chromo-
Studies of humoral deficiencies in 22q11.2 DS
account for <1% of patients.8,9 The majority of
and functional aspects of the syndrome
(endocrine, immunological, cardiac, neuropsy-
chiatric, etc.), so as to begin a prompt thera-
peutic program. We concluded that hematol-
 gist should consider the possibility of the
22q11.2 DS in children of all ages who present with
Evans syndrome associated with hypo-
gammaglobulinemia and mild facial anom-
malies.

## Discussion

The immunodeficiency arises as a conse-
quence of thymic hypoplasia in patients with
the deletion syndrome. Patients with a com-
plete absence of the thymus (“complete” DiGeorge syndrome) exhibit severe T-cell
immunodeficiency with a severe combined
immunodeficiency phenotype requiring
immune reconstitution by bone marrow trans-
plantation or thymic transplantation.5-7

Evidence of partial antibody deficiency (IgA
deficiency, IgM deficiency, IgG subclass defi-
cency, specific antibody deficiency, or specific
antibody responses to pneumococcal polysac-
charide antigen) has been reported rarely,11,13,14
but no mention of a deficiency of almost two
classes of antibodies associated with chromo-
some 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 endo-
 crinopathies, and autoimmune arthritis.15,18
Previous studies reported cases of autoimmune
hemolytic anemia and immune thrombocy-
tenopathy, but only a few patients with
Evans syndrome have been described.15,18,11,13-15
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

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<th>Table 1. Lymphocyte subsets – absolute number.</th>
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<tr>
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<td>CD3⁺CD16-CD56⁺</td>
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<td>CD4⁺CD8⁻</td>
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1.25-dihydroxyvitamin D, serum osteocalcin levels, urinary deoxypyridinoline concentra-
tion, 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.