



DiGeorge sequence with hypogammaglobulinemia: a case report

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The most common immunodeficiency in DiGeorge sequence patients is defects in T-cell production due to insufficient thymic tissue. However, because T-lymphocytes are important in regulating antibody responses, DiGeorge sequence is no longer regarded as a pure deficiency of cellular immunity but also a form of variable-combined immunodeficiency. Here we presented a 4-month-old male infant with characteristic facial dysmorphism, thymus dysplasia, tetralogy of Fallot, and documented deletion of chromosome 22q11.2 who had decrease B-lymphocyte numbers and hypogammaglobulinemia. The mitogen responses of T-lymphocytes function were normal with adequate number of CD4⁺ lymphocytes. This case report highlights the importance of evaluating not only the cellular but also the humoral immune function in patients with DiGeorge sequence.

Key words: DiGeorge sequence, humoral immunodeficiency, hypogammaglobulinemia

DiGeorge sequence (DGS) (OMIM 188400) comprises hypocalcemia arising from parathyroid hypoplasia, thymic hypoplasia, and characteristic facial and cardiovascular abnormalities [1]. Most cases result from a submicroscopic deletion within chromosomal region of 22q11.2. Several genes, including TUPLE1/HIRA, IDD/DGCR2/LAN, DVVL-22, UFD1L, GSCL, and TBX1, are located within critical region of DGS and are potential candidate genes [2]. A collective acronym CATCH22 has been proposed for differing presentations of cardiac abnormality or abnormal facies, T-cell deficit due to thymic hypoplasia, cleft palate, and hypocalcemia due to hypoparathyroidism resulting from 22q11 deletion.

Due to thymic hypoplasia, patients with DGS may show variety of immunological abnormalities depending on the degree of T-cell deficiency and increased susceptibility to infection [3]. With regard to humoral immunity, patients usually have normal or increased numbers of circulating B-lymphocytes and normal serum immunoglobulin levels [4]. However, it has seldom been reported that patients with DGS have hypogammaglobulinemia [4,5]. Here, we describe a male patient with characteristic facial dysmorphism, thymus dysplasia, tetralogy of Fallot, and documented deletion of chromosome 22q11.2 who had decreased B lymphocyte numbers and hypogammaglobulinemia.

This report highlights the importance of evaluating not only the cellular but also the humoral immune function in patients with DGS.

Case Report

A 4-month-old male infant was admitted because of crying cyanosis and failure to thrive. The patient was the third child of healthy non-consanguineous parents, and there was no familial evidence of immunodeficiency. He was a small-for-date premature infant (2000 g, 36 weeks of gestational age). Vaccination history included hepatitis B vaccine for twice and diphtheria and tetanus toxoids with pertussis combined vaccine plus oral polio vaccine for once without major complication. There was no history of tetany in early infancy or chronic diarrhea. Physical examination on admission revealed dysmorphic face, fever, a grade 2/6 continuous heart murmur heard at left sternal border, and bilateral inguinal hernia. The dysmorphic face included a hypoplastic mandible with U-shaped mouth, hypertelorism, broad nose bridge, and malformed, dorsal rotated ears. There was no cleft palate or high-arched palate.

Laboratory investigations were as follows: hemoglobin 1.96 mM, white blood cell counts 8860 x 10⁶ cells /L (82% segmented neutrophils, 15% lymphocytes, 1% eosinophils, 1% monocytes), serum urea 2.5 mM, creatinine 35 μM, albumin 30 g/L, globulin 21 g/L, calcium 2 mM, phosphate 2.9 mM. Chest X-ray showed heart apex elevation and no thymus shadow. Cardiac catheterization showed tetralogy of Fallot with pulmonary atresia. He received operation

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Fig 1. Deletion of 22q11.2 revealed by fluorescence *in situ* hybridization analysis. The TUPLE1 gene labeled with spectrum orange is located within critical region of DGS and ARSA gene labeled with spectrum green is located within 22q13.3 and is used as control signal (Vysis, IL, US). All metaphase and interphase cells analyzed showed hemizygous deletion of TUPLE1 gene.

for ventricular septal defects repair and right ventricle outlet tract and main pulmonary artery reconstruction when he was 5-month-old. All cultures in admission including virus, bacteria, and fungus showed no growth although he had intermittent fever and received antibiotics. He was admitted again when he was 6- and 9-month-old due to cyanosis, tachypnea, and fever. Tracheobronchomalacia and brain atrophy with ventriculomegaly were also noted during hospitalization by bronchoscopy and brain magnetic resonance imaging, respectively. He had persistent fever due to repeated sepsis and pneumonia caused by *Chlamydia*, *Burkholderia cepacia*, oxacillin-resistant coagulase-negative *Staphylococcus*, and fungus. Proper antibiotics and antifungal medications were used and his condition improved gradually.

Due to the characteristic dysmorphic face, thymus dysplasia, and congenital heart disease, fluorescence *in situ* hybridization analyses were performed using a probe located within a critical region of DGS to detect submicroscopic deletions of 22q11.2. All metaphase cells and interphase cells analyzed showed deletion within the critical region (Fig. 1). Results of immunological investigation when he was 1 year old were as follows: immunoglobulin (Ig)G 95.2 mg/dL; IgA 6.58 mg/dL; and IgM 43.6 mg/dL. A lymphocyte subset analysis showed T cell 48%, B cell 8%, NK cell 39%, CD4⁺ 36% (naive 26%, memory 10%), and CD3⁺CD8⁺ 8%. Total lymphocyte counts were 2390 / mm³. The proliferative responses of T cells to concanavalin A (40 µg/mL), phytohemagglutinin (4 µg/

mL), pokeweed mitogen (4 µg/mL), and anti-CD3/anti-CD28 (each 2 µg/mL) were not different from the control. The ultrafast computed tomography showed no thymus tissue at normal position. The family refused bone marrow aspiration. He received regular intravenous immunoglobulin treatment 1 g/kg per month and remained hypogammaglobulinemia after 3 months when he was discharged. However, he was admitted 1 month later due to thrombocytopenia and hypotension and then expired when he was 2-year-old due to acute renal failure suspecting cardiac failure or sepsis induced.

Discussion

The most common immunodeficiency in DGS patients was defects in T-cell production due to insufficient thymic tissue, followed by impaired T-cell function, and humoral dysfunction [6]. The immunodeficiency did not correlate with any individual clinical finding or constellation of clinical findings [6]. The absolute lymphocyte count and the CD3, CD4, and CD8 counts were significantly lower in the chromosome 22q11.2 deletion syndrome group [7]. The most reliable predictors of a persistent immune defect were a mitogen response to phytohemagglutinin of less than 10 times background and a total of less than 400 CD4⁺ T lymphocytes /mm³ [8]. However, this case showed adequate CD4⁺ lymphocyte and adequate response to mitogens. Because of this inability to accurately predict which patient will have significant immunocompromised, each patient with a deletion of chromosome 22q11.2 should be evaluated for immunodeficiency [6] and the risk associated with immunodeficiency may represent a critical factor in the management of these patients.

Humoral immune function has not been well studied in DGS. Sullivan *et al* [6] found that impaired humoral function was observed in 15% DGS patients and no patients with severe combined immunodeficiency. These patients can have hypergammaglobulinemia, autoantibodies, and elevated levels of antibodies to natural antigens [3,6] mainly due to remained thymus tissue, but the response to bacterial polysaccharides immunization was poor which may be due to circumscribed lesions in helper T-cell populations [9, 10]. However, B cell numbers were not significantly different between the chromosome 22q11.2 deletion group and the control group although the numbers improved when the thymus-derived lineages improved in the first year of life [7]. There is only little or no somatic mutation in B-lymphocyte immunoglobulin genes in severely T-cell-deficient patients with DGS [11]. Since obviously T lymphocytes have an important

role in regulating antibody responses by B-lymphocytes, DGS is no longer regarded as a pure deficiency of cellular immunity, but has been found to be a form of variable-combined immunodeficiency [6].

In most cases of the DGS, T-cell subpopulation studies have shown an increase in the helper (CD4)-to-suppression (CD8) ratio, due mainly to a decrease in the CD8 population [12]. The decrease in suppressor T-cell number caused marked reduction in suppressor activity [13]. The decrease in suppressor function in this syndrome may even lead to autoimmune disease [14,15]. Lymphocytes of DiGeorge patients spontaneously produced immunoglobulin *in vitro* with low numbers of CD8⁺ cells and stop production when the CD8⁺ number increased [12]. Previously, this phenomenon of cellular immunodeficiency with normal or exaggerated autoimmune manifestations is most probably due to the fact that thymic hormones induce T-suppressor lymphocytes [16]. However, in this case, the decrease of T-suppressor lymphocytes was associated with low B-cell numbers. The case points the importance of further studies to evaluate the exact function of the thymus and its hormones in the development and function of the various T-cell subsets and the regulation to B-lymphocyte maturation.

Hypogammaglobulinemia in DGS has seldom been reported, and the pathogenesis remains unclear [4]. Since DGS patients usually have normal or increased numbers of B cells, it is likely that deficient regulatory T-cell functions due to T-cell immaturation may cause insufficient helper activity, especially at the terminal differentiation stage of B cells, resulting in hypogammaglobulinemia [4]. Another possibility is the deletion of 22q11.2 in this case also involves the lambda light chain gene located in this region. Minegishi *et al* [17] found that mutations in the human lambda 5/14.1 gene result in B-cell deficiency and agammaglobulinemia, and these findings indicated that expression of the functional lambda 5/14.1 is critical for B-cell development in human. In this case, he had low CD8⁺ lymphocytes and low B-lymphocyte counts with low immunoglobulin production, contrasted to the case presented by Mayumi *et al* [4] and the study of Durandy *et al* [12]. Long-term follow up including a clinical history and repeated immune studies is necessary for the child's immune status, although there could be spontaneous significant improvement in thymus-derived cell lineages as well as B-cell numbers over the first year of life which may be due to improved T-cell help [7, 8]. Human leukocyte antigen-identical bone marrow transplantation and postnatal or fetal thymus transplantation might be helpful for normalizing

immunoglobulin production if persisted immunodeficiency being demonstrated [4,18].

In conclusion, DGS is no longer regarded as a pure deficiency of cellular immunity but a form of variable combined immunodeficiency. Each patient with a deletion of chromosome 22q11.2 should be evaluated for immunodeficiency, and the risk associated with a cellular and a humoral immunodeficiency may represent a critical factor in the management of these patients.

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