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Case Report
Partial DiGeorge Syndrome Presenting with Congenital Heart Disease and Palatal Abnormalities in Children: A Case Report

Shirin Tarafder

Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Abstract

The term complete DiGeorge Syndrome (DGS) is used to describe patients with DGS who are athymic and have no circulating T-cells, this group constitutes less than 1% of all DGS cases. Patients with partial DGS have thymic hypoplasia that is evidenced by the presence of circulating T-cells. The case report is of a 1.3 year (15 months) boy with recurrent upper respiratory tract infections, congenital heart defects, cleft palate and predominant motor delay. The laboratory investigations confirmed the diagnosis as partial DiGeorge syndrome as there was decreased CD3+T-cells and its subsets (CD3+CD4+T-cells and CD3+CD8+T-cells), but not below 50 cells μL^{-1}, thymic aplasia, hypoparathyroidism and chromosome 22q11.2 deletion by fluorescence *in situ* hybridization (FISH) analysis. This case report demonstrates that DiGeorge syndrome should be considered when there is congenital cardiac abnormalities, recurrent infections, developmental delay, hypoparathyroidism and immune deficiencies as the early diagnosis of 22q11.2 DS is critically important to effectively treat this disorder.

Key words: Partial DiGeorge syndrome, chromosome 22q11.2 deletion, primary immunodeficiency disorder, congenital heart defect, cleft palate

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Corresponding Author: Shirin Tarafder, Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

DiGeorge syndrome type 1 (DGS1), also known as 22q11.2 deletion syndrome (22q11.2 DS) is estimated to be the most prevalent inheritable genetic deletion syndrome, occurring in ~1 in 3,000 live births[1]. DiGeorge syndrome is a well-defined primary immunodeficiency disorder caused by an embryopathy it presents with a number of clinical symptoms arising from the disturbed development of the 3rd and 4th pharyngeal arches, chief amongst which are congenital heart, great vessel and parathyroid gland defects as well as a typical malformation of the face and soft palate[2]. Other clinical abnormalities include psychosocial, cognitive, developmental delay, psychiatric illnesses, growth retardation, immune defects, renal anomalies and abnormal craniofacial findings[3,4]. Depending on whether thymic hypoplasia or aplasia is present, DGS can be classified as partial or complete. The term complete DGS is used to describe patients with DGS who are athymic and have no circulating T-cells this group constitutes less than 1% of all DGS cases. Patients with partial DGS have thymic hypoplasia that is evidenced by the presence of circulating T-cells[5]. However, despite the obvious phenotypic abnormalities in many patients with 22q11.2 DS, the average age of diagnosis for a person with this syndrome is 6-7 year[6]. The early diagnosis of 22q11.2 DS is critically important to effectively treat this disorder.

Children and adolescents with congenital heart defects and palatal abnormalities can be admitted in a pediatric department initially before being diagnosed with DGS. Here, a case of a child has been reported who demonstrated similar features of partial DGS and were initially admitted to a pediatric department prior to the exact diagnosis.

CASE REPORT

The patient was a 1.3-year-old boy born to unrelated healthy parents. The boy was admitted in a hospital under pediatrician to evaluate recurrent upper respiratory tract infections. He was referred to our department to evaluate cellular and humoral immunity status. Past medical history showed no known exposure to radiation or drugs during mother's pregnancy. Birth weight of the boy was 2.6 kg was admitted in Neonatal Intensive Care Unit (NICU) since birth for respiratory distress due to aspiration of amniotic fluid. The child was diagnosed with atrial septal defect (ASD, 3.0 mm) and Ventricular Septal Defect (VSD, 1.8 mm) at day 1 of life. However, no intervention was required. Currently the VSD has closed and 1.5 mm ASD present. At 10 months of age he developed aspiration pneumonia and was discovered to have cleft palate. It was operated at 12 months of age. The boy had history of recurrent respiratory infections since 4 months of age in form of fever, cough, runny nose and was treated on OPD basis with antipyretics and oral antibiotics. At 14 months of age he developed fever for 15 days, relieved for 2-3 days but recurred. There was no history of ear discharge, oral thrush, diarrheal illness and skin lesions. On physical examination there was sub-centimetric cervical lymphadenopathy. X-ray chest for lung was normal. The boy had predominant motor delay, could not stand without support. Immunization history was complete. There was no family history of similar illness. Genetic consultation was taken in view of some dysmorphic features, however they were opined to be not significant for this age.

LABORATORY INVESTIGATIONS

The immunological studies revealed lymphocytes were 18.7% (ref. value upto 61%) of total leukocyte population, but absolute count was decreased, 2805 cells μL^{-1} (ref. range 3320-7006). There was decreased absolute count of CD3+T-cells (844 cells μL^{-1}, ref. range: 2542-4933 cells μL^{-1}), CD3+CD8+T-cells (508 cells μL^{-1}, ref. range 636-1432 cells μL^{-1}) and grossly decreased CD3+CD4+T-cells (17 cells μL^{-1}, ref. range: 1573-2949 cells μL^{-1}) with altered CD4: CD8 ratio (0.03, ref. range: 1.34-3.04) (Fig. 1). Absolute count of CD19+B-cells and CD56+NK cells were within normal range. Naïve T-lymphocytes (CD3+CD45RA+) and naïve cytotoxic T-cells (CD3+CD8+CD45RA+) were slightly decreased. Immunoglobulin levels were as follows: IgM 50 mg dL^{-1} (ref. range: 50-220 mg dL^{-1}), IgA 30 mg dL^{-1} (ref. range: 30-120 mg dL^{-1}) and IgG 871 mg dL^{-1} (ref. range: 310-1380 mg dL^{-1}). In this case IgM and IgA levels were decreased. A complete blood count was as follows: Hemoglobin, 9.5 g dL^{-1}, ESR, 60 mm 1st h, platelets, 350000 cm m^{-1} and white blood cell count 15000 cm m^{-1} with 74% neutrophils, 22% lymphocytes, 2% monocytes and 2% eosinophils. Serum calcium level was decreased, parathyroid hormone and vitamin D levels were normal, but phosphorus level was increased. Despite the normal parathormone levels, the presence of hyperphosphatemia and low serum calcium level suggested a possible diagnosis of hypoparathyroidism. Possibility of partial DiGeorge syndrome was kept as there was decreased CD3+T-cells and its subsets (CD3+CD4+ and CD3+CD8+T-cells), but not below 50 cells μL^{-1} which is a cardinal feature for the diagnosis of complete DiGeorge syndrome. Serum sodium, potassium, alkaline phosphatase, transaminases and serum proteins were normal. Urine calcium/creatinine ratio was 0.15. Test for

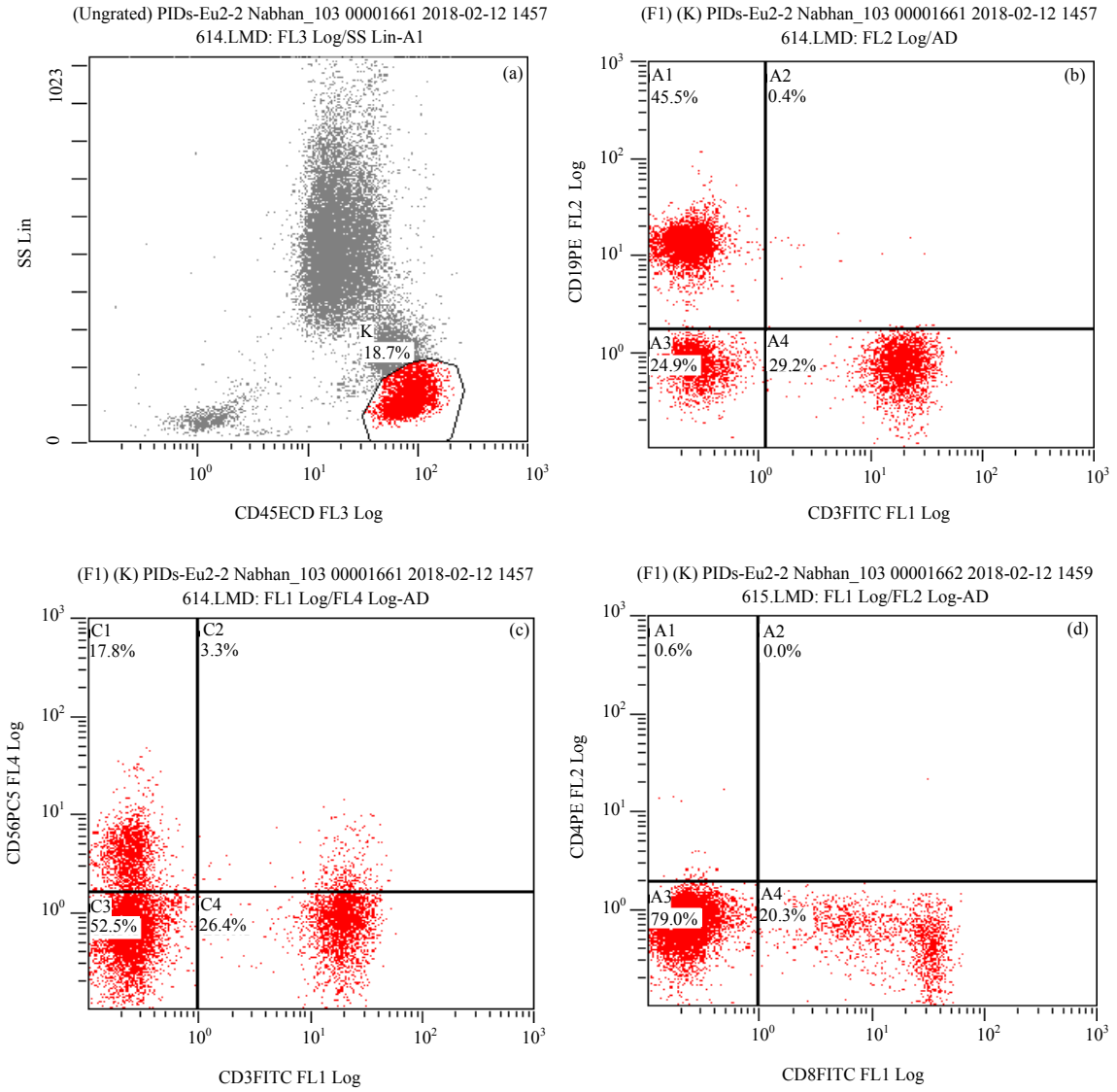

Fig. 1(a-d): Flow cytometric immunophenotyping of lymphocytes in blood (a) Low SSC with bright CD45 expression in lymphocyte window (18.7%), (b) CD19+B-cells in SSC, CD3+T-cells in FSC, (c) CD56+NK cells in SSC and CD3+T-cells in FSC and (d) CD4+T-cells (grossly decreased) in SSC and CD8+T-cells in FSC

[x]This dot plot diagram is original laboratory work analyzed in our department in blood of the boy of this case report

chronic granulomatous disease was negative. Ultrasonogram and CT scan revealed absent thymus. Fluorescent *in situ* hybridization (FISH) by using VYSIS DNA probe kit for TUPLE1 (22q11.2)/ARSA (22q13.3) dual color probe was performed showed the chromosome 22q11.2 deletion and confirmed the diagnosis of DiGeorge syndrome. The child was finally diagnosed as partial DiGeorge syndrome having decreased CD3+T-cells and its subsets along with chromosome 22q11.2 deletion. The child was started on Cotrimoxazole prophylaxis.

DISCUSSION

DiGeorge syndrome was initially described by Angelo DiGeorge a physician and pediatric endocrinologist in 1968[7]. It is also known as velocardiofacial syndrome or CATCH 22 syndrome to describe the classical features of this syndrome (C-Congenital heart disease, A-Abnormal facies, T-Thymus hypoplasia, C-Cleft Palate and H-Hypocalcemia) due to hypoparathyroidism. Autoimmune disorders, skeletal defects, renal abnormalities, psychiatric and behavioral

disorders are also associated with this syndrome[8]. The congenital heart defects, cleft palate and thymic aplasia observed in this reported patient are compatible with a diagnosis of DiGeorge syndrome.

Congenital conotruncal cardiac defects that involve truncoaortic sac can present in 70% patients with DiGeorge syndrome. The most common cardiac anomalies are interrupted aortic arch, tetralogy of fallot, atrial septal defect and ventricular septal defects[8-10]. The boy in the reported case had Atrial Septal Defect (ASD) and Ventricular Septal Defect (VSD) at day 1 of life. However, no intervention was required. Currently the VSD has closed and 1.5 mm ASD present. The cardiovascular malformations observed in this child were consistent with those in the reported cases of DiGeorge syndrome.

The severity of immunodeficiency varies among DGS patients. Most have a mild form characterized by a small, histologically normal thymus, low absolute T-cell numbers and normal or near-normal T-cell functions[11]. The thymus could not be revealed by ultrasonogram and CT scan, but serum parathyroid hormone level was within normal limit in this reported case. Lischner[12] proposed that a partial DiGeorge syndrome exists. There may be some thymic tissue in such cases. There was decreased cellular immunity in this boy, which is in favor of partial DiGeorge syndrome.

The specific FISH test for chromosome 22q11.2 deletion is the standard method for diagnosis of DGS. The wide availability of commercial FISH probes has enhanced the clinician's ability to diagnose and treat the affected children rapidly[13]. Chromosome 22q11.2 deletion has been demonstrated by FISH method in this patient.

CONCLUSION

The DGS is relatively common and this diagnosis should be considered in patients who have congenital cardiac abnormalities, recurrent infections, developmental delay, hypoparathyroidism and immune deficiencies, as the early diagnosis of 22q11.2 DS is critically important to effectively treat this disorder.

SIGNIFICANCE STATEMENT

This study observes that pediatricians should be aware of DiGeorge syndrome when children and adolescents with congenital heart defects and palatal abnormalities can be admitted in a Pediatric Department. The early diagnosis of 22q11.2 DS is critically important to effectively treat this disorder because 75% of children with DGS1 have severe congenital heart disease requiring early intervention.

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