



# Cardiac aspects of DiGeorge syndrome: a report of two cases with molecular analysis

Senka Mesihović Dinarević, Emina Vukas\*

Pediatric Clinic, Clinical Centre University of Sarajevo, Patriotske lige 81, 71000 Sarajevo, Bosnia and Herzegovina

## ABSTRACT

DiGeorge syndrome (DGS) which is also known as velocardiofacial syndrome is caused by a submicroscopic chromosome deletion of band 22q11. It is associated with a disturbed development of the pharyngeal arches. In this report we describe two unrelated male children with clinical features consistent with 22q11.2 microdeletion syndrome characterized by cardiac defect, recurrent respiratory infections and developmental deficiency. Definitive diagnosis is made by Fluorescence In Situ Hybridization analysis (FISH). Children underwent surgical correction of congenital heart defects. During surgery thymic aplasia was confirmed in both children, postoperative course proceeded without major complications. Our report suggests that the criteria in searching for microdeletion 22q11.2 should be expanded and applied in patients with conotruncal and non-conotruncal congenital heart defects and at least one typical feature of this syndrome.

**Keywords:** DiGeorge syndrome, congenital heart disease, microdeletion

## INTRODUCTION

Congenital heart disease (CHD) is the most common birth defect and the leading cause of mortality in the first year of life with a prevalence of 1% in live births and 10% in spontaneously aborted fetuses (1). CHD is a disorder mainly characterized by: a) 90% multifactor disorders, b) 8% chromosomal and single gene disorders and c) 2% environmental teratogens (2). Among chromosomal disorders is DiGeorge syndrome (DGS) which is also known as velocardiofacial syndrome, caused by a submicro-

scopic chromosome deletion of band 22q11. It has malformations attributed to abnormal development of the pharyngeal arches and pouches. The common thread among all the organs involved in DiGeorge anomaly is that their development depends on migration of neural crest cells to the region of pharyngeal pouches.

Clinical features of this syndrome are: congenital cardiac defects, congenital immunodeficiency secondary to aplasia or hypoplasia of the thymus, and hypocalcaemia due to small or absent parathyroid glands, cognitive, behavioral, and psychiatric problems and increased susceptibility to infections (3,4).

One of the most widely cited article estimated that prevalence rate for DiGeorge syndrome is approximately 1 in 4,000 live births (5,6). In Federation of Bosnia and Herzegovina in the period between 2008

\*Corresponding author: Emina Vukas  
Pediatric Clinic, Clinical Centre University of Sarajevo,  
Patriotske lige 81, 71000 Sarajevo, Bosnia and Herzegovina  
Phone: +387 61 364 347  
E-mail: emina.vks@gmail.com

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**TABLE 1.** Findings related to DiGeorge syndrome in the two patients

Features of DGS	Patient 1	Patient 2
Dysmorphic findings	broad nose, nostrils in anteversion, wrinkled forehead, deep-set eyes. Ears were low set, deficient in vertical diameter and dysplastic	-
Thymic hypoplasia/aplasia	Thymic aplasia	Thymic aplasia
Recurrent infection	Four episodes of respiratory infection	-
Hypoparathyroidism	-	-
Heart defect	Tetralogia Fallot	Interruption of the aortic arch, VSD, DAP, stenosis of the left pulmonary artery.
Count of Lymphocytes	16.5%	16.7%

– 2013, there have been two cases of DiGeorge syndrome, prevalence rate is approximately 1:10.000 live births, probably because we do not have the data from whole country of Bosnia and Herzegovina, as well as because certain number of this syndrome is not associated with CHD and remain undiagnosed. We report two cases of congenital heart disease with confirmed microdeletion chromosome 22q11.2 by karyotype and Fluorescence In Situ Hybridization analysis (FISH).

## CASE REPORTS

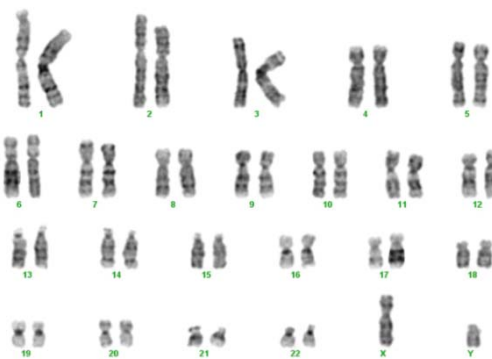
### Case 1.

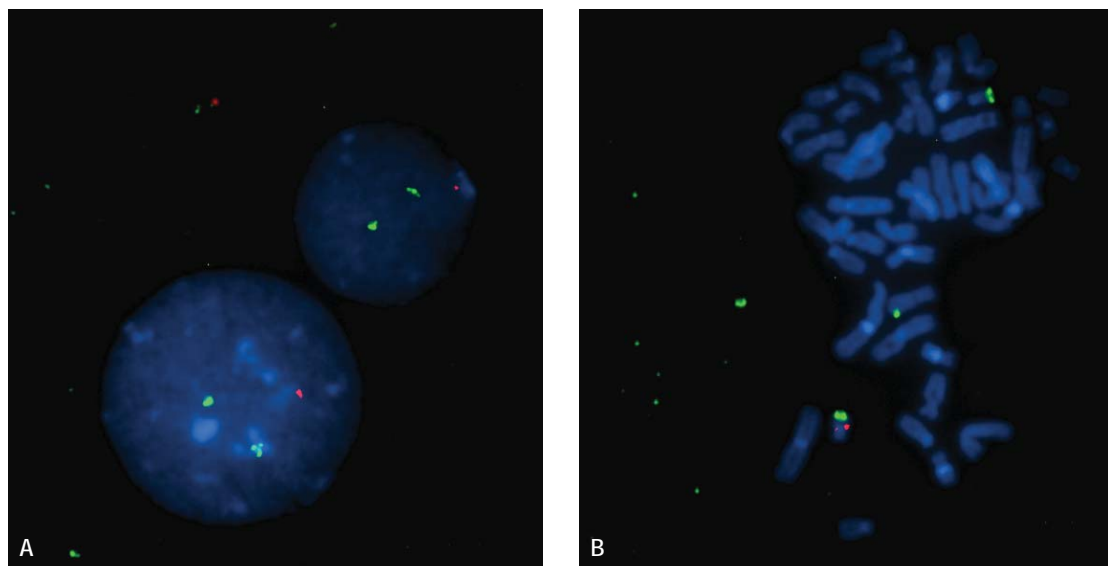
A ten months old male infant was referred to our Clinic for operative correction of congenital heart defect. The child was born as a preterm neonate in 35 week of gestation by vaginal delivery at local hospital, birth weight 2900 grams. He was forth born child. Other children were normal. There was no history of antenatal complications. Sucking reflex was normal. Early psychomotor development was delayed, he was unable to sit, had recurrent episodes of respiratory infection, for which he was hospitalized for the treatment. There was no similar problem in the family in either sides. Physical examination revealed dysmorphic features, hypotrophic musculature, dyspnea, pallor. His weight was 6.29 kg,  $p < 3$ , had broad nose, nostrils in ante version, wrinkled forehead, deep-set eyes. Ears were low set, deficient in vertical diameter and dysplastic. Slim and long fingers on hands and feet. Extensive cardiovascular work up including echocardiography, confirmed Tetralogy of Fallot. There was no hypocalcemia, normal count of immunoglobulins and decreased

number of lymphocytes. On X ray of the chest, thymus shadow was not visible. Thymic aplasia was confirmed during the operation of CHD. Operative and postoperative course, passed without complications, child was discharged home, recovered, on 10<sup>th</sup> day of hospitalization. Three years follow up, child is in good general condition, body weight 15.2 kg ( $p$  10), echocardiogram shows unchanged hemodynamic without residual shunt at the ventricular level, RVOT with PG 28/10 mmHg, without effusion, thrombus, vegetation, LV EDD (end diastolic diameter), 30 mm, 18 mm ESD (end systolic diameter), septum and LVPW (left ventricular posterior wall) 5 mm, 40% FS.

### Case 2.

A seven days old male newborn was admitted in local hospital in a state of circulatory shock, cardio respiratory decompensated, in severe metabolic acidosis. After condition has stabilized (intubation, complete

**FIGURE 1.** Karyotype – patient 1



**FIGURE 2.** FISH for Case 1. Metaphase and interphase cells hybridized with LSI N25 region probe by Visisa, Inc. The absence of one red signal indicates that the region 22q11.2 microdeletion is present.

mechanical ventilation, inotropic support), echocardiogram was realized, which confirmed complex congenital heart anomaly, prostaglandins were administered and the newborn was transferred to the Pediatric Clinic, Department of Neonatal Intensive Care Unit for additional diagnostic and surgical treatment. The child was born as a term neonate by vaginal delivery at local hospital, birth weight 3130 grams. He was second born child. There was no history of antenatal complications. Sucking reflex was normal. His weight was 2.89 kg,  $p < 3$ . Extensive cardiovascular work up including echocardiography and CT angiography confirmed interruption of the aortic arch, ventricular septal defect, patent ductus arteriosus, pulmonary artery dilatation and stenosis of the left pulmonary artery. There was no hypocalcaemia. During the operation of CHD thymic aplasia was confirmed. Surgical correction was uneventful, except the appearance of nodal tachycardia which was successfully treated by medications. Postoperatively patient was hemodynamic stable, eighth postoperative day control ultrasound of the heart showed good postoperative result, except pericardial effusion (3 mm), the treatment included non-steroidal anti rheumatic drugs on which we received a favorable response. Discharged from the hospital fourteenth postoperative day, recovered.

On the control examination, nine months after operative procedure, body weight 9.9 kg, vital parameters in the reference values for age. An ultrasound of the heart hemodynamic unchanged, Ao ascendens flow in the systole normal. Ao descendens at systole PG 30 mmHg, LK EDD 23 mm, ESD 13 mm, S and LVPW 6 mm, FS 40%.

Since the both patients had findings suggestive on DiGeorge syndrome, karyotype and FISH analysis was done. Deletion of 22q11.2 region on the q arm of chromosome 22 has been determined by the LSI N25 Spectrum Orange/LSI ARSA SpectrumGreen FISH probe and 90% cells had deletion of 22q11. Deletion 22q11.2 region, is a microdeletion that cannot be determined by karyotype analysis (Figure 1.), only by the FISH analysis (Figure 2).

## DISCUSSION

Approximately 75–80% of patients with DGS have congenital heart disease with conotruncal and ventricular septal defects. Various cardiac malformations are seen, particularly affecting the outflow tract (6). In a series of 545 patients with 22q11 deletions (7), only 20% had no cardiac defects (ie, based on clinical examination and echocardiography findings). The most common cardiac anomalies included Te-

tralogy of Fallot (17%), ventricular septal defect and interrupted aortic arch (14% each), pulmonary atresia/ventricular septal defect (10%), and truncus arteriosus (9%), other anomalies included pulmonic stenosis, atrial septal defect, atrioventricular septal defect, and transposition of the great arteries. Thy-mic hypoplasia/aplasia, palate defects and thyroid and parathyroid abnormalities were described as well. A congenital heart defect is the main cause of morbidity and mortality, but the underlying molec-ular pathobiology is not well understood. Mortality rate was 8% in a study with 558 patients (7). Most deaths in this study occurred within 6 months after birth. Infections due to severe immune deficiency are the second most common cause of mortality.

According to the current literature, in patients with Tetralogy of Fallot with/without pulmonary atresia and truncus arteriosus, in spite of the complex cardiac anatomy, the presence of 22q11.2 deletion syndrome does not worsen the surgical prognosis. On the contrary in children with pulmonary atresia with ventricular septal defect and in those with interrupted aortic arch the association with 22q11.2 deletion syndrome is probably a risk factor for the operative treatment (8).

In both our patients we had good postoperative out-come, although it was a complex CHD (Tetralogia Fallot and Interruption aortic arch).

The complex cardiovascular anatomy in association with depressed immunological status, pulmonary vascular reactivity, neonatal hypocalcemia, bron-chomalacia and broncospasm, laryngeal web, and tendency to airway bleeding must be considered at the time of diagnosis and surgical correction. Spe-cific diagnostic, surgical, and perioperative protocols should be applied in order to provide appropriate treatment and reduce surgical mortality and mor-bidity (8).

As for its diagnosis, high-resolution karyotyping has limitations and is able to identify less than 15% of affected patients. Fluorescence *in situ* hybridization (FISH), which can detect over 90% of the cases, is considered the gold standard (9). The wide avail-ability of commercial FISH probes has enhanced the clinicians' ability to diagnose and treat the af-fected children rapidly (10). Identification of these patients is essential for their adequate management and genetic counseling.

## CONCLUSION

Our report suggests that the criteria in searching for microdeletion 22q11.2 should be expanded and applied in patients with conotruncal and non-conotruncal congenital heart defects and at least one typical feature of this syndrome (facial dysmorphism, thymus hypoplasia/aplasia, cleft palate or hypocal-caemia). The phenotype can be extremely variable, frequently leading to clinical confusion, diagnostic delay, excess morbidity, early mortality. A multidis-ciplinary approach is fundamental to ensure that the patient will be able to attain his or her maximal potential.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

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