General approach to velocardiofacial anomalies: a pediatric case presenting with Fallot tetralogy

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ABSTRACT

Velocardiofacial syndrome (VCFS), also known as “Shprintzen syndrome” or “22q11.2 deletion syndrome” is an autosomal dominant genetic disorder with a wide range of phenotypical findings. It is majorly characterized by cleft palate, dysmorphic face, conotruncal cardiac anomalies, growth retardation, neurologic disorders and learning disabilities. Our case was the first child of her family and she had a cleft palate, dysmorphic face, tetralogy of Fallot (TOF), growth retardation and a mild neuromotor developmental delay. It is important to recognize this syndrome and inform the family about the probable future health problems of their babies as early as possible. Genetic counselling is crucial for the subsequent pregnancies. Therefore, we wanted to review the literature about the differential diagnosis and genetics of velocardiofacial anomalies.

Key words: Conotruncal cardiac anomaly; dysmorphic face; genetic counselling; 22q11 deletion.

CASE REPORT

Z.T. was a 11-month-old female baby. She was born at the 37th week of gestation weighing 2650 gr, and delivered by a cesarean section. She was followed in the neonatal intensive care unit for 2 weeks due to the respiratory insufficiency, cleft palate and feeding difficulty. At the first hospital visit after her discharge, pulmonary valvular stenosis and tetralogy of Fallot (TOF) were diagnosed on her echocardiograms. Balloon valvuloplasty was performed
when she was 4 month-old. She was referred to our hospital for the surgical correction of her cardiac anomalies at the 11 months. On her physical examination in our clinic, her body weight was 6300 gr. (<3 percentile), height 62 cm. (<3 percentile) and head circumference, 41 cm. (<3 percentile). She had a wide forehead, low nasal bridge, cleft palate, micro/retrognathia, hypoplastic maxilla and hypertelorism (Figure 1). Her heart rate was 130 bpm, respiratory rate was 32 breaths per minute with an oxygen saturation of 82% while breathing room air and her systemic blood pressure was 80/50 mmHg. She had bilateral sibilant rales and 2/6 systolic murmur at the pulmonic area on auscultation. Her liver was 3 cm. palpable below the subcostal margin and the spleen was nonpalpable. She had 3 hemangiomas with the diameters of 3 to 5 cm on her back. Her musculoskeletal and the genital examinations were within normal limits.

The mother of Z.T. was 26 and the father was 28 years old. There was no consanguinity between them and they had no dysmorphic facial appearance or any systemic illnesses. The mother had not received regular medical follow-ups during her pregnancy. She had never used tobacco or alcohol. There was no history of drug use or exposure to X-ray after she became pregnant. She had no history of infection, abortus or stillbirth, either. Their first degree relatives had not any congenital anomalies.

Biochemical and microbiological examinations of Z.T. showed mild infection with a white blood cell count of 13500/mm3, C reactive protein level of 2 mg/dl and 64% neutrophil dominancy (63%) on the peripheral blood smear, iron deficiency anemia and hypocalcemia with a serum calcium level of 7.3 mg/dl. Her 25 OH-D level was low (10 ng/ml), parathyroid and thyroid hormone levels were normal (15.2 pg/ml and 2.1 IU/ml, respectively). After treatment with calcium and vitamin D, her serum calcium levels have sustained within normal ranges. Serologic test results for toxoplasma, rubella and cytomegalovirus (TORCH) were negative. Her cardiothoracic ratio increased and the cardiac apex was elevated on the chest X-ray. On her echocardiogram, there was perimembranous ventricular septal defect, pulmonary stenosis, straddling tricuspid valve with a moderate degree of incompetence, patent ductus arteriosus, 50% dextroposition of aorta, tetralogy of Fallot and coronary arterial fistula on the ventricular septum. Abdominal ultrasonograms were normal except for a mild hepatomegaly.

As there were two afebrile seizure attacks in her neonatal history, electroencephalography (EEG) was performed. EEG reports indicated that there were sharp wave activities on the frontocentral, centrooccipital and temporococcipital regions of the left cerebral hemisphere in relation with the centrooccipital region of the right cerebral hemisphere. Ophthalmic and audiological examinations of Z.T. were unremarkable. Cranial and spinal magnetic resonance examinations (MRI) showed mild dilation of the lateral ventricles and a lipoma on the philum terminale.

The karyotype analysis of our case was reported as 46, XX. On her fluorescence in situ hybridization (FISH) analysis performed using DG (22q11) probe, deletion of band 11 on the long arm of chromosome 22 was detected.

After a successful total correction of TOF, tricuspid valvuloplasty and PDA ligation operations, she was discharged from our hospital on the twentieth postoperative day. We informed the family about the necessity of multidisciplinary approach for the children with VCFS to deal with their gastrointestinal, neurological, hematological, endocrinological,
of complete type and rarely of submucosal type to-gether with a bifid uvula and velopharyngeal insuf-ficiency [6]. Our case had a submucosal cleft palate,
bifid uvula, micro/retrognathia, wide prominent forehead, low nasal bridge and hypertelorism. We
directed the family to a plastic surgery clinic and a palatal obturator was provided until accomplish-
ment of her cardiac surgery. As the children with
velopharyngeal insufficiency have short soft palate
and hypotonic velopharyngeal muscles, they have
difficulty in speaking and swallowing, which create
a tendency to aspiration and speech disorders [7].
Our case also had a short soft palate, difficulty in
speaking and swallowing and her endoscopic ex-
amination in the ear-nose and throat clinic (ENT)
showed velopharyngeal insufficiency. Ha and col-
leagues reported that the repair of the cleft palate
after 18 months of age would lead to a higher risk of
developing articulatory speech problems resulting
in the need for more speech therapy [8]. Therefore,
the children with VCFS should be consulted with
plastic surgeons, orthodontists, ENT specialists
and speech therapists for the monitorization and
resolution of their facial and velopharyngeal prob-
lems as early as possible [6, 7, 8]. The cleft palate
of our case was corrected in the fifteenth postnatal
month and she has being followed by ENT special-
ists and speech therapists in a university hospital
since then.

Conotruncal cardiovascular anomalies diag-
nosed in 75% of the VCFS cases, especially in those
with 22q11 deletion, are the main causes of mor-
bidity and mortality. The most common cardiac
anomalies are aortic arch anomalies (28%), pul-
monary atresia and ventricular septal defect (23%),
ventricular septal defect (21%), tetralogy of Fallot
(15%) and truncus arteriosus (13%) [1, 9]. Rouch
and colleagues screened 217 cases with aortic arch
anomalies and found 22q11.2 deletions in patients
with subclavian artery anomalies (n=38/47; 81%),
right (n=24/52; 46%), and left aortic (n=35/118;
30%) arches [10].
Fallot tetralogy is not a common cardiac pa-
thology in VCFS with 22q11 deletion. Maeda and
colleagues examined 212 patients with TOF and
found 22q11 deletion only in 28 (13%) of VCFS
patients [11].

Our case had tetralogy of Fallot, perimembra-
nous ventricular septal defect, pulmonary stenosis, straddling tricuspid valve with a moderate degree of incompetence, patent ductus arteriosus, 50% dextroposition of aorta, and coronary arterial fistula on the ventricular septum. These anomalies were corrected by total correction of TOF, tricuspid valvuloplasty and PDA ligation operations.

Amelswoort and colleagues performed quantitative MRI studies and reported that the VCFS cases had differences in their brain anatomies affecting the midline structures (septum pallidum, corpus callosum), the cerebellum, white and grey matters of the temporal and left frontal regions. Fusion in the cervical vertebra, and narrowing of the spinal canal may also be detected. These abnormalities may partially explain the cognitive profile and the neuropsychiatric problems encountered in VCFS cases. Therefore, it is necessary to perform cranial and spinal MRIs of the people with VCFS [12, 13].

As our case had two afebrile seizure attacks in the neonatal period with a mild neurodevelopmental delay, we performed cranial and spinal MRI and the EEG studies. We informed the family about the possible future problems of their child as neuromotor retardation, learning disability, speech disorder and psychiatric problems (psychosis, schizophrenia). They have been attending to a neurologist, a psychiatrist, a psychologist and a speech therapist since then.

On their urogenital system examinations, 35% of the children with VCFS showed urinary system abnormalities such as renal agenesis, multicystic kidneys, urolithiasis, horseshoe kidneys, hydronephrosis, vesicoureteral reflux or double collecting system, Besides they had 20-30% inguinal hernia (20-30%), hypospadias (8%), and undescended testicle(s)(6%) [2, 3]. Therefore, the urogenital system examinations should be carefully made and the urinary ultrasonography should be performed in the children with VCFS. The urogenital system examination of our case was normal as well as her urinary system ultrasonography.

The microdeletions on the long arm of chromosome 22, leading to VCFS, are usually sporadic and affect a region containing 30 genes in 90% of the cases. However, in 7–8% of VCFS cases microdeletions may take place in smaller regions containing 20-25 genes, which explain the high phenotypical variations of VCFS cases [14, 15]. It is important to perform genetic analysis of both parents of a child with VCFS even if they don’t have facial dysmorphism or history of a cardiovascular disease. As the VCFS is an autosomal dominant disorder, a deletion in the chromosome of any parent will increase the risk of VCFS with more dramatical clinical presentations in the subsequent pregnancies [16]. The FISH analysis of our case revealed 22q11 deletion, so we directed the family to a university hospital for genetic counselling. The FISH analysis results of the parents were normal and they were informed about the importance of amniocentesis for the subsequent pregnancies.

As a result, VCFS requires a multidisciplinary approach to deal with multiple systemic anomalies. Therefore, it is vital to recognize the syndrome and inform the family as early as possible to get good results from the necessary interventions.

**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study has received no financial support.

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