PRENATAL DIAGNOSIS OF DIGEORGE SYNDROME

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Velocardiofacial syndrome, conotruncal congenital heart disease and DiGeorge syndrome present different aspects of the same clinical situation, but congenital heart disease is common to them all [1]. Other defects found in these syndromes include abnormal facies, thymic hypoplasia, cleft palate, and hypocalcemia. A deletion at chromosome 22q11 is the second most common chromosomal defect detected in patients with congenital heart disease. Although familial inheritance occurs, most cases are sporadic [2].

A patient aged 29 years, gravida 2, para 1, presented to our outpatient clinic with an initial diagnosis of polyhydramnios at the 33rd week of gestation. Her medical history revealed that her first delivery was at term by cesarean section, but the baby died in infancy of cyanotic heart disease, diffuse bronchopulmonary disease, and infection.

Postmortem genetic investigation revealed that the neonate had a 22q11 deletion, with associated cardiovascular anomalies. The parents were genetically normal. Obstetric examination determined that the patient was at 33 weeks of gestation, and fetal biometric measurements suggested a gestational age of 31–32 weeks. The amniotic index was 18 cm and mild polyhydramnios was detected. Systematic ultrasonographic investigation revealed a ventricular septal defect, a secundum-type atrial septal defect, pulmonary atresia, and an anomaly of the overriding aorta. These findings were interpreted as components of tetralogy of Fallot (TOF). The patient had not attended the hospital for prenatal screening during her second trimester. Cordocentesis was performed for prenatal diagnosis. The cytogenetic analysis was evaluated as normal, but considering the clinical findings and the patient's prior history, locus-specific fluorescence *in situ* hybridization (FISH) was planned to detect possible DiGeorge syndrome. A Tuple1-Hira FISH probe (Vysis; Abbott Laboratories, Abbott Park, IL, USA) was used and a heterozygous deletion was detected at 22q11.2 (Figure). Genetic counseling was given to the family, and the patient was followed up until the 38th week of gestation. The same chromosomal defect had been present in the previous infant, while the parental chromosomal structures were normal. A second *de novo* mutation was thought to be responsible for the development of the syndrome in this case. A pediatric cardiologist and a pediatric surgeon assisted at delivery by cesarean section, and the baby, who weighed 3,000 g, was transferred to the neonatal care unit. Biochemical analysis and echocardiographic investigations were carried out postpartum and DiGeorge syndrome was diagnosed.

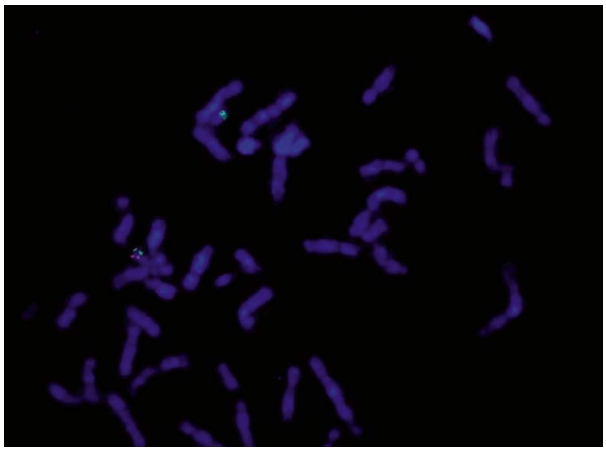

Figure. The fluorescence *in situ* hybridization result of cordocentesis material.

Prenatal diagnosis is essential, especially in patients that have had previous pregnancies involving chromosomal defects, even those due to spontaneous mutations. Counseling should be provided, and the parents should be referred to an appropriate center.

22q11 deletion is the second most commonly seen chromosomal defect in congenital heart diseases after Down syndrome. It is observed in 1/4000 births on average [3]. Cardiovascular anomalies are reported in 83% of cases with 22q11 deletion [4]. These anomalies frequently include the conotruncal region, and patients present with TOF. TOF is responsible for 10% of cyanotic heart disease observed in infancy. In parallel with the

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developments in ultrasonography, the prenatal diagnosis of cardiac defects has increased and diagnosed cases are followed up closely. If the detected defect is fatal, pregnancy termination can be planned after consultation with appropriate clinics, such as pediatric surgery and genetics. If the pregnancy is beyond the termination limit, it is important that patients are referred to a clinic with a pediatric cardiologist and a surgeon, where neonatal care can be given.

Only 8% of 22q11 deletion cases are inherited, while most develop by *de novo* mutation [3]. Even if one of the parents is affected, they may not be symptomatic, and the chromosomal inheritance rate from a genetically affected person is only 50%. If a 22q11 deletion is detected prenatally in a fetus with a cardiovascular disorder diagnosed through ultrasonography, then genetic investigation of the parents should be performed.

Phenotypic abnormalities associated with the chromosome 22q11.2 deletion syndrome include thymus and parathyroid hypoplasia or aplasia, cardiac outflow tract abnormalities, cleft palate, velopharyngeal insufficiency, and dysmorphic facial features. The pharyngeal arches and pouches are a common embryonic precursor for the thymus, parathyroid, and conotruncal region of the heart. Defects in these organs can be caused by impaired migration of neural crest cells into the pouch endoderm. The phenotype of chromosome 22q11.2 deletion syndrome is very variable and the extent of the deletion does not seem to correlate with disease severity, thus identifying a single gene responsible for all the phenotypic features is difficult [5].

The clinical findings associated with 22q11.2 deletion are highly variable. Approximately 75% of patients with 22q11 deletion are born with congenital heart defects, mainly of the cardiac outflow tract and aortic arch. Other common features include a characteristic facial appearance, immunodeficiency from thymic hypoplasia, velopharyngeal dysfunction with or without cleft palate, hypocalcemia as a result of hypoparathyroidism, developmental and behavioral problems, and psychiatric disorders in adulthood [6].

If patients undergo *in vitro* fertilization, preimplantation genetic investigations should be carried out [7].

The incidence of 22q11 deletion is about 48% in infants with conotruncal congenital cardiac anomaly [8], and is 13% in patients with a diagnosis of TOF [9]. Careful evaluation of ultrasound examinations carried out during the second trimester is needed to detect cardiovascular anomalies. Early prenatal diagnosis is important for the management of the pregnancy and delivery, postnatal surgical management, neonatal care, and decisions regarding cesarean section in cases of fetal distress. Decision making should involve close cooperation between obstetricians, pediatric cardiologists, and surgeons.

Fetuses diagnosed prenatally with TOF should undergo genetic investigations to check for 22q11 deletion.

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