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Case Report

Complete trisomy 9 with unusual phenotypic associations: Dandy-Walker malformation, cleft lip and cleft palate, cardiovascular abnormalities

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ABSTRACT

Objective: Trisomy 9 is a rare chromosomal abnormality usually associated with first-trimester miscarriage; few fetuses survive until the second trimester. We report two new cases of complete trisomy 9 that both present unusual phenotypic associations, and we analyze the genetic pathway involved in this chromosomal abnormality.
Case report: The first fetus investigated showed Dandy-Walker malformation, cleft lip, and cleft palate) at the second trimester scan. Cardiovascular abnormalities were characterized by a right-sided, U-shaped aortic arch associated with a ventricular septal defect (VSD). Symmetrical intrauterine growth restriction and multicystic dysplastic kidney disease were associated findings. The second fetus showed a dysmorphic face, bilateral cleft lip, hypoplastic corpus callosum, and a Dandy-Walker malformation. Postmortem examination revealed cardiovascular abnormalities such as persistent left superior vena cava draining into the coronary sinus, membranous ventricular septal defect, overriding aorta, pulmonary valve with two cusps and three sinuses, and the origin of the left subclavian artery distal to the junction of ductus arteriosus and aortic arch.
Conclusion: Complete trisomy 9 may result in a wide spectrum of congenital abnormalities, and the presented case series contributes further details on the phenotype of this rare aneuploidy.

Introduction

Complete trisomy 9 refers to trisomy of the entire chromosome 9 with no evidence of mosaicism. This uncommon aneuploidy accounts for only 2.7% of all trisomies and mainly results in early miscarriage [1]. Few cases of liveborn babies have been described, but the outcome was extremely poor [2]. Complete trisomy 9 presents a wide variety of congenital abnormalities, affecting most of the organs and systems, with complex phenotypes [1,3]. Although the head and neck area and the cardiovascular, skeletal, and central nervous systems are almost always involved, the type of malformation and its severity is highly variable from case to case. We report two new cases of complete trisomy 9 with an unusual association of Dandy-Walker malformation (DWM), bilateral cleft lip and palate (CLP), central cleft palate (CP), and cardiovascular abnormalities.

Case reports

Case 1

A 37-year-old primigravida underwent screening for Down syndrome at 12 2/7 weeks according to Fetal Medicine Foundation guidelines [4]. The corrected risk for trisomy 21 and trisomy 13/18 were low at 1:774 and 1:891, respectively. Transabdominal Level II

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ultrasound (US) examination performed at 20 3/7 weeks gestation detected overall decreased fetal growth parameters. The examination was carried out using a Voluson E8 ultrasound apparatus (GE Healthcare, Milwaukee, WI, USA) with a multifrequency transabdominal RAB 4-8D probe. Biparietal diameter (BPD) was 46.2 mm (10^{th} percentile for gestational age), fronto-occipital diameter was 57.5 mm (< 5^{th} percentile), cranial circumference was 167 mm (5^{th} percentile) and abdominal circumference was 129 mm (< 5^{th} percentile). Femur (FL) and humerus length (HL) were both below the 5^{th} percentile for age and measured 28.2 mm and 27.4 mm, respectively. The BPD/FL ratio was 1:638 (95^{th} percentile), indicating symmetrical intrauterine growth restriction (IUGR). A detailed fetal neurosonogram was performed with the transvaginal transfontanelle approach. Cavum septum pellucidum, corpus callosum, third and lateral ventricles (7.5 mm in diameter), thalami, and basal ganglia were normally structured. In the posterior fossa, the cerebellar vermis was hypoplastic with a wide cleft between the cerebellar hemispheres and direct communication between the fourth ventricle and the cisterna magna. An elevated tentorium was also seen. The overall findings were consistent with DWM. Face scanning detected median CLP that was subsequently confirmed by postmortem examination (Fig. 1).

Fetal two-dimensional/three-dimensional echocardiography showed levocardia and situs solitus. On the three-vessel trachea view (3VT) performed in grayscale and using Doppler with color flow mapping, an aortic arch located to the right of the trachea and esophagus was seen (Fig. 2). The four-chamber view revealed an apical, muscular, ventricular septal defect (VSD) using Doppler color flow mapping. Three volumes of interest were recorded using spatiotemporal image correlation in glass body rendering with Doppler angiography. The ductus and the aorta formed a U-shaped vascular ring around the midline structures (trachea and esophagus), which is consistent with a clinical diagnosis of a right aortic arch (Fig. 3).

The kidneys were both hyperechogenic, and multiple cysts were found in the left kidney, which strongly suggested multicystic dysplastic kidney disease. Because of the multiple congenital abnormalities, amniocentesis for a rapid aneuploidy test using quantitative fluorescent-polymerase chain reaction and culture was performed after signed informed consent was obtained. The test revealed an abnormal male karyotype with complete trisomy 9. Pregnancy was terminated at 22 0/7 weeks gestation with vaginal administration of prostaglandin E subsequent to hospital admission (Cervidil, Serono, Latina, Italy).

The parents declined a full postmortem examination and consented to photographs and skin biopsy only. Skin fibroblast culture confirmed the amniocentesis finding of a male with complete trisomy 9.

Case 2

A fetal scan performed at 22 0/7 weeks gestational on a 28-year-old gravida 4, para 1 woman detected multiple abnormalities including DWM, ventriculomegaly, large CLP, cardiac abnormalities, and echogenic kidneys. The woman underwent amniocentesis which revealed an abnormal female karyotype with complete trisomy 9 (47, XX, +9). Pregnancy was terminated at 23 4/7 weeks gestational age. Consent was obtained for a complete necropsy examination that confirmed the multiple abnormalities detected on ultrasound. The female fetus was small for gestational age; it weighed 387 g (< 3^{rd} percentile) and measured 26 cm in crown-heel length (between the 5^{th} percentile and 10^{th} percentile). The foot length of 3.6 cm was shorter than expected for gestational age (4.38 ± 0.26 cm) [5]. The face was dysmorphic with a triangular head and broad forehead, double hair whorl, hypertelorism, underdeveloped supraorbital ridges, wide nasal bridge, and low-set, misshapen, and posteriorly rotated ears with small lobes. Fontanelles were soft and widely open. Fetal X-rays showed 11 pairs of ribs, mild bowing of the ulnas, absent ossification of the middle and distal phalanges in the hands, bilateral hip dislocation and acetabular dysplasia, knee dislocation with genu recurvatum, equinus talipes, and absent ossification in the distal phalanges of the feet (Fig. 4). A bilateral CL was continuous with the nares and a central CP. The oral cavity showed a tethered tongue, prominent alveolar ridge and a short, split uvula (Fig. 5). Upper and lower limbs were contracted with mild pterigia. Hands showed bilateral camptodactyly, clinodactyly, and absent fingernails. There were bilateral talipes with posteromedial rotation, bilateral sandal gap, and absent fingernails. Other abnormalities observed at the external examination included a skin tag on the anterior chest, a prominent coccyx and sacral dimple, and an anteriorly located anus. Internal examination revealed cardiovascular abnormalities such as persistent left superior vena cava, membranous VSD, overriding aorta, pulmonary valve with two cusps and three sinuses, and the origin of the left subclavian artery was distal to the junction of the ductus arteriosus and aortic arch (Fig. 6). The lungs had abnormal lobation with two lobes on the right and three on the left. The brain showed sulcation consistent with 22 weeks gestational age; cerebellar vermis was small and dorsally rotated with an enlarged fourth ventricle aperture (DWM; (Fig. 7). There was corpus callosum hypoplasia, mild dilatation of the lateral ventricles and hippocampal malrotation. Microscopic examination demonstrated Probst bundles and a small, mildly dysplastic vermis. Other abnormalities observed at postmortem examination included hypoplastic gallbladder, mobile cecum and ascending colon, left kidney with cystic dysplasia, accessory splenule, bicornuate uterus, and elongated ovaries.

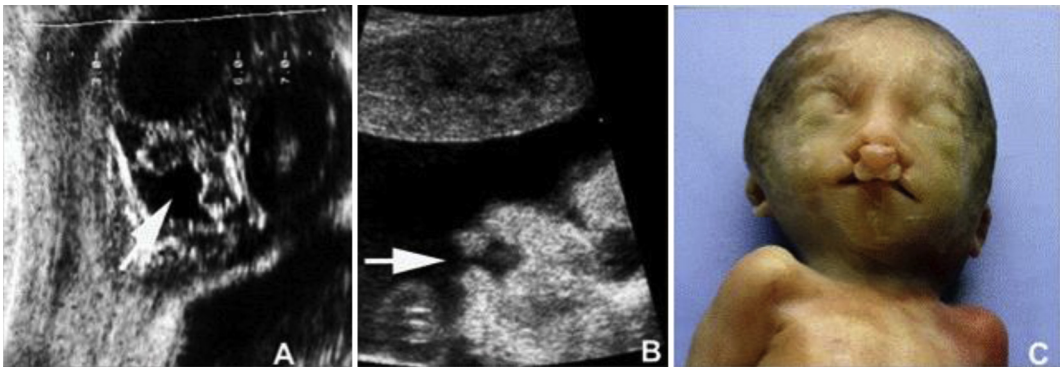

Fig. 1. (A) Transabdominal scan performed at 20 3/7 weeks of gestation showing the defect at the level of the cerebellar vermis consistent with Dandy-Walker malformation (white arrow). (B) Fetal profile demonstrating cleft lip and (C) postmortem examination documenting a bilateral cleft lip and cleft palate.