Antenatal diagnosis of left atrial isomerism and heterotaxy syndrome in fetus with Meckel-Gruber syndrome

Meckel-Gruber sendromlu bir fetüste sol atriyum izomerizmi ve heterotaksi sendromunun antenatal tanısı

Seçil Kurtulmuş, M.D., Savaş Demirpençe, M.D.,# Deniz Can Öztekin, M.D., Altuğ Koç, M.D., Vedide Tavlı, M.D.*

Department of Maternity and Gynecology, Ege Training and Research Hospital, Izmir;
#Department of Pediatric Cardiology, Dr. Behçet Uz Training and Research Hospital, Pediatric Diseases and Surgery, Izmir;
*Department of Pediatric Cardiology, Sifa University Faculty of Medicine, Izmir

Summary– We aimed to present a fetus with Meckel-Gruber syndrome (MKS) who had left atrial isomerism, heterotaxy syndrome and complete heart block. A 26-year-old healthy female was referred to our clinic in the 23rd week of her pregnancy. The fetus had multiple systemic anomalies including fetal heart. Fetal echocardiography revealed a horizontal liver, left-sided stomach and vena cava interruption with azygos continuation. There was also an apical trabecular ventricular septal defect, aorta and pulmonary artery arising from the left ventricle, pulmonary artery hypoplasia, pulmonary valve stenosis and left atrial isomerism. The heart rate was 46/min, consistent with third-degree atrioventricular block. Multiple anomalies including occipital encephalocele, bilateral polycystic kidneys, cleft lip, cleft palate, and polydactyly were also detected in the obstetric ultrasonography. The pregnancy was terminated in the 23rd gestational week based on the consensus of perinatology council. The autopsy examination confirmed the diagnosis of MKS, left atrial isomerism and heterotaxy syndrome. Although some cardiac defects have been reported previously in MKS fetuses, here we expand the cardiac spectrum of anomalies associated with MKS to include left atrial isomerism and heterotaxy syndrome.

Özet– Bu yazıda, sol atriyum izomerizmi, heterotaksi sendromu ve tam kalp bloğu olan Meckel-Gruber sendrom'lu (MKS) bir fetüs sunuldu. Yirmi altı yaşındaki sağlıklı anne gebeliğinin 23. haftasında kliniğimize başvurdu. Fetüsün kalbi de içeren çok sayıda sistemik anomalisi vardı. Fötal ekokardiyografide horizontal karaciğer, sol yerleşimli mide ve azigos devamlılığı olan kesintili kaval veni vardı. Ayrıca apikal trabeküler ventriküler septal defekt, sol ventrikülden çıkan aorta ve pulmoner arter, pulmoner arter hipoplazisi, pulmoner kapak stenozu ve sol atriyum izomerizmi mevcuttu. Kalp hızı 46/dk idi ve üçüncü derece kalp bloğu ile uyumlu idi. Obstetrik ultrasonografisinde oksipital ensefalosel, iki taraflı polikistik böbrekler, yarık dudak, yarık damak ve polidaktiliyi içeren çok sayıda anomali saptandı. Perinatoloji konseyi kararı ile 23. gebelik haftasında gebelik sonlandırıldı. Otopsi incelemesi sol atriyum izomerizmi heterotaksi sendromu ve MKS tanısını doğruladı. Meckel-Gruber sendromlu fetüslerde daha önce birtakım kardiyak defektler bildirilmiş ise de, biz burada sol atriyum izomerizmi ve heterotaksi sendromunu da içeren MKS ile ilişkili kardiyak anomaliler spektrumunu genişletmiş olduk.

Meckel-Gruber syndrome (MKS) was first defined by the German anatomist Johann Frederick Meckel[1] in the 19th century. The incidence of MKS ranges from 1 in 13,250 to 1 in 40,000 live births.[2] MKS is the most severe form of the inherited spectrum of diseases called ciliopathies. The other conditions with ciliary involvement are Joubert syndrome, nephronophthisis (NPHP), Bardet-Biedl syndrome, COACH syndrome, and Senior-Løken syndrome. MKS is autosomal recessively inherited and caused by dysfunction of primary cilia

Abbreviation:
MKS Meckel-Gruber syndrome

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Correspondence: Dr. Savaş Demirpençe. İzmir Buca Kadın Doğum ve Çocuk Hastalıkları Hastanesi, Hoca Ahmet Yesevi Caddesi, No: 27/95, Buca, İzmir, Turkey.
Tel: +90 232 - 454 01 01 e-mail: savasdemirpence@yahoo.com

during early embryogenesis. Bergmann et al.[3] demonstrated in patients and mice that Nephrocystin-3 (NPHP3/Nphp3) gene mutations can cause embryonic lethality, Meckel-Gruber-like syndrome, situs inversus, renal-hepatic-pancreatic dysplasia, and congenital heart defects including aortic stenosis, atrial septal defect (ASD), right ventricular hypertrophy, and patent ductus arteriosus (PDA).

In MKS, the typical fetal sonographic triad includes polycystic renal dysplasia (100%), occipital encephalocele (90%) and postaxial polydactyly (83%).[4] Other associated features include Dandy-Walker malformation (or other posterior fossa defects), microphthalmia, cleft lip and palate, heart defects, genital abnormalities, bowing of long bones, and complete or partial situs inversus, and other laterality defects.[5] Despite various cardiac anomalies reported in MKS, none of them is specific to the disease. However, cardiac anomalies including hypoplastic left heart syndrome, truncus arteriosus, pulmonary artery atresia, and atrioventricular septal defect have been detected in cases with MKS.[6,7] Taweevisit et al.[7] demonstrated the togetherness of hypoplastic left heart syndrome and cor triatriatum in a 33-week male fetus by ultrasonography, and established the diagnosis by autopsy. In this report, we present a fetus with MKS who had left atrial isomerism, heterotaxy syndrome, and complete heart block. We also emphasize the importance of fetal echocardiography in the detection and management of the congenital cardiac defect.

CASE REPORT

A 26-year-old healthy female was referred to our clinic in the 23rd week of her 4th pregnancy for the antenatal evaluation of congenital heart defects by fetal echocardiography. Routine obstetric ultrasonography in the second trimester screening showed multiple extracardiac anomalies. Her previous pregnancy was terminated at the 23rd gestational week due to similar fetal anomalies, but neither post-mortem examination nor genetic study was performed. There was no consanguinity between the parents and they had a normal six-year-old son. Segmental analysis through fetal echocardiography revealed a horizontal liver, left-sided stomach and vena cava inferior interruption with azygos continuation (Fig. 1a). Apical trabecular ventricular septal defect, aorta and pulmonary artery arising from the left ventricle (Fig. 1b), pulmonary artery hypoplasia, pulmonary stenosis, and left atrial isomerism (Fig. 2a) were also determined. The heart rate was 46/min, which was consistent with third-degree atrioventricular block. Multiple anomalies including occipital encephalocele, bilateral polycystic kidneys, cleft lip and palate, and polydactyly were also detected in the obstetric ultrasonography. The pregnancy was terminated in the 23rd gestational week based on the consensus of the perinatology council. Autopsy examination revealed encephalocele, microphthalmia, micrognathia, cerebral hypoplasia, cleft lip and palate, bilateral postaxial polydactyly of hands and feet, pes equinovarus, bilateral polycystic kidneys, right-sided polysplenia, symmetric liver, hyparterial bronchi, bilobed lungs, aorta

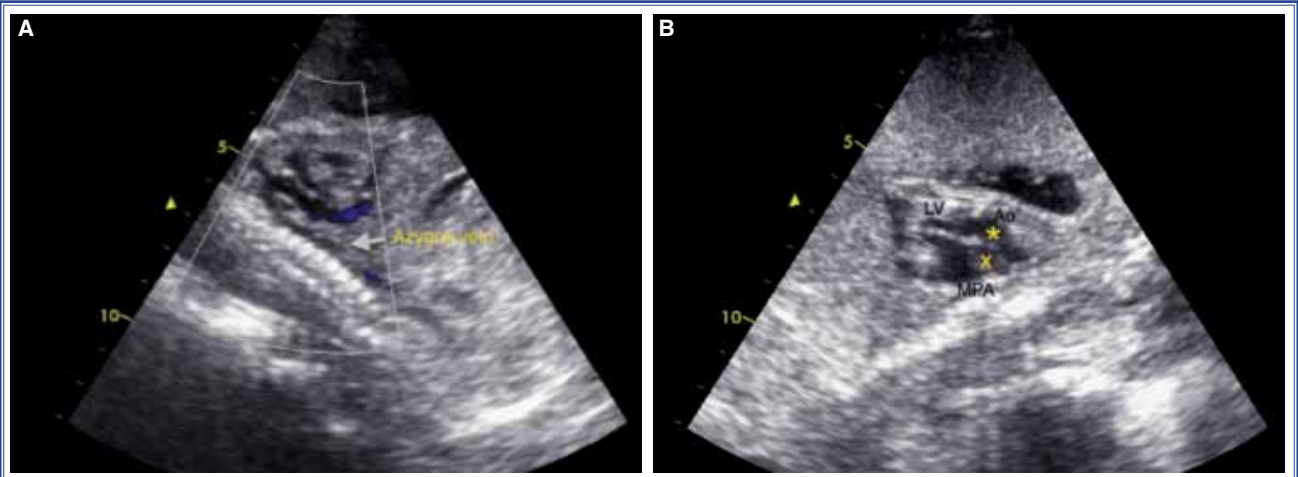

Figure 1. **(A)** Sagittal view of the chest demonstrating the azygos vein posterior to the aorta. **(B)** Echocardiographic view demonstrating the main pulmonary artery (MPA) and aorta (Ao) arising from the left ventricle (LV).

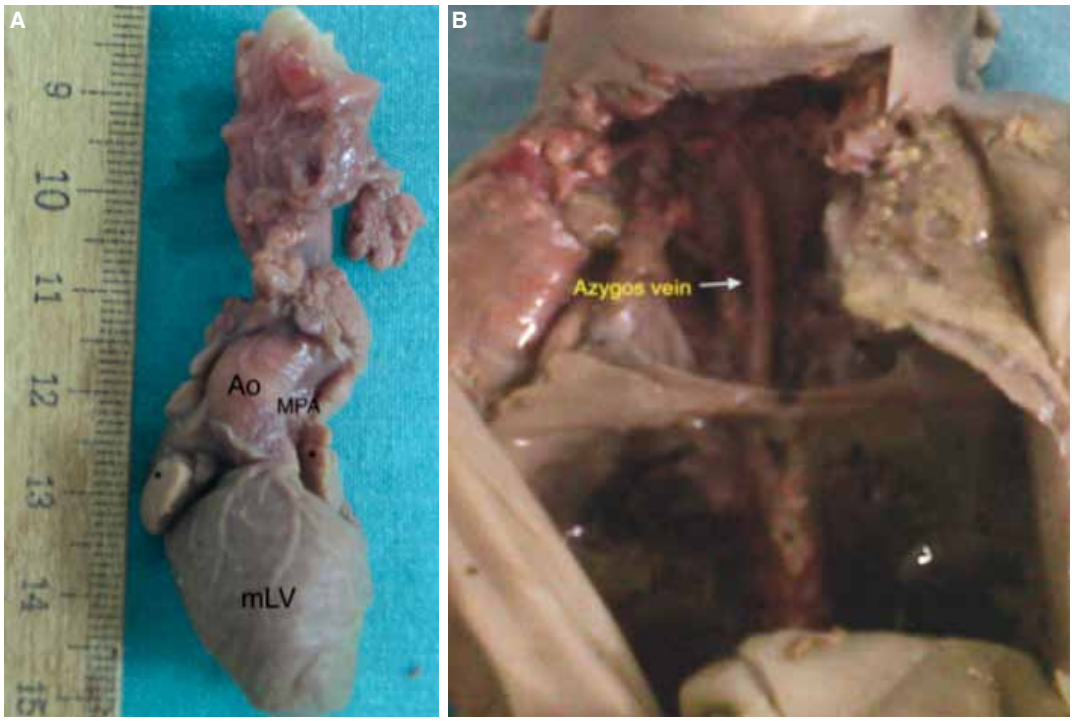

Figure 2. **(A)** Autopsy specimen from the fetus showing bilateral left atrial appendages (*) and hypoplastic main pulmonary artery (MPA) and aorta (Ao) arising from the morphological left ventricle (mLV). **(B)** Autopsy specimen from the fetus showing azygos vein.

and pulmonary artery arising from the left ventricle, pulmonary artery hypoplasia and left atrial isomerism, and vena cava inferior interruption with azygos continuation (Fig. 2b). Hepatic portal fibrosis, bile duct proliferation, bilateral renal polycystic dysplasia, and gonads in testicular morphology were observed on tissue biopsies. Considering the autopsy findings, a diagnosis of MKS was made, and molecular genetic examination was planned for possible gene loci.

DISCUSSION

In our case, the fetus had occipital encephalocele, bilateral polycystic kidneys, bilateral postaxial polydactyly of hands and feet, and a horizontal symmetric liver in the macroscopic pathological examination. Hepatic portal fibrosis, bile duct proliferation, and bilateral renal polycystic dysplasia were observed on tissue biopsies. All these findings were in accordance

Table 1. **Loci associated with Meckel-Gruber syndrome**

Location	Phenotype	Gene/Locus
17q22	Meckel syndrome 1	MKS1, MKS, BBS13
11q12.2	Meckel syndrome 2	TMEM216, JBTS2, CORS2, MKS2
8q22.1	Meckel syndrome 3	TMEM67, MKS3, JBTS6, NPHP11
12q21.32	Meckel syndrome 4	CEP290, KIAA0373, 3H11AG, JBTS5, SLSN6, LCA10, BBS14
16q12.2	Meckel syndrome 5	RPGRIP1L, KIAA1005, JBTS7, MKS5
4p15.32	Meckel syndrome 6	CC2D2A, KIAA1345, MKS6
3q22.1	Meckel syndrome 7	NPHP3, NPH3, RHPD, MKS7
12q24.31	Meckel syndrome 8	TCTN2, TECT2, MKS8
17p11.2	Meckel syndrome 9	B9D1, MKSR1, MKS9
19q13.2	Meckel syndrome 10	B9D2, MKS10

with the minimum diagnostic criteria that should be found in MKS.[5,8] The fetus also had cerebral hypoplasia, microphthalmia, micrognathia, cleft lip and palate, and pes equinovarus.

Along with other findings, our case also had the features of heterotaxy-left atrial isomerism and cardiac anomalies. These included polysplenia, right-sided stomach, horizontal liver, vena cava inferior interruption with azygos continuation, bilobed lungs in the morphology of the left lung, both aorta and pulmonary artery arising from the left ventricle, pulmonary artery hypoplasia accompanied by pulmonary stenosis, apical trabecular ventricular septal defect, and third-degree complete atrioventricular block. In 1984, Salonen et al.[9] reviewed a series of 67 Finnish MKS cases and showed an increased risk of situs inversus totalis, with the ratio of 3/67. Khaddour et al.[10] performed MKS1 and MKS3 mutation analysis in 120 fetuses presenting with the diagnostic criteria of MKS and found that of the eight cases with MKS1 mutation, two of them had situs inversus.

The MKS reveals a wide clinical and genetic heterogeneity: At least 10 phenotypes and more than 30 loci related with MKS are reported, and the genetic diagnosis of MKS is an obvious challenge (Table 1). In this case, sequencing of the fetal and parental blood-derived DNA samples could be performed only for the MKS1 gene (exons 16 and 17), but no mutation was found, and further, karyotypes of the family members were in normal constitution. When MKS is suspected, karyotype analysis should be done to exclude especially trisomy 13.[2] The present case had a normal karyotype with 46 XY. MKS can be seen in those with consanguineous marriage due to mutant genes and in those without consanguineous marriage due to single gene defect.[11] The present case did not have a history of consanguineous marriage.

In conclusion, although various cardiac anomalies have been reported previously in MKS fetuses, here we expand the cardiac spectrum of anomalies associated with MKS to include left atrial isomerism and heterotaxy syndrome. We suggest that since MKS is a syndrome showing 100% fatal progression, prenatal diagnosis should be made as early as possible, termination of the pregnancy should be offered, and genetic counseling should be provided due to the high risk for recurrences.

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REFERENCES

1. Stocker JT, Dehner LP. Pediatric pathology. Washington: J.B. Lippincott; 1992.
2. Alexiev BA, Lin X, Sun CC, Brenner DS. Meckel-Gruber syndrome: pathologic manifestations, minimal diagnostic criteria, and differential diagnosis. Arch Pathol Lab Med 2006;130:1236-8.
3. Bergmann C, Fliegauf M, Brüchle NO, Frank V, Olbrich H, Kirschner J, et al. Loss of nephrocystin-3 function can cause embryonic lethality, Meckel-Gruber-like syndrome, situs inversus, and renal-hepatic-pancreatic dysplasia. Am J Hum Genet 2008;82:959-70. CrossRef
4. Sergi C, Adam S, Kahl P, Otto HF. Study of the malformation of ductal plate of the liver in Meckel syndrome and review of other syndromes presenting with this anomaly. Pediatr Dev Pathol 2000;3:568-83. CrossRef
5. Logan CV, Abdel-Hamed Z, Johnson CA. Molecular genetics and pathogenic mechanisms for the severe ciliopathies: insights into neurodevelopment and pathogenesis of neural tube defects. Mol Neurobiol 2011;43:12-26. CrossRef
6. Gilbert-Barness EF, Opitz JM. Congenital anomalies: malformation syndromes. In: Wiggleswoth SS, Singer DB, editors. Textbook of fetal and perinatal pathology. 2nd ed. England: Blackwell Science; 1998. p. 323-57.
7. Taweevisit M, Treetipsatit J, Tantbirojn P, Thorner PS. Combination of cor triatriatum sinistrum and hypoplastic left heart syndrome in Meckel-Gruber syndrome: a case report. Pediatr Dev Pathol 2009;12:404-9. CrossRef
8. Meckel JF. Beschreibung zweier, durch sehr aehnliche Bildungsabweichungen entstellter geschwister. Deutsches Archiv für Physiologie 1822;7:99-172.
9. Salonen R. The Meckel syndrome: clinicopathological findings in 67 patients. Am J Med Genet 1984;18:671-89. CrossRef
10. Khaddour R, Smith U, Baala L, Martinovic J, Clavering D, Shaffiq R, et al. Spectrum of MKS1 and MKS3 mutations in Meckel syndrome: a genotype-phenotype correlation. Mutation in brief #960. Online. Hum Mutat 2007;28:523-4. CrossRef
11. de Silva MV, Senanayake H, Siriwardana KD. Meckel Gruber syndrome: occurrence in non-consanguineous marriages. Ceylon Med J 2004;49:30-1.

Key words: Abnormalities, multiple/genetics; atrial isomerism, left; encephalocele/genetics/pathology; liver/pathology; Meckel-Gruber syndrome.

Anahtar sözcükler: Anormallik, çoklu/genetik; atriyum izomerizmi, sol; ensefalosel/genetik/patoloji; karaciğer/patoloji; Meckel-Gruber sendromu.