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The Power of Prenatal Insight: Early Diagnosis of Meckel Gruber Syndrome

Reema Bhatt[1], Annu Kumari[2], Jaishree Tewari[3], Siddharth Tewari[4] *

[1]Professor and Head, Department of Fetal Medicine, Amrita Hospital, Sector 88, Faridabad, Haryana 121002
[2]Department of Fetal Medicine, Amrita Hospital, Sector 88, Faridabad, Haryana 121002
[3]Senior Consultant and Head, Department of Obstetrics and Gynaecology, Jaishree Hospital (Tewari Maternity Centre and Nursing Home), Haldwani , Uttarakhand 263139
[4]Fellow, Department of Fetal Medicine, Amrita Hospital, Sector 88, Faridabad, Haryana 121002
***Corresponding Author:**
Siddharth Tewari
Department of Fetal Medicine, Amrita Hospital, Sector 88, Faridabad, Haryana 121002
Email id: tewari.siddharthmd@yahoo.com

ABSTRACT

The Meckel-Gruber syndrome (MKS) is a rare autosomal recessive disorder that is characterized by typical sonographical findings: occipital encephalocele, postaxial polydactyly and cystic enlargement of the kidneys. we presented case series of patients with Meckel Gruber syndrome. In the first presented case, 2 of the hallmark features of MKS were identified, i.e., an occipital encephalocele & bilateral renal dysplasia. Bilateral clubfoot was also noted. The second case revealed a pathogenic variant in the MKS1 gene (heterozygous) , associated with Meckel syndrome. In this instance, the presence of orofacial clefts and bilateral clubfoot raised the possibility of this diagnosis. The second case was found to have a pathogenic variant in the AMER1 gene associated with Osteopathia striata with cranial sclerosis (OS-CS). These two cases emphasize the critical role of early prenatal screening, the wide phenotypic spectrum of Meckel Gruber syndrome, the necessity of genetic testing for accurate diagnosis, and counselling to support informed decision-making in future pregnancies

KEYWORDS: Bilateral Clubfoot, Meckel-Gruber Syndrome, Occipital Encephalocele

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INTRODUCTION

Meckel-Gruber syndrome is a rare disease with prevalence of 1 in 13,000 to 1 in 140,000 live births . It is characterized by occipital encephalocele, enlarged dysplastic kidneys, hepatic duct proliferation, polydactyly, posterior fossa abnormalities, and various craniofacial and heart defects. This lethal autosomal recessive condition is associated with mutations in several ciliary genes. The classic triad of large echogenic kidneys, encephalocele, and postaxial polydactyly can enable diagnosis as early as 14 weeks of gestation. [1,2] However, oligohydramnios in later stages of pregnancy may obscure the identification of some features. Its features overlap with those of Joubert syndrome-related disorders (JSRS). It needs to be particularly differentiated from autosomal recessive polycystic kidney disease and trisomy 13, with which it has a number of striking similarities. [2,3]

Case 1

We present a 35-year-old woman who came to us at 18 weeks 3 days of gestation. She is G3P1L1A1 , with a 2-year-old female child. delivered vaginally and weighed 3500 g at birth. She also has previous history of missed abortion.

In the present pregnancy, she had not undergone NT scan, and no early pregnancy scan was done. Ultrasound scan with us showed overall Fetal growth normal for gestation . However, the BPD was on 7th centile with a skull defect in occipital region in midline causing herniation of the meninges and brain structures, suggestive of occipital encephalocele. Large echogenic kidneys were seen bilaterally with tiny cystic structures within (Figure 1).

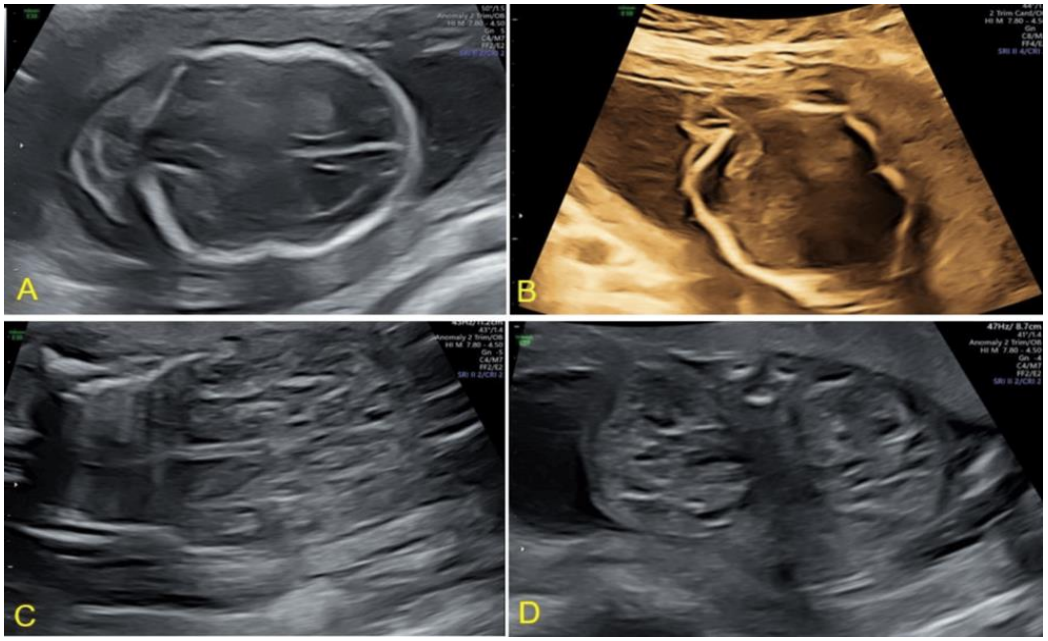

Figure 1: Ultrasound images of fetus showing occipital encephalocele with bilateral multicystic hyperechogenic kidneys

A and B showing occipital encephalocele (axial)

C (coronal) and D (axial) showing bilateral multicystic hyperechogenic kidneys

Bilateral clubfoot was noted. Open hands were documented. No evidence of polydactyly was observed (Figure 2). The abdominal wall appeared intact. Amniotic fluid was normal for gestation. Good fetal movements were noted on the scan.

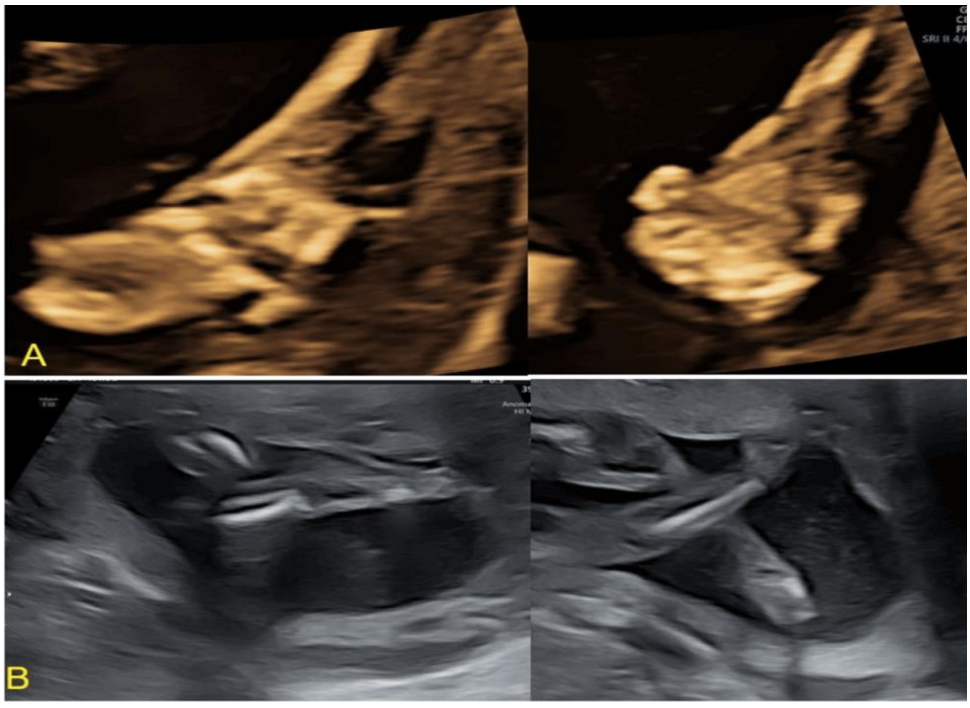

Figure 2: Ultrasound of fetus showing bilateral clubfoot. No polydactyly was noted

A: Open hands were documented. No polydactyly was observed

B: Bilateral clubfoot seen

The above findings raise possibility of Meckel Gruber syndrome. The syndrome exhibits diverse phenotypic expression, reflecting its complex genetic basis. A characteristic triad, consisting of occipital encephalocele, cystic renal dysplasia, and post-axial polydactyly, is observed in roughly 60% of cases. [1] In our case 2 findings were seen (cystic renal dysplasia and occipital

encephalocele) .

The couple was explained that the prognosis of the fetus was extremely guarded, and they opted for termination of pregnancy. The abortus was sent for fetal autopsy (Figure 3) . Genetic testing revealed pathogenic variant of MKS 1 gene (heterozygous) in exon 8 [c.844C>T p.(Arg282*)] and a likely pathogenic variant in exon 5 [c.457_461dup p.(Leu155Hisfs*76)

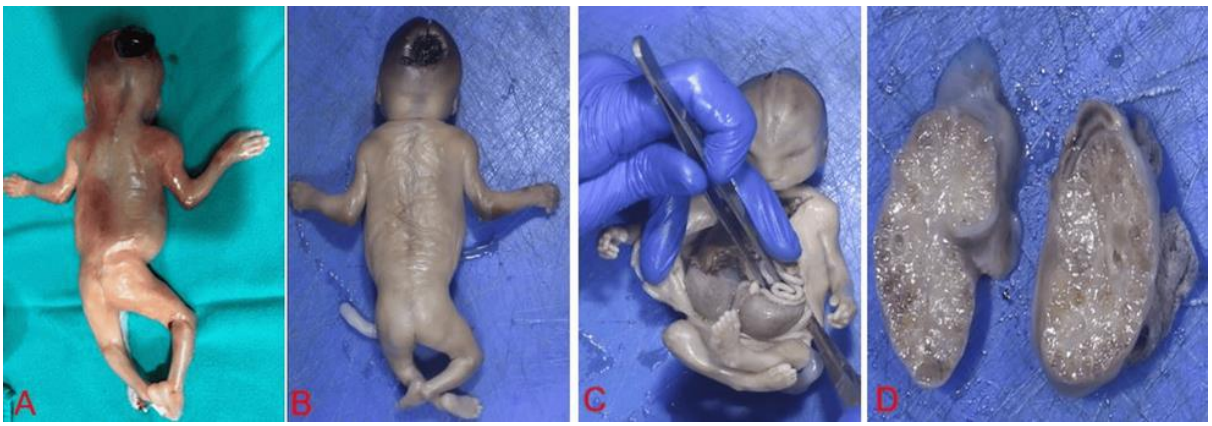

Figure 3: Fetal autopsy was done and revealed occipital encephalocele with bilateral enlarged multicystic kidneys and clubfoot

A (at time of delivery) and B (on autopsy) : Occipital encephalocele noted with bilateral clubfoot

C: Cut-section of the fetus showing bilateral enlarged kidneys . Bilateral clubfoot noted

D: Cut section of the kidneys in the coronal plane reveals enlarged multicystic kidneys bilaterally

Case 2

We present a 29-year-old woman (G2P1L1) who came to us at 24 weeks 4 days of gestation. She had a previous pregnancy which was medically terminated in view of congenital heart disease (suspected tetralogy of Fallot) and micrognathia.

In the present pregnancy, we observed cleft lip with left axis deviation of the heart and ventricular septal defect (inlet) . Bilateral clubfoot (CTEV) was also noted (Figure 4) .

d (Figure 4) .

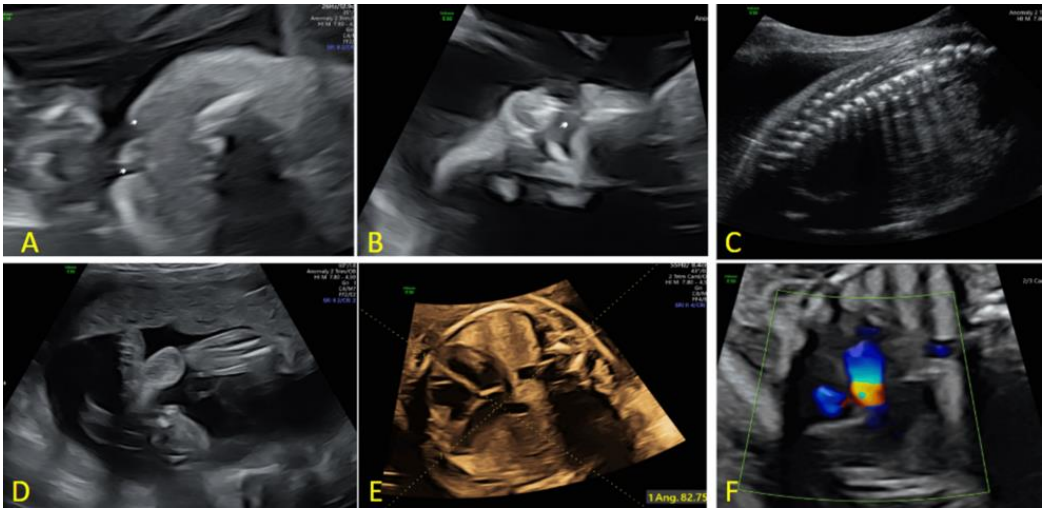

Figure 4: Ultrasound images of the fetus demonstrating the bilateral cleft lip (A and B) and clubfoot(D) . Left axis deviation of the heart (E) with inlet VSD (F) was noted . No evidence of tethered cord or spinal deformity was noted (C)

In view of multiple congenital abnormalities, there was a strong suspicion of associated genetic syndrome. The couple opted for invasive testing (amniocentesis) . Sample was sent for qfPCR and whole exome sequencing. Electrophoretogram analysis for chromosome specific markers indicated a normal complement of 13, 18, 21 and sex chromosomes.

Whole exome sequencing for the reported phenotype reported:

- Pathogenic variant in the AMER1 gene associated with Osteopathia striata with cranial sclerosis (OS CS)

- Heterozygous for a Pathogenic variant in the MKS1 gene associated with Meckel syndrome, type 1(MKS1)

- Heterozygous for a variant of uncertain significance (VOUS) in the NECTIN1 gene associated with Cleft lip/palate-ectodermal dysplasia syndrome (CLPED1). American College of Medical Genetics and Genomics (ACMG) guidelines strongly advise against using VOUS results for clinical decision-making.

The couple was explained that the grave prognosis of the fetus. They opted for termination of pregnancy.(Figure 5). The couple decided not to proceed with a fetal autopsy.

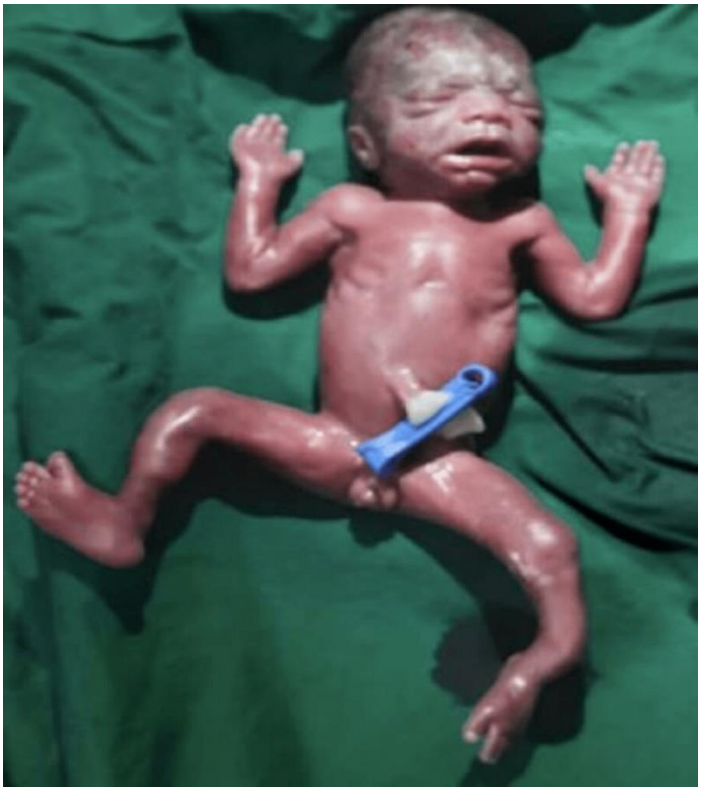

Figure 5: Image of the baby taken at time of delivery showing bilateral clubfoot. The couple decided not to proceed with a fetal autopsy

The couple was advised to undergo genetic testing using whole exome sequencing (with copy number variations) to help us prognosticate the next pregnancy. However , they refused

DISCUSSION

Meckel syndrome (MKS), also known as Dysencephalia splanchnocystica or Meckel-Gruber syndrome, is a lethal ciliopathy. It is commonly characterized by occipital encephalocele , renal cystic dysplasia, and postaxial polydactyly of the extremities. Liver involvement, specifically ductal plate malformations, is frequently present. This syndrome, with a prevalence between 1 in 13,250 and 1 in 140,000 across U.S. and European populations respectively , is the most common syndromic form of neural tube defects and polydactyly, contributing to roughly 5% of all neural tube defect cases.[1,2]

Meckel syndrome (MKS) is caused by mutations in genes involved in primary ciliary function. Currently, at least 13 genes are linked to MKS, including MKS1-10, TMEM231, TMEM237, and C5orf42. [1] Polydactyly is frequently associated with MKS1 mutations but is rare with MKS3 mutations. The condition follows an autosomal recessive inheritance pattern and exhibits significant phenotypic variability. The genetic basis of Joubert syndrome also overlaps with MKS. [3,4]

Meckel syndrome (MKS) can be identified prenatally as early as 11 to 14 weeks of gestation. Almost all cases (95-100%) exhibit cystic dysplastic kidneys, which develop microscopic cysts that progressively destroy the kidney parenchyma and can cause the organs to enlarge by 10-20 times their normal size. Other differentials (Figure 6) should also be kept in mind while assessing hyperechoic bulky kidney. [5 ,6]

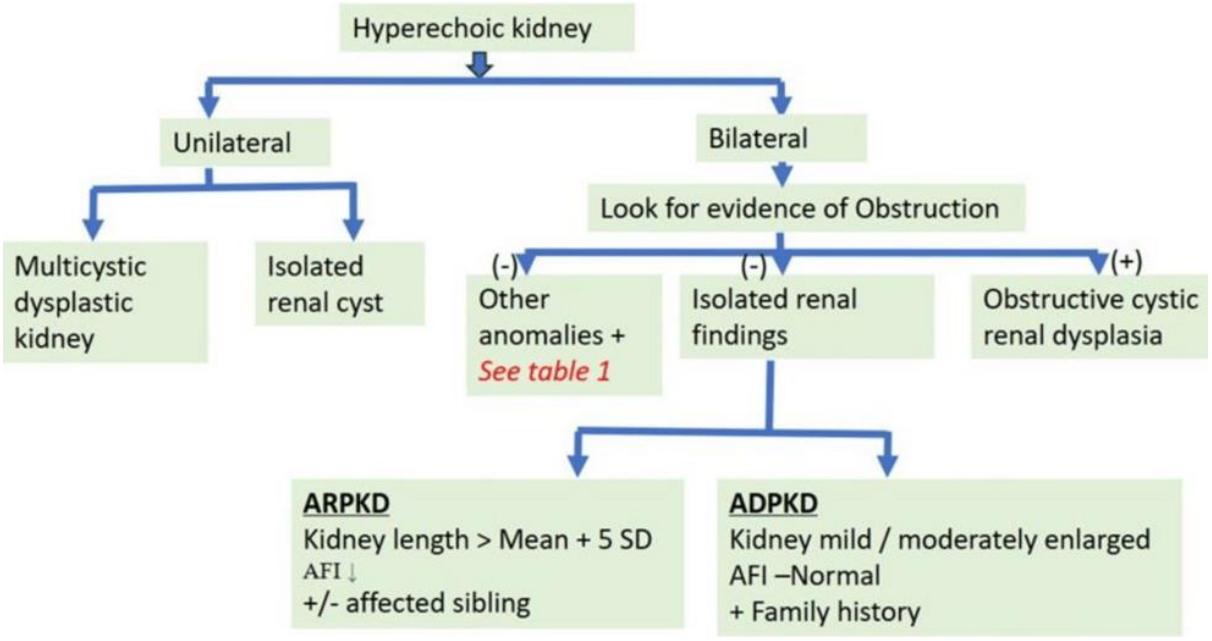

Figure 6: Differential diagnosis for enlarged hyperechogenic kidneys

Table 1: Syndromic associations with enlarged echogenic kidneys

Syndrome	Liquor	Associated anomalies	Inheritance	Kidney volume
Beckwith Weidmann	N/↑	LGA, Macroglossia, omphalocele gigantism, genital anomalies	AD/Sporadic	↑
Perlman	↑/↓	Visceromegaly, LGA,CDH, cystic hygroma	AR	↑
Trisomy 13	N/↓	↑NT. CNS (holoprosencephaly) & cranio-facial abnormalities, FGR, Congenital heart disease . Post-axial polydactyly, exomphalos	Sporadic	↑
Bardet-Biedl	N	Polydactyly .Congenital heart disease. Poor cognition ; obesity	AR	↑
Meckel Gruber	↓	Occipital encephalocele , post axial polydactyly,large dysplastic kidneys	AR	↑
Zellweger	N	Hepatomegaly,FGR,hypertelorism	AR	N
Elejalde	↓	LGA with organomegaly, thick skin	AR	↑

Occipital encephalocele is observed in 60-80% of MKS cases. Maternal serum or amniotic fluid alpha-fetoprotein (AFP) levels may appear normal if the encephalocele is covered by a membrane. It is important to distinguish encephalocele from other conditions such as neck haemangioma, or cystic hygroma. Skull defect will not be seen in these cases. Encephalocele can also occur in other non-chromosomal syndromic conditions like amniotic band syndrome, which involves limb or digit amputations and facial abnormalities. Cephalocele is associated with a 7-18% risk of aneuploidy. [4]

Additional central nervous system (CNS) abnormalities in MKS include Dandy-Walker malformation and hydrocephalus. Orofacial clefts, such as cleft lip and palate, microphthalmia, and micrognathia, are observed in about 31.8% of cases.

Cardiac anomalies, including atrial septal defect, aortic coarctation, patent ductus arteriosus, and valvular pulmonary stenosis, may also occur. Genital abnormalities are common and may include ambiguous genitalia in female and cryptorchidism in males. Rare features include urothelial atresia and bone dysplasia. [2] Limb abnormalities, such as bowing or shortening, are often present, along with postaxial polydactyly, which is seen in 55% to 75% of foetuses with MKS. [7] Polydactyly has other associations as well (Table 2)

Liver histology frequently reveals ductal plate malformations in MKS.

Diagnosing MKS can be challenging because of oligohydramnios. Oligohydramnios results from renal dysfunction and typically

develops early in the second trimester when the kidneys replace extracellular diffusion as the primary source of amniotic fluid. However, in some cases, like ours, amniotic fluid levels may remain normal.[1]

Differential diagnoses to consider, due to overlapping clinical features, include Bardet-Biedl syndrome, Joubert syndrome , Smith-Lemli-Opitz syndrome , trisomy 13 and trisomy 18. Genetic analysis is required for definitive diagnosis.[1,2]

In the first presented case, 2 of the hallmark features of MKS were identified, i.e., an occipital encephalocele & bilateral renal dysplasia . Bilateral clubfoot was also noted .

The second case revealed a pathogenic variant in the MKS1 gene (heterozygous) , associated with Meckel syndrome. In this instance, the presence of orofacial clefts and bilateral clubfoot raised the possibility of this diagnosis.[1,8]

The second case was found to have a pathogenic variant in the AMER1 gene associated with Osteopathia striata with cranial sclerosis (OS-CS), a profoundly rare disorder with a prevalence below 0.1 per million. This clinically heterogeneous condition exhibits a wide spectrum of severity and presentation, even among family members. OS-CS can involve a range of pathologies, from subtle skeletal abnormalities to complex multisystem involvement. Associated features include developmental delay, hearing loss, cranial nerve palsies resulting from narrowed nerve canals and foramina, and cataracts. Prenatal ultrasound findings suggestive of Osteopathia striata with cranial sclerosis (OS-CS) may include macrocephaly, characteristic facial dysmorphisms such as frontal bossing and hypertelorism, cardiac defects like ventricular septal defect and aortic stenosis, and extremity anomalies, such as clubfoot. Radiographic examination of affected individuals reveals sclerosis of the long bones and skull, along with longitudinal striations in the long bones, pelvis, and scapulae. In males, this condition frequently results in foetal or neonatal death [9,10]

Given the autosomal recessive inheritance of Meckel-Gruber syndrome (MKS), with its 25% recurrence risk and rare reports of sporadic cases, correct diagnosis is crucial to facilitate early ultrasound monitoring in subsequent pregnancy

CONCLUSION

These two cases emphasize the critical role of early prenatal screening, the wide phenotypic spectrum of Meckel Gruber syndrome, the necessity of genetic testing for accurate diagnosis, and counselling to support informed decision-making in future pregnancies

REFERENCES

1. Ferro, F.; Vezzali, N.; Comploj, E.; Pedron, E.; Di Serafino, M.; Esposito, F.; Pelliccia, P.; Rossi, E.; Zeccolini, M.; Gianfranco, V. Pediatric Cystic Diseases of the Kidney. J. Ultrasound 2019, 22, 381–393.
2. . Kathryn Johnson Gray, Louise Wilkins-Haug: Ultrasound Features of Fetal Syndromes. Callen's Ultrasonography in Obstetrics & Gynecology . 6 (ed): Elsevier , 2016. 554-556.
3. .Paladini, D., & Volpe, P: Syndromic conditions. Ultrasound of congenital fetal anomalies. 3 (ed): CRC Press, 2024. 581 - 631.
4. . Chen, C: Syndromes, Disorders and Maternal Risk Factors Associated with Neural Tube Defects (III). Taiwanese Journal of Obstetrics and Gynecology. 2008, 47:131-140. 10.1016/S1028-4559(08)60070-4
5. . Shin S. J., Ahn E. H., Moon M. J., et al.: P38. 10: A case of Meckel-Gruber syndrome diagnosed by ultrasonography at 14 weeks' gestation. Ultrasound in Obstetrics and Gynecology. 2007, 30:595.
6. . Charles J Lockwood , Joshua Copel , Dugoff Lorraine: Fetal Urogenital Imaging. Creasy and Resnick's Maternal Foetal medicine : Principles and Practice. 9 (ed): 400-432, 2023. 9:400-432.
7. . Paladini, D., Volpe, P: .Urinary Tract Anomalies. Ultrasound of congenital fetal anomalies. 3 (ed): CRC Press, 2024. 493 – 522.
8. . Paladini, D.,Volpe, P: Skeletal dysplasias and Muscular anomalies - A Diagnostic Algorithm. Ultrasound of congenital fetal anomalies. 3 (ed): CRC Press, 2024. 537 -579.
9. Sleurs E., Gonçalves L., Johnson A., et al.: First-trimester three-dimensional ultrasonographic findings in a fetus with frontonasal malformation. The Journal of Maternal-Fetal & Neonatal Medicine. 2004, 16:187-197. 10.1080/jmf.16.3.187.197
10. . Fradin M, Collet C, Ract I, Odent S, Guggenbuhl P: First case of osteopathia striata with cranial sclerosis in an adult male with Klinefelter syndrome. Joint Bone Spine. 2017, 84:87-90. 10.1016/j.jbspin.2016.04.012
11. . Keppler-Noreuil KM, Martinez-Agosto JA, Hudgins L, Carey JC. 37th Annual David W: Smith Workshop on Malformations and Morphogenesis: Abstracts of the 2016 Annual Meeting. Am J Med Genet A. 2017, 173:2007-2073. 10.1002/ajmg.a.38229.