Meckel's Gruber With Dandy-Walker Syndrome

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Abstracts: Background: Meckel-Gruber syndrome (MGS) is a classic triad of occipital encephalocele, postaxial polydactyly and dysplastic cystic kidney with or without other associated malformations. Dandy-Walker malformation (DWM) is the association of three signs: hydrocephalus, partial or complete absence of the cerebellar vermis, and posterior fossa cyst contiguous with the fourth ventricle. Methodology: A 30 weeks dead fetus fixed in formalin was sent at Genetic Health And Research Center, Nasik for further evaluation. It was diagnosed by ultrasonography as Dandy walker syndrome with multiple congenital anomalies. Autopsy finding confirmed that it was Meckel's Gruber syndrome. Results & Discussion**:** Meckel-Gruber syndrome is extremely heterogenous syndrome with six different loci and it inherits in families as autosomal recessive disease with 25% of chance of recurrence in each pregnancy. MGS affects multiple organ systems of the body leading to many other pathological conditions such as Arnold-Chiari malformation or Dandy-Walker malformation. It is suggested to be caused by failure of the mesodermal induction leading to ciliopathies caused by dysfunction of cilia. The occurrence of a Dandy-Walker malformation in Meckel-Gruber syndrome confirms disturbance in rhombencephalon development and such variants are very uncommon. Many cases of Dandy Walker Syndome as such have been published throughout but Dandy Waker associated with Meckel's Gruber Syndrome is extremely rare. Conclusion: We propose that proper autopsy of all still birth should be conducted to guide parents for possible risks in subsequent pregnancies. Prenatal and postnatal counseling and prenatal diagnosis should be encouraged in all disease prone cases. [Ambekar S et al NJIRM 2015; 6(3):125-130]

Key Words: Occipital Encephalocele, Polycystic Kidneys, Post axial Polydactyly, Dandy-Walker Syndrome.

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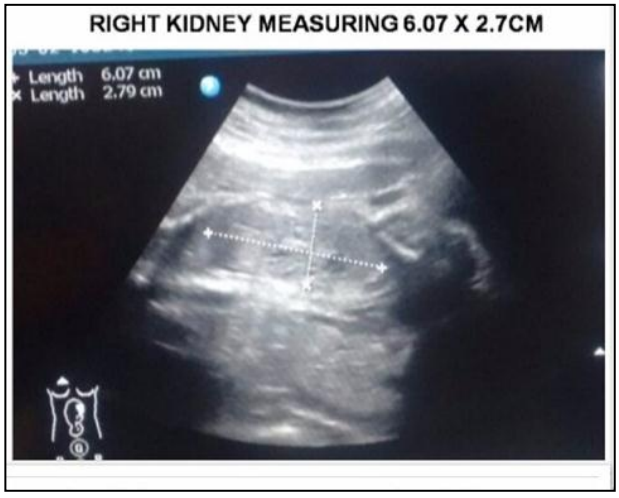
Introduction: Meckel-Gruber syndrome (MGS) is a rare and lethal syndrome characterized by classic triad of occipital encephalocele, postaxial polydactyly and dysplastic cystic kidney[1,2,3,4,5] with or without other associated congenital malformations. We report a classic case of Meckel-Gruber syndrome with Dandy-Walker malformation in the stillborn fetus delivered at 30 weeks.

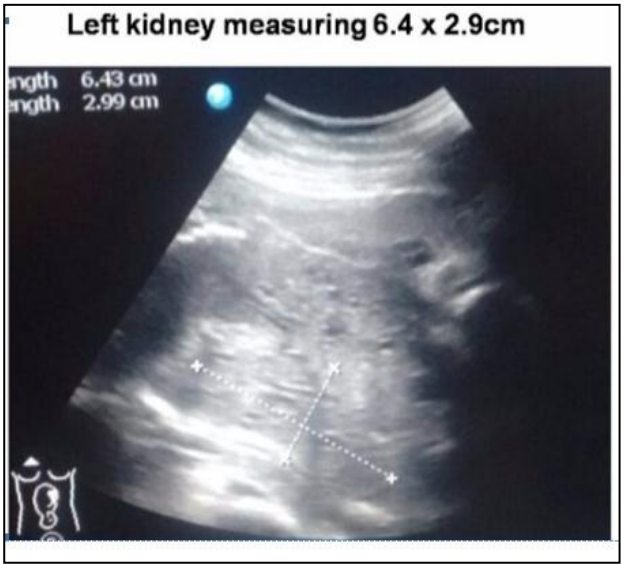
Material and Methods & Results: A 30 weeks dead fetus fixed in formalin was sent at Genetic Health And Research Center, Nasik for further evaluation. Pedigree did not reveal any significant genetic history in the family; however, there was 3rd degree consanguinity in the parents of the fetus and this was the first pregnancy of the couple.

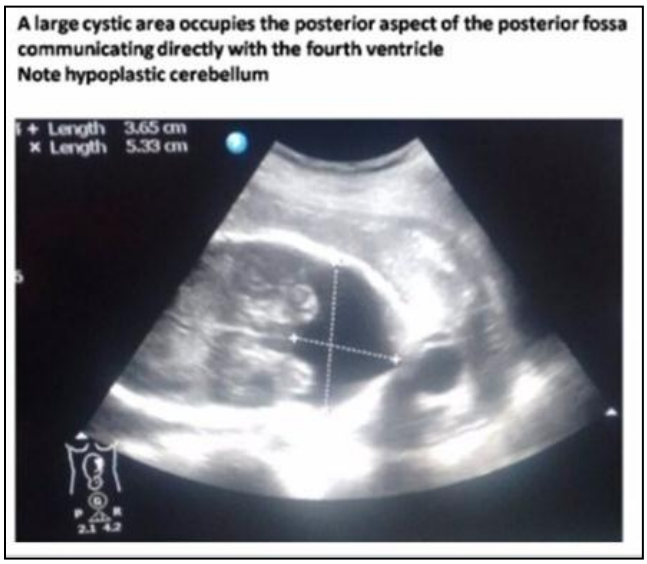
Ultrasonographic examination (figure 1) before delivery had revealed a dead fetus with oligohydramnios, dolicocephaly, cystic lesion in posterior cranial fossa communicating with fourth ventricle, hypoplastic bilateral cerebellar hemispheres and vermis, posterior encephalocele measuring 24 ×17 mm bilateral dysplastic kidneys with multiple cysts. It was diagnosed as supratentorial mild hydrocephalous with hypoplastic cerebellum with Dandy walker syndrome with multiple congenital anomalies.

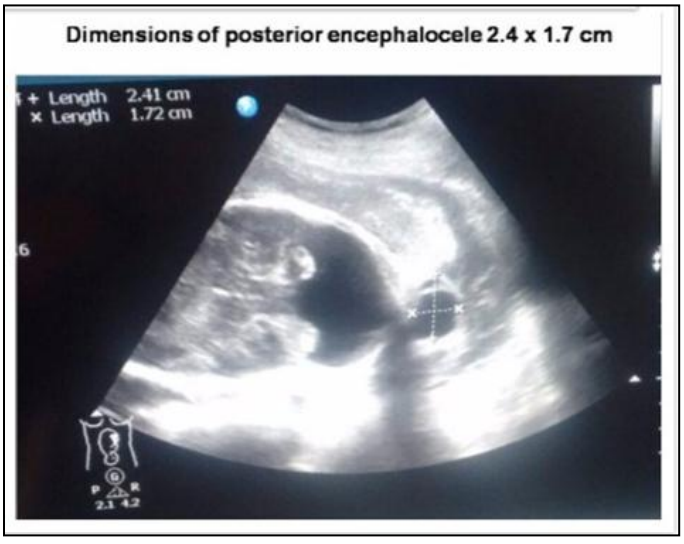
Proper physical examination and autopsy was performed on the fetus. Important findings were noted and photographed.

Figure 1: USG Reports Confirming Dandy Walker Syndrome









Important findings were

- Head neck and face showed dolichocephaly, occipital meningocele, low placed ears, short neck, depressed nose, micrognathia, low set frontal hair line, hypertelorism, potter facies (figure 2 &3)

- Thorax externally appeared normal but autopsy showed hypoplastic lungs (figure 4)
- Upper limb had unilateral postaxial polydactyly on left side and both feet had talipus equino varus (figure 2)

- Abdomen appeared distended where umbilical cord showed normal three blood vessels and external genitalia were of male patient with normally descended testis (figure 4)

- Autopsy of abdomen was significant and revealed bilateral bulky polycystic kidneys with rudimentary urinary bladder (figure 5)

- From the autopsy findings it was diagnosed as a case of Meckle- Gruber syndrome with Dandy-Walker malformation and parents were counselled properly to minimize mental trauma and advised for prenatal diagnosis for subsequent pregnancies since the recurrence rate is 1: 4.

Figure 2: External Features Of Baby

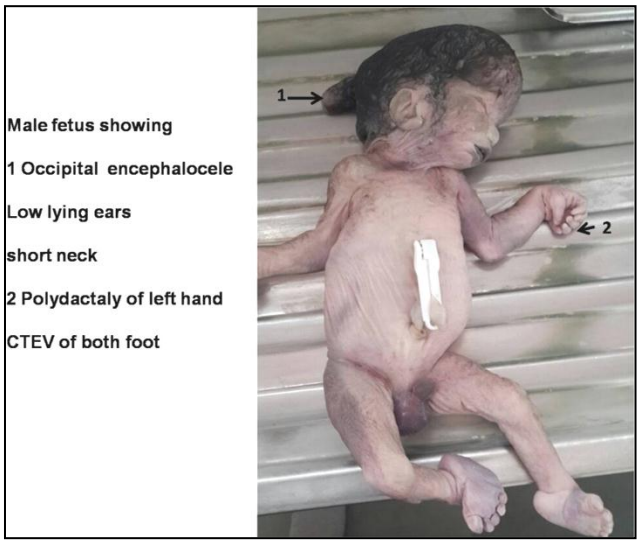


Figure 3: Typical Face Of Meckel's Gruber Syndrome

Figure 4 Autopsy Findings Showing Hypoplastic Lungs

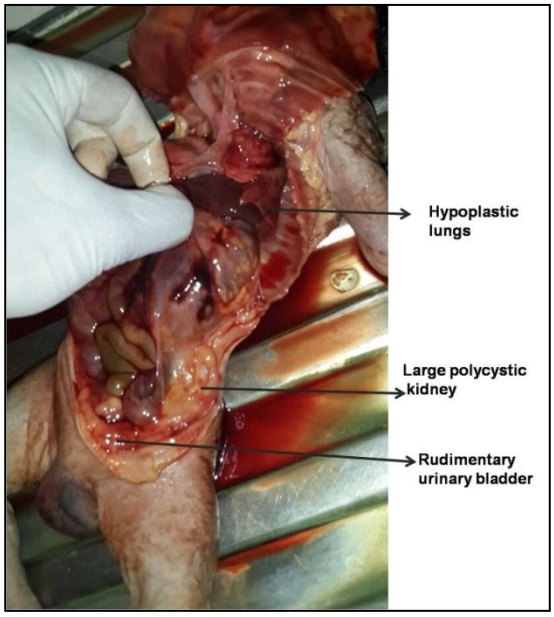


Figure 5: Autopsy Showing Enlarged Kidneys And Rudimentry Urinary Bladder

Discussion: Everyone wish happiness in life and the major part of it is related to having children. It is a real mental trauma for parents, especially the mother to deliver a dead baby and if that baby is not looking normal or simply monstrous in laymen's language, then mother has to pay a lot till she delivers next normal child.

Meckel- Gruber syndrome is one of such condition, where usually the baby does not survive till birth. Others being neural tube defects including an anencephaly or meningocele or spina bifida[6] or chromosomal abnormalities like polyploidy resulting from triploidy (69 chromosomes) or tetraploidy .

Meckel-Gruber syndrome inherits in families as autosomal recessive disease with 25% of chance of recurrence in each pregnancy. MGS was first described by Johann Friedrich Meckel in 1822 in two siblings with identical malformations of occipital encephalocele, polycystic kidneys and polydactyly. These signs are considered as the diagnostic features of MGS by many researchers. George B Gruber in 1934 reported many familial cases with similar features and coined the term "dysencephalia splanchnocystica". In 1969, Opitz and Howe proposed the name Meckel's syndrome (MKS) [1,7].

The condition is lethal due to dysgenesis of kidneys. It is presented either as still birth or baby dies within 24 hours of birth but prolonged survival up to 28 months has been reported by Mandeep[7] etal. Review of literature reveals only ten neonates surviving beyond birth[5].

Incidence of MGS is I: 1, 40,000 to I: 13,250 more common among Yemenite Jews[1, 5, 7]. In Finland with high frequency of recessive diseases, the probable incidence of MGS was found to be 1: 9000 births which mean one person in 50 is a carrier and 1: 3000 in Belgium [5]. The highest incidence reported in the Gujarati Indians settled in Leicestershire, is 1: 1,300 (carrier rate, 1 in 18). Cases of MGS have been reported in North America, Europe, Israel, Indonesia, India, Kuwait, and Japan[2, 3]. Incidence is seen more with consanguine marriages[5].

According to Hima etal[1] the major diagnostic criteria include classic manifestations of cystic renal dysplasia associated with either occipital

encephalocele or other anomalies of central nervous system in 90% or polydactyly in 83.3%. Fraser[8] etal mentioned that all cases of MGS had cystic dysplasia of kidneys and 63% had occipital meningocele, 55% had polydactyly so the most evident diagnostic criteria of Meckel's syndrome is the absence of cystic renal dysplasia.
Aarya etal[9] had reported multicystic kidneys in 95% and posterior encephalocele in 80%, and polydactyly 75%. According to Gupta[4] etal 57% of the cases had 3 cardinal findings, but 16% had only polycystic kidney and polydactyly.

. According to Usal etal[10] till 2015, only one case of MGS with unilateral renal agenesis was reported to the literature and he reported the second case.
MGS affects multiple organ systems of the body is associated with many other pathological conditions and including CNS manifestation or facial abnormalities or heart, liver or lung failures, gastro intestinal anomalies like omphalocele or pseudohermaphroditism[2,3,5]. Arnold-Chiari malformation or Dandy-Walker malformation may also be associated[1, 2, 4]. Dandy-Walker malformation (DWM) is the association of three signs: hydrocephalus, partial or complete absence of the cerebellar vermis, and posterior fossa cyst contiguous with the fourth ventricle[11] which are all observed in our case.

Myageri A[12] mentioned that only 200 cases of Meckel Gruber Syndrome are repored till 2013. Gupta etal[4] has reported a case of MGS with DWS. Balci etal[13] prenatally diagnosed a case of MGS with DWS in a consanguineous family. Yepar etal[14] in 1996 reported two such cases. According to Cincinnati etal[15], the occurrence of a Dandy-Walker malformation in Meckel-Gruber syndrome confirms disturbance in rhombencephalon development and such variants are very uncommon.

Many cases of Dandy Walker Syndrome as such have been published throughout but Dandy Walker associated with Meckel's Gruber Syndrome is extremely rare. With extensive online research we could find only above mentioned 5 cases. It could be because of either all cases are not being reported online or may be neglected by labeling as still birth. We propose that proper autopsy of all still birth should be conducted so as to guide parents for possible risks associated with subsequent pregnancies and to have a better and healthy community. We also request that every variable case should be reported.

Abnormalities like lung hypoplasia[2] and club foot[3] are secondary to oligohydromnios.
Mohammad[16] etal reported a case of MGS where genitalia were undermined with 1cm phallus with single opening, labioscrotal folds but no palpable inguinal mass.

Malformations like cleft lip, cleft palate, polydactyly, syndactyly and congenital heart defect occur in relatives of MGS more frequently than expected [3].

MGS has to be differentiated from other disorders like Smith-Opitz syndrome, trisomy 13, hydrolethalis syndrome, Senior-Loken syndrome, Joubert syndrome and Bardet-Biedl syndrome[1,2] Ivemark syndrome[7]. MGS has been suggested to be caused by failure of the mesodermal induction leading to ciliopathies caused by dysfunction of cilia[5].

The induction cascades of early morphogenesis involve numerous growth factors, homeobox genes, and paired domain genes. it is a genetically heterogeneous disease with minimum 10 different defined genes. The role of the genetic testing is still in progress and several loci for MGS syndrome have been mapped on 17q, 11q, and 8q[10].

According to Prasad[2] etal MGS is an extremely heterogenous syndrome with six different loci. MKS 1 was mapped to chromosome 17q21-q24, in Finnish population where there was disruption of the homeo-box B (*HOXB*). The tissue expression of this gene was reported mainly in the brain, liver, kidney and cartilage of the developing digits. MKS2 was mapped to chromosome11q13 proving its heterogeneity. This locus was commonly observed in North Africa and Middle East. MKS3 is mapped to 8q 24, which was having expression in the adrenal gland, brain, kidney, lung and spinal cord explaining the rarity of polydactyly in MKS3. Cases of MKS3 were from Pakistan and Oman [17]. MKS4 is caused by homozygous or compound heterozygous mutation in the CEP290 gene on chromosome 12q21. Mutations in the *RPGRIP1L* gene in

chromosome 16q12.2 (MKS5) have also been identified in patients with clinical features consistent with MGS. A gene on chromosome 4p15 (*CC2D2A*) was recently considered as the most likely candidate for the clinical features of Meckel syndrome in probands from 11 Finnish families (MKS6). Hima[1] etal mentioned three types of MKS and stated that polydactyly appears to be less common in MKS3 when compared to MKS1 and 2 types. Uma[5] etal also mentioned about similar six loci of MGS.

Saolnen[18] studied gene mutations in all 6 different types of MGS and according to him if the causative gene and mutation of MGS can be identified, carrier screening of the relatives becomes possible and molecular prenatal diagnosis and preimplantation diagnosis can be done.

OMIM online article number 249000[19] has given list of 12 types of MKS with mutation on gene locus of that particular chromosome. We have already mentioned about first six so the next are MKS7 caused by mutation in the NPHP3 gene on chromosome 3q22; MKS8 caused by mutation in the TCTN2 gene on chromosome 12q24.31; MKS9 caused by mutation in the B9D1 gene on chromosome 17p11.2; MKS10 caused by mutation in the B9D2 gene on chromosome 19q13; MKS11 caused by mutation in the TMEM231 gene on chromosome 16q23; and MKS12 caused by mutation in the KIF14 gene on chromosome 1q31.
According to Naveen[3] etal prenatal diagnosis of MGS can be done by vaginal ultrasound scan after 11-12 weeks of gestation and chorionic villi sampling at 14 weeks for molecular diagnosis. MRI can also be used to see foetal defects. According to Uma[5] etal MGS can be diagnosed by ultrasonography as early as 12-14 weeks gestation with demonstration of polydactyl and an encephalocele or by estimation of α-fetal protein in maternal serum during first trimester. Maternal and foetal alpha fetoprotein levels are elevated due to CNS malformation but if encephalocele contain a closed sac then alpha fetoprotein level will not be elevated[7] Usal[10] etal suggested molecular genetic testing to verify the diagnosis in families with genetic suspicion of MGS.

Conclusion: Meckel's Gruber syndrome is a fatal condition caused due to genetic mutations. Though it's rare, many cases have been reported from India but MGS associated with DWS is extremely rare.

We suggest autopsies of all still births should be encouraged as these may form the basis of new insight for research. Prenatal and postnatal counselling is utmost important to combat such mental trauma. Prenatal diagnosis should be encouraged in suspected or disease prone cases.

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