# Prenatal diagnosis of Meckel-Gruber syndrome and Dandy-Walker malformation in four consecutive affected siblings, with the fourth one being diagnosed prenatally at 22 weeks of gestation

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**We report a 23-week-old male fetus affected by Meckel-Gruber syndrome. Posterior encephalocele, post-axial polydactyly, and Dandy-Walker malformation were observed on ultrasonographic (USG) examination at 22 weeks' gestation, and lobar holoprosencephaly was demonstrated on postmortem magnetic resonance imaging (MRI) prior to autopsy. After the termination of the pregnancy, polycystic dysplastic kidneys were also noted at postmortem investigation.**

**The proband was the product of the fourth pregnancy of a consanguineous family in which all three siblings were also similarly affected. Interestingly, both the two-year-old affected sister and 23-week-old male fetus had Dandy-Walker complex.**

***Key words: Meckel-Gruber syndrome, Dandy-Walker malformation, four consecutive siblings, lobar holoprosencephaly, MRI findings.***

Meckel-Gruber syndrome (MGS) is a rare and lethal autosomal recessive disorder characterized by occipital encephalocele, bilateral polycystic, dysplastic kidneys and post-axial polydactyly[1,2].

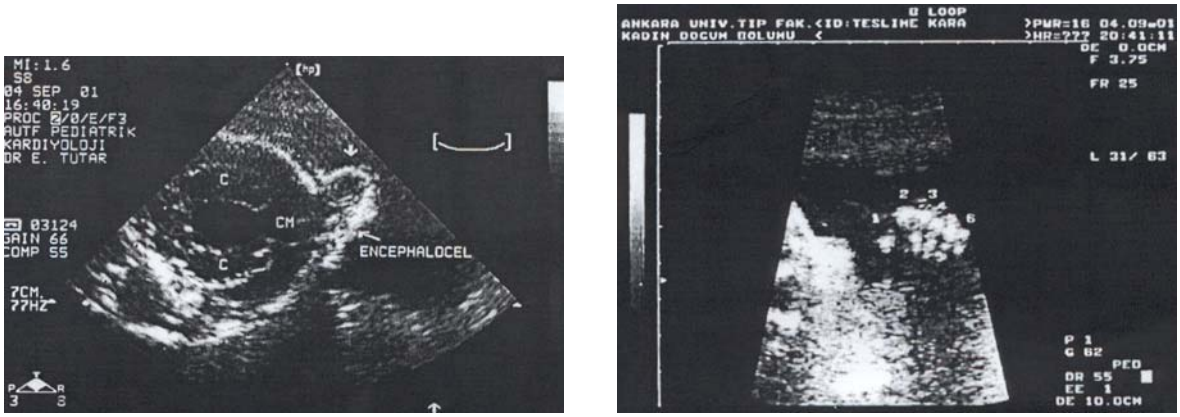
Although numerous abnormalities associated with Meckel-Gruber syndrome were previously reported in the literature, Dandy-Walker malformation[3-5], microcephaly, intrauterine growth retardation (IUGR), single umbilical artery, cardiovascular defects, cleft palate[6,7], several genital abnormalities[4,6,7], and oligohydramnios[3,7] are the most well known. Hepatic periportal fibrosis[5] and hydrocephalus[8] were also noted in some cases. The incidence of this rare syndrome has been estimated as 1 in 50,000[9] by some authors. We report a 23-week-old male fetus prenatally diagnosed at 22 weeks of gestation and induced with the findings of occipital encephalocele, post-axial polydactyly, Dandy-Walker malformation, lobar holoprosencephaly and polycystic kidneys. Interestingly, three other siblings of the fetus also had MGS phenotypes with some variabilities, showing the genetic heterogeneity of the entity.

## Case Report

A 23-year-old woman was admitted to Ankara University, Faculty of Medicine, Obstetrics and Gynecology Department at 22 weeks' gestation for the possible diagnosis of occipital encephalocele and hydrocephalus (Fig. 1a) and polydactyly in the fetus (Fig. 1b). Family history revealed that the previous three pregnancies were affected with polydactyly and hydrocephalus (Fig. 2) (2 females, 1 male).

Maternal alpha-fetoprotein (AFP) was relatively high (162 ng/ml) suggesting a neural tube defect (NTD) risk of 1/50. Isolated left ventricular dilatation and perimembranous ventricular septal defect on fetal echocardiography were observed.

Cordocentesis was performed giving a normal 46, XY karyotype. Therapeutic abortion was performed at 23 weeks' gestation because of




(a) (b)

**Fig. 1.** a) Ultrasonographic appearance of the fetus at 22 weeks' gestation characterized by occipital encephalocele b) Polydactyly demonstrated by fetal sonography.

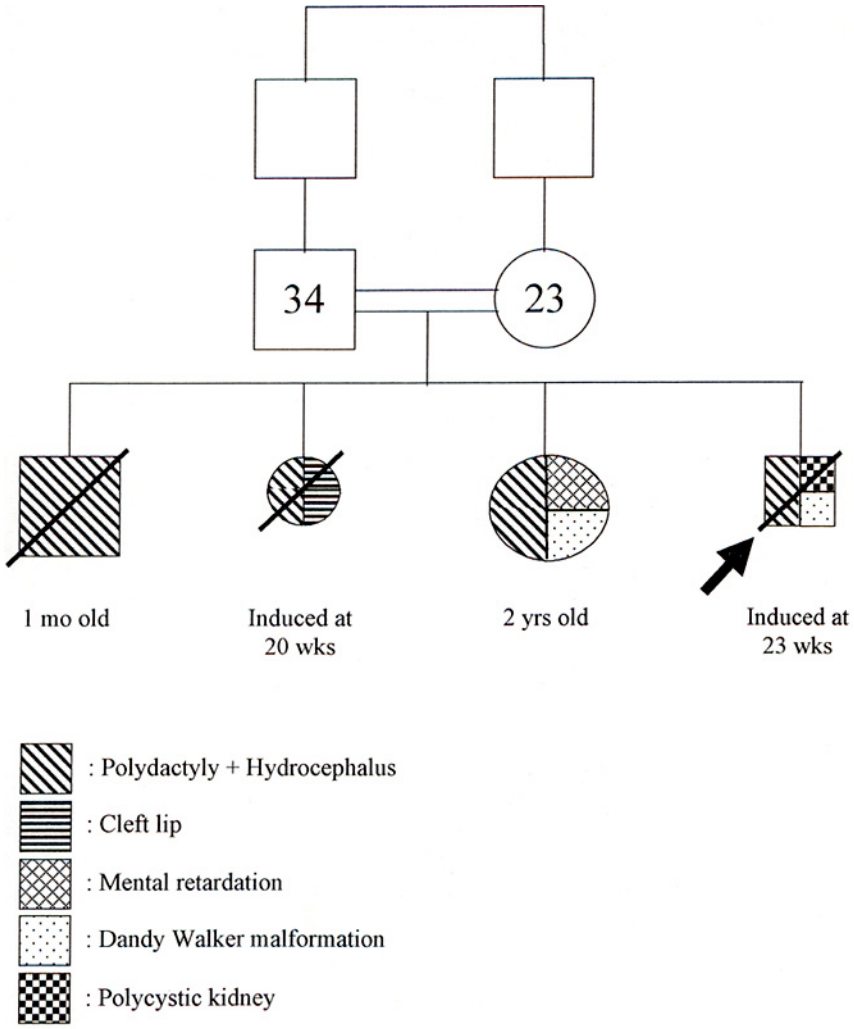
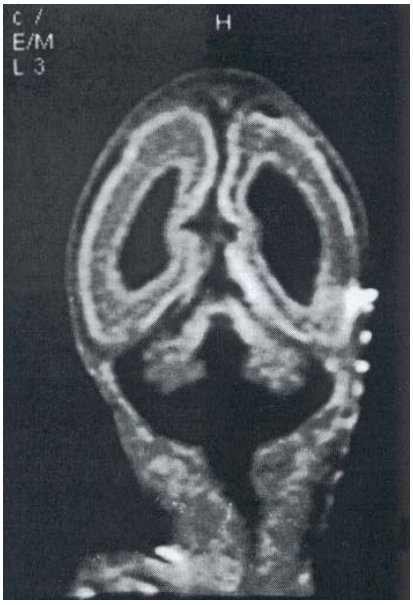


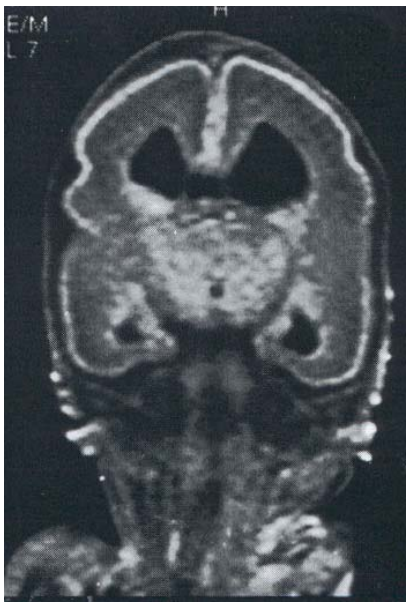

**Fig. 2.** Pedigree of the family.

multiple congenital malformations. Postmortem magnetic resonance imaging (MRI) was performed before the autopsy, revealing vermian hypoplasia, posterior fossa cyst (Fig. 3a), lobar holoprosencephaly (Fig. 3b), and Dandy-Walker malformation (Fig. 3c).

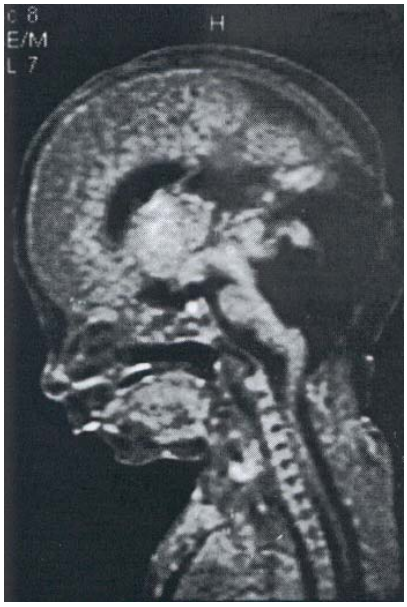
Postmortem external examination revealed a male fetus with a weight of 580 g and crown-heel length of 30 cm. Head circumference was 25 cm. The fetus had occipital encephalocele, post-axial polydactyly of hands (Fig. 4) and polydactyly in the hands and feet. Bilateral




a) Coronal T1 weighted image demonstrating vermian hypoplasia, dilatation of lateral ventricles and posterior fossa cyst.




b) Coronal T1 weighted image of lobar holoprosencephaly. The cerebral hemispheres were only fused at the level of thalamus.




c) Sagittal T1 weighted image demonstrated the key features of Dandy-Walker malformation such as the fourth ventricle was being directly communicating with a cyst of the posterior fossa. The hypoplastic vermis had incomplete rotation. Tentorium was high.

**Fig. 3.** Postmortem MRI findings of the 22-week-old fetus.

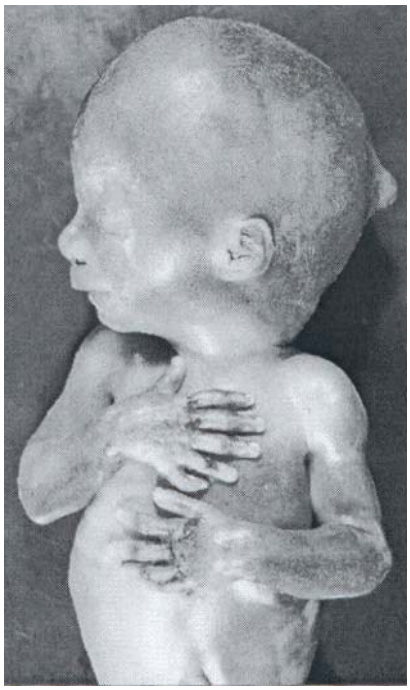


**Fig. 4.** External appearance of the fetus with post-axial polydactyly of the hands and occipital encephalocele.

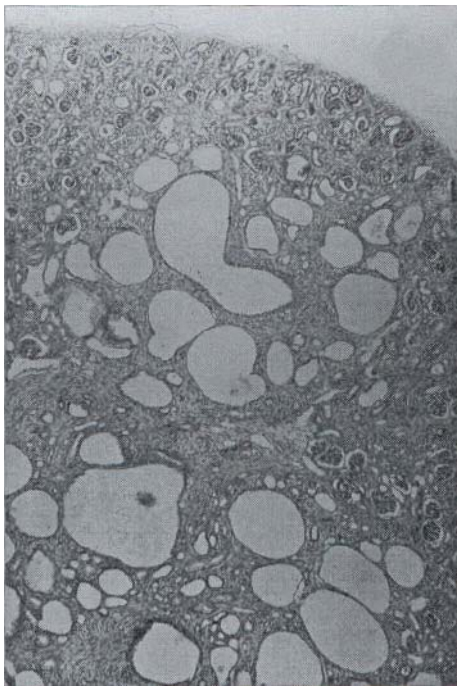


**Fig. 5.** Microscopic appearance of the fetal kidneys showing cystic collecting ducts, normal glomerulus and dilatation of the tubules (HEx40).

lobulated kidneys were noted. Bilateral total renal weight was 6 g (normal 4±1.7 g).

Macroscopic examination of central nervous system (CNS) revealed dilatation of lateral ventricles and severe hypoplasia of cerebellar vermis covered by an arachnoidal cyst of about 1 cm in diameter. Protruded leptomeningeal tissue was detected through to the occipital osseous defect about 1 cm in diameter.

On cross-section, the cut surfaces of kidneys were cystic in appearance like a sponge kidney. Microscopically cystic proximal, distal and collecting tubules of varying sizes were observed especially in the medulla of both kidneys (Fig. 5). The ureters and bladder were normal. The liver weighed 26 g (normal 21±7 g). Microscopically portal tract revealed fibrosis by immature mesenchymal connective tissue not associated with biliary duct dysgenesis. The first pregnancy was terminated with cesarean section due to hydrocephalus at 34 weeks' gestation and he died in the first month (Fig. 2). Fetus had hydrocephalus and post-axial polydactyly in both hands and feet. He also had heart defect, and was thus thought to be affected by MGS, but unfortunately the family refused a postmortem examination.

The second pregnancy was terminated by induction and female fetus was born at 23 weeks' gestation with the similar findings observed sonographically: hydrocephalus, occipital encephalocele, post-axial polydactyly and cleft lip. Microscopic evaluation was not possible because of severe autolytic changes.

The third pregnancy was followed by another medical center, and similar CNS malformations were observed at 28 weeks' gestation and cesarean section was performed at 36 weeks' gestation. This female patient also had bilateral post-axial polydactyly in the hands and feet. Magnetic resonance imaging findings of this severely mental and motor retarded patient at two years showed dilatation of the 4$^{th}$ ventricle (Fig. 6), cortical atrophy, Dandy-Walker variant and delayed myelinization in white matter. In addition to these malformations, ventricular septal defect (VSD) and pulmonary stenosis were observed. Sonographically the kidneys were found in normal limits; thus, kidney biopsy was not performed for ethical reasons.

Findings of the four siblings are summarized in Table I.

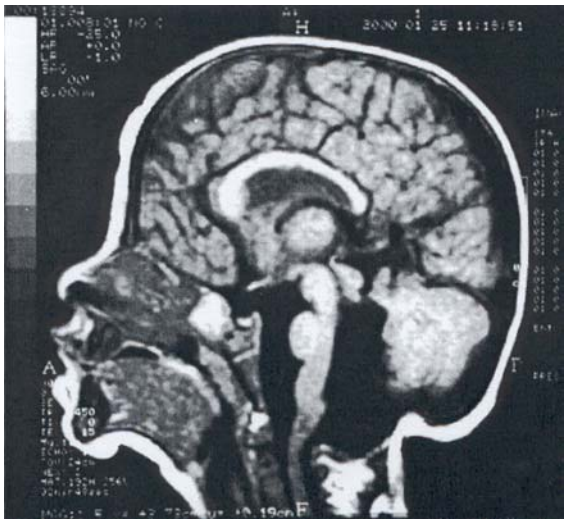


**Fig. 6.** MRI of two-year-old sister of the proband showing the features of Dandy-Walker variant. A retrocerebellar cyst freely communicating with the fourth ventricle and causing partial inferior vermian hypoplasia was observed on sagittal T1 weighted image; the torcular herophili was not elevated.

**Table I.** The Anomalies Observed in the Four Siblings of the Family

| | Sibling no. | | | |
|---|---|---|---|---|
| Anomaly | 1 | 2 | 3 | 4 |
| Post-axial polydactyly | + | + | + | + |
| Dysplastic polycystic kidneys | ? | ? | – | + |
| Posterior encephalocele | ? | + | + | + |
| Hydrocephalus | + | + | + | + |
| Dandy-Walker malformation | ? | ? | – | + |
| Dandy-Walker variant | ? | – | + | – |
| Cleft lip | ? | + | – | – |
| Mental retardation | ? | ? | + | ? |
| Heart defect | + | – | + | + |

## Discussion

Meckel-Gruber syndrome is characterized by cystic kidneys, occipital encephalocele and post-axial polydactyly. Two of the three major anomalies are sufficient for the definitive diagnosis. It was reported that 57% of the cases had three cardinal findings, but 16% had only polycystic kidney and polydactyly. The remainder exhibit other variations. Farag et al.[10] reported five Bedouin sibs with MGS lacking polydactyly; this could be explained by the phenotypic variability of MGS pleiotropic gene[10].

The spectrum of the phenotype in the MGS is very wide, encompassing various combinations of some quite common anomalies. Some cases may even be evaluated as a different syndrome[11]. Similarly in our family, four sibs had different phenotypic findings of MGS, again supporting the pleiotropic effect of the gene.

In the presented case, the fourth pregnancy, from a consanguineous family the prenatal diagnosis was made sonographically by the detection of polydactyly and CNS malformations at 22 weeks' gestation. In view of these findings, the fetus and the previous similarly affected siblings were accepted as MGS. CNS malformations of MGS are variable and show a broad spectrum ranging from occipital encephalocele, Chiari malformation, hydrocephalus, polymicrogyria, arhiencephaly, holoprosencephaly, agenesis of corpus callosum and anencephaly.

Unfortunately the previously affected siblings also had CNS malformations but could not be diagnosed as Meckel-Gruber syndrome. If the correct diagnosis could have been made, these cases would have been diagnosed. The other two findings of the classical triad, namely, renal cystic dysplasia and post-axial polydactyly, were present in the affected fetus. In addition to these abnormalities, Dandy-Walker malformation, including lobar holoprosencephaly and posterior fossa cyst, was also noted in our case with MGS.

Meckel-Gruber syndrome (MGS) is a lethal syndrome, generally resulting in utero or neonatal death within a few hours of life; thus, earlier prenatal diagnosis is very important.

The condition can be diagnosed sonographically in the first and second trimester[12,13].

Earlier diagnosed cases were reported at 12+2 weeks' gestation by transabdominal ultrasound[14], at 10 weeks by embryoscopy[15] and at 11 weeks of menstrual age, again by embryofetoscopy[16].

In our case, due to the late attendance of the patient, ultrasonographic examination was only performed in a later period at 22$^{nd}$ weeks of gestation, but we had the advantage of determining the high maternal serum alpha-fetoprotein level in the second trimester, which confirmed the diagnosis by showing the presence of the occipital encephalocele. Another interesting point in the presented consanguineous family was the observation of this syndrome in the four consecutive affected siblings with different phenotypes. Two consecutive pregnancies from a Polish family[17]; six children (five of whom died), three definitely, two possibly affected by MGS from a Papua New Gunean family[18]; two siblings

in two different families from Spain[19]; again two consecutive siblings from United Kingdom[20]; three affected cases in the same family from Saudi Arabia[21] and Ceylan[22]; and five Bedoun siblings but not consecutive from Kuwait[10], were reported previously in the medical literature.

To the best of our knowledge this is the first report with four consecutive affected cases with MGS in the same family, but having different phenotypes such as cleft lip and varying kidney pathologies in the children. This may be explained by the pleitropy of the MGS gene. In conclusion, family history, accurate prenatal diagnosis with ultrasonography and measurement of maternal or aminotic fluid alpha-fetoprotein levels in the second timester are essential in the pregnancies complicated by Meckel-Gruber syndrome for pregnancy management and counseling for abortion and for evaluation of recurrence risk in the future pregnancies. Furthermore, and for the first time, MRI was performed in this fetus before the postmortem examination. Thus holoprosencephaly and Dandy-Walker malformation were well demonstrated. As these fetuses are complicated with autolytic changes, these kind of anomalies cannot be diagnosed successfully in autopsy.

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