

Meckel–Grüber syndrome: sonography and pathology

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KEYWORDS: cysts; fetus; kidney; Meckel–Grüber syndrome; ultrasound

ABSTRACT

Objective To define a specific sonographic pattern for the appearance of the kidneys in fetuses affected by Meckel–Grüber syndrome (MGS).

Methods This was a retrospective analysis of 30 cases, collected from five centers, with ultrasound features suggestive of MGS. Only fetuses with a confirmed diagnosis of MGS were finally included. Analysis included a detailed evaluation of the sonographic findings and comparison with pathological follow-up.

Results Seventeen cases met the pathological criteria for a diagnosis of MGS and were included in the study. In all cases, a typical sonographic pattern was seen: the kidneys were enlarged (mean, +4.8 SD) and showed unusual corticomedullary differentiation, occurring as early as the first trimester. In most cases, the medullary areas appeared excessively large and mottled due to the presence of multiple small cysts.

Conclusions The kidneys of fetuses with MGS are enlarged, cystic and have unusual corticomedullary differentiation. These features can be observed as early as the first and early second trimesters. Copyright © 2006 ISUOG. Published by John Wiley & Sons, Ltd.

INTRODUCTION

Meckel–Grüber syndrome (MGS) was first described in 1822 by Meckel¹ and thereafter in 1934 by Gruber². It is a rare congenital polymalformative syndrome with an autosomal recessive mode of inheritance and the postnatal outcome of affected fetuses is invariably lethal.

The first reports included the association of occipital encephalocele, microcephaly, cleft palate, polycystic kidneys and polydactyly¹. Since then, other anomalies have been added to the description (posterior fossa, face, heart, spleen, digestive tract, genital tract and limb anomalies)^{3–6}. Phenotypic variability is well-described even among siblings presenting a recurrence of the disease, rendering a precise diagnosis difficult. The most frequent clinical presentation includes cystic kidneys, central nervous system (CNS) anomalies and polydactyly, but this association is not always present.

The clinical diagnosis of MGS relies on the pathological analysis of the syndrome's renal and hepatic anomalies, but its genetic characterization is still in progress^{7–9}. Because of the rapidly lethal prognosis, combined with the risk of recurrence in future pregnancies, an early and precise antenatal diagnosis would be of great value¹⁰.

While most reports in the literature have correlated clinical and pathological data, none has evaluated the merit of using a specific sonographic pattern of the kidneys as a diagnostic tool for MGS^{10,11}. The objectives of this study were: to analyze the sonographic anomalies encountered in fetuses with MGS, to correlate these anomalies with pathological findings in order to define more precisely the sonographic features of affected kidneys, and to examine whether the renal sonographic pattern is sufficiently specific to be useful as a criterion for direct diagnosis of the syndrome.

METHODS

This multicenter observational study was conducted in association with the French Group for Research in Pediatric and Fetal Imaging. Data from 30 cases suspected of having MGS were collected from five hospitals in Brussels, Bordeaux, Nancy, Paris and Rouen. For each

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Table 1 Characteristics of the 17 cases of Meckel–Grüber syndrome

Case	GA at diagnosis (weeks)	Ultrasound findings	Amniotic fluid volume	Associated anomalies	Recurrence
1	12	Nephromegaly, unusual CMD, cysts < 5 mm	Normal	Occipital encephalocele	+
2	13	Nephromegaly, unusual CMD, cysts < 5 mm	Normal	Occipital encephalocele, polydactyly	+
3	14	Nephromegaly, unusual CMD, cysts < 5 mm	Normal	Occipital encephalocele, neuronal anomalies, SGA, single umbilical artery	+
4	14	Nephromegaly, unusual CMD, cysts < 5 mm	Oligohydramnios	Occipital encephalocele, polydactyly, microcephaly, bowed femur	
5	16	Nephromegaly + 4 SD, unusual CMD, cysts < 5 mm	Oligohydramnios	Occipital encephalocele, cervical cystic hygroma, SGA	+
6	16	Nephromegaly, unusual CMD, cysts < 5 mm	Oligohydramnios	Occipital encephalocele	+
7	17	Nephromegaly + 3 SD, unusual CMD, cysts < 5 mm	Normal	Occipital encephalocele, microcephaly	+
8	17	Nephromegaly + 3 SD, unusual CMD, cysts < 5 mm	Oligohydramnios	Occipital encephalocele, polydactyly, campomesomelia, cuneiform vertebrae, pelvic spurs	
9	18	Nephromegaly + 5 SD, unusual CMD, cysts < 5 mm	Oligohydramnios	Occipital encephalocele	
10	21	Nephromegaly + 5 SD, unusual CMD, cysts > 5 mm	Oligohydramnios	Occipital defect, Dandy–Walker, ventriculomegaly	+
11	23	Nephromegaly + 5 SD, unusual CMD, cysts > 5 mm	Oligohydramnios	Dandy–Walker, ventriculomegaly	+
12	23	Nephromegaly + 6 SD, unusual CMD, cysts < 5 mm	Oligohydramnios	Occipital encephalocele, polydactyly, cleft palate, hydrocephalyhepatic cysts	+
13	23	Nephromegaly + 8 SD, unusual CMD, cysts < 5 mm	Oligohydramnios	Occipital encephalocele, polydactyly, Dandy–Walker	+
14	24	Nephromegaly, unusual CMD, cysts < 5 mm	Oligohydramnios	Occipital encephalocele, polydactyly, single umbilical artery	
15	24	Nephromegaly + 4.5 SD, unusual CMD, cysts < 5 mm	Oligohydramnios	Occipital encephalocele, polydactyly	+
16	24	Nephromegaly + 4 SD, unusual CMD, no cysts	Normal	Polydactyly, Dandy–Walker, brain stem dysplasia, neuronal heterotopias, genital anomaly	
17	25	Nephromegaly + 5 SD, unusual CMD, cysts of 5 mm	Oligohydramnios	Occipital meningocele, vermian agenesis	+

CMD, corticomedullary differentiation; GA, gestational age; SGA, small-for-gestational age.

patient, a data sheet was completed. Information gathered included: year of diagnosis, gestational age at the time of ultrasound examination, detailed sonographic features (including the size of the kidneys in SDs according to Cohen *et al.*¹², cortical echogenicity compared with the liver or spleen, medullary echogenicity (normal, absent or reversed), corticomedullary differentiation (CMD), presence and size of any cysts, amniotic fluid volume and presence of associated anomalies and details of any follow-up.

All ultrasound images were reviewed by two of the authors (V.I. and D.E.), both experienced obstetric sonologists, who reached an agreement by consensus for each sonographic feature recorded. Pathological findings were available in all cases and all pathological data were reviewed by two pediatric pathologists (M.C.G. and A.L.).

Only patients with a confirmed pathological diagnosis (cystic kidneys with corticomedullary gradient, hepatic fibrosis (ductal plate anomalies) and CNS anomalies)¹³ and a complete ultrasound description were included in the study. Patients with obvious familial recurrence were

also included even if some diagnostic criteria were missing in the new cases, while in the previous case the findings were characteristic.

RESULTS

Thirty patients suspected of having MGS were collected over a 16-year-period (1987–2003). Thirteen cases were excluded because of their pathological findings: the pathology was incomplete or inconclusive in six cases; there were no hepatic anomalies in two cases; there were no CNS anomalies in three cases and two cases had atypical renal involvement with cortical cysts. Pathology confirmed the diagnosis in 17 cases (Table 1), all of which had sonographic images available for analysis, and these were included in the final study. In four families there was at least one recurrence. They represented 12 of the 17 cases.

The mean gestational age at diagnosis was 19 (range, 12–25) weeks. When measurements were available, the kidney size varied from +3 SD to +8 SD (mean,

+4.8 SD). In all cases, the sonographic appearance of the fetal kidney was reported as abnormal, with unusual heterogeneous CMD and large, hypoechoic medullary areas. Cystic lesions were visualized in 16/17 fetuses and were numerous, small and located in the medulla. The cysts were <5 mm in the four cases detected during the first trimester, resulting in a mottled appearance of the medulla. After 12 weeks' gestation, the cysts were <5 mm in nine cases and 5–10 mm in three cases. There were no cysts >1 cm. There was no correlation between gestational age and size of the cysts. In one fetus (24 weeks), no cysts were visible. The amniotic fluid volume was reduced after 17 weeks' gestation in all but two fetuses. Amniotic fluid levels were normal in one fetus at 17 and one at 22 weeks.

CNS anomalies were present in all cases (occipital encephalocele in 15/17, Dandy–Walker syndrome in 5/17 and combined anomalies (encephalocele and Dandy–Walker syndrome) in 3/17 cases). Polydactyly was present in 8/17 cases. The so-called 'classical' clinical symptoms (encephalocele, renal anomalies, polydactyly) were present together in 7/17 cases. Cleft palate ($n = 1$), cystic hygroma ($n = 1$), single umbilical artery ($n = 2$), external genital tract ($n = 1$) and skeletal system ($n = 2$) anomalies were also detected. Hepatic lesions were found in only one fetus, appearing as cystic lesions at 21 weeks' gestation.

Pathological examination confirmed all sonographic findings. Histological examinations revealed the presence of renal medullary microcysts in all cases, even if they were not visible macroscopically on ultrasound examination (Figure 1).

DISCUSSION

Since its original description during the 19th century, the origin of MGS has been under debate. Inadequate tissue recognition or lack of corporeal determinism have been suggested^{7,14}. Genetic mapping of the syndrome is still incomplete and several loci have been proposed, which may, in part, explain the observed phenotypic variability^{8,9,15}; this variability has been underlined in many reports^{3,6,16–18}, particularly the study of 67 cases by Salonen¹⁶.

The diagnosis of MGS is often difficult. In our original series of 30 patients, we were able to confirm the clinical suspicion in only 17 (57%) cases. Positive clinical and pathological data are mandatory in order to ascertain the diagnosis. Several minor and major criteria have been considered in the diagnosis of MGS^{16,19–21}. As has been done previously, we based the final diagnosis of MGS on the association of renal cystic involvement (where the cysts are located in the medulla), CNS anomaly and hepatic fibrosis on pathology (ductal plate malformation). Polydactyly is a minor criterion^{11,16} and was encountered in only 8/17 patients in our series. We found the most common CNS anomaly to be occipital encephalocele, encountered in over 88% of cases, whereas

Dandy–Walker syndrome was present in only 29%. This finding is similar to those of previously reported cases^{22,23}.

Since 1984 the presence of hepatic anomalies has been considered as a major criterion in the diagnosis of MGS¹⁶ and more recent publications have confirmed the importance of the recognition of liver ductal plate anomaly. In this malformation, the development of the intrahepatic biliary system stops at the embryonic stage, with no remodeling of the biliary tubules and proliferation of the portal mesenchyme, leading to dysplastic biliary ducts. The tubules are progressively dilated and encased by portal fibrosis^{7,24}. On ultrasound examination, a liver lesion could be visualized in only one of our patients, confirming that hepatic anomalies can only be ascertained on pathology.

Conversely, as we have shown, renal lesions are obvious and appear on ultrasound examination at quite an early gestational age, correlating well with pathological findings. The cystic lesions affect the more mature collecting tubules and nephrons. The medulla is preferentially affected (Figure 1), while normal nephrogenic areas persist in the cortical periphery¹³. The lesions develop in a centrifugal pattern and involve the whole kidney by the time the fetus reaches term.

In the ultrasound literature, kidneys of fetuses affected by MGS are described globally as being enlarged,

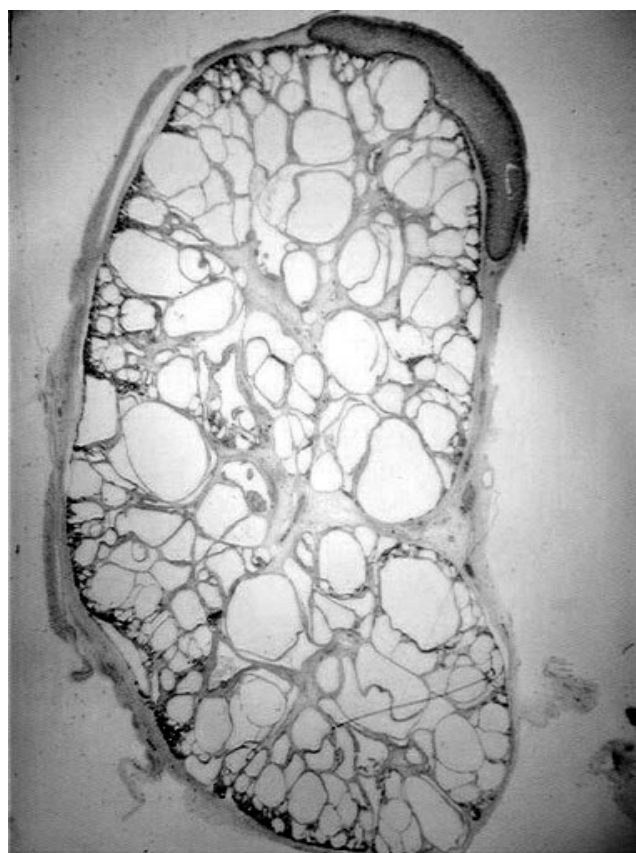


Figure 1 Histological preparation of a kidney (Case 5) affected by Meckel–Grüber syndrome, showing multiple cysts located throughout the kidney (largest ones within the medulla) and the peripheral less affected cortex. (Hemalun-eosin-safran stain; original magnification $\times 10$).



Figure 2 Meckel–Grüber syndrome at 14 gestational weeks (Case 4): transverse view of the fetal abdomen. The kidneys are markedly enlarged and heterogeneous. There are multiple diffuse cystic lesions, surrounded by a more homogeneous echogenic rim corresponding to the cortex.

hyperechoic and containing small cysts with no specific appearance^{10,11}. Our findings allow a more specific diagnosis. In our series, the kidneys were markedly enlarged (mean, $+4.8$ SD), although this cannot be considered a differentiating feature, as the kidneys may also be enlarged in fetuses with recessive polycystic kidney disease. Rather than enlarged kidneys, we consider the early demonstration of an unusual CMD-like appearance during the first trimester and early second trimester to be a more significant differentiating feature. During the first trimester, the normal kidney is relatively hyperechoic on ultrasound and CMD is rarely observed before 20–21 weeks²⁵. In our series, the unusual CMD was evident (as early as the 12th week) in all four patients that were suspected of having MGS in the first trimester. Furthermore, in 16/17 patients, cysts mostly < 5 mm (but always < 10 mm) were observed within the pyramids, producing a mottled appearance in the medulla (Figures 2–3). A heterogeneous pattern for the medulla is never observed in normal kidneys during early pregnancy. Also, no other pathological entity has been described with such an abnormal pattern. There was only one patient in our series in which the pattern of hypoechoic medulla was present with no evidence of cysts.

In older pregnancies, the kidney is affected more globally and the cysts are more diffuse within the cortex and the medulla, with the pattern of CMD therefore being less obvious. It is worth noting that we observed no cases in the third trimester. Also, in our experience, the pattern of CMD was more distinct in more recent cases, probably as a result of better equipment.

The differential diagnosis should include trisomy 13, Zellweger syndrome, Agostino syndrome and Jeune syndrome. In each of these syndromes, complementary investigations, in particular morphological, karyotypic and genetic analyses, are necessary to help differentiate them from MGS. In all these conditions, amniotic fluid

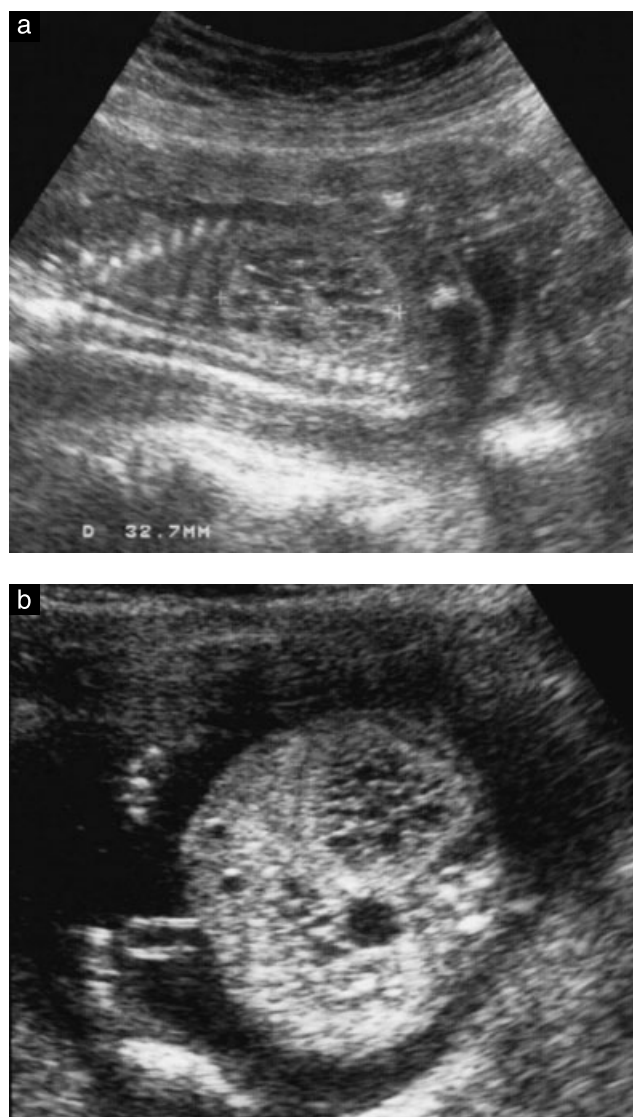


Figure 3 Meckel–Grüber syndrome at 16 gestational weeks (Case 6). (a) Sagittal scan of the left kidney showing the mottled appearance of the pyramids surrounded by the hyperechoic cortex. (b) Transverse scan of the fetal abdomen showing the same mottled appearance of the pyramids (proximal kidney) surrounded by the hyperechoic cortex.

volume generally remains normal. This is in contrast to MGS, in which oligohydramnios occurs earlier in the pregnancy. Autosomal recessive polycystic disease is another differential diagnosis to be discussed, but medullary lesions are very unusual, especially during the first trimester.

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