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Antenatal Diagnosis of a Rare Entity- Meckel Gruber Syndrome.

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ABSTRACT

In 1822 Johann Friedrich Meckel and in 1934 G.B. Gruber published reports of a lethal and rare condition having peculiar anomalies like cystic or dysplastic kidneys, polydactyly, syndac-tyly,occipital encephalocoele, fibrocystic changes of liver, cleft lip or palate and various CNS defects (Dandy walker or Arnold chair malformations). Meckel-Gruber syndrome (MGS) is also called dysencephalia splanchnocystica. The disease have autosomal recessive inheritance pattern with re-ported incidence of 1 in 15,000–400,000 births. MGS is genetically heterogeneous and many chro-mosomes appear to be involved in inheritance. The importance of antenatal diagnosis of this syn-drome lies in the fact that since the inheritance pattern is autosomal recessive there are25% chance of recurrence in each pregnancy. Moreover MGS is not compatible with life hence an early antenatal diagnosis can definitely help the prospective parents and treating obstetrician in taking an informed decision regarding continuation or termination of pregnancy. Case Report: A twenty six years old primigravida came to us at 17 weeks of gestation for obstetric ultrasound. There was no previous history of a baby with congenital malformations or early neonatal death in any of the first degree relatives of the patient. There was no history of consanguinity. The patient denied taking any medications during pregnancy other than vitamins and iron which was started early in pregnancy. Ultrasound revealed the fetus to be having occipital encephalocoele, polydactyly with syndactyly, bilateral cystic dysplastic kidneys and club foot. Depending upon the constellation of abnormalities a provisional diagnosis of Meckel-Gruber syndrome was made and parents were referred for genetic counseling. Conclusion: MGS is a lethal syndrome having autosomal recessive pattern of inheritance. Since there are 25% chances of recurrence in each pregnancy antenatal diagnosis is important. Early prena-tal diagnosis can help parents make an informed decision about continuation or termination of pregnancy.

Keywords: Meckel Gruber Syndrome, Autosomal Recessive, Antenatal diagnosis, Genetic counselling.

INTRODUCTION

Meckel Gruber syndrome is a rare autosomal recessive disorder which is invariably lethal. It was first described by Johann Friedrich Meckel in 1822.[1] Later in 1934 G.B Gruber also reported patients with the similar features and gave it the name of dysencephalia splanchnocystica.[2] More than 12 different loci in different chromosomes have been found to be related to MGS. Some of which are 17q21-24, 12q21.31-q21.33, 12q24.31 and 16q23.1 (MKS11).[3] MGS is characterized by triad of occipital encephalocoele, polycystic kidneys and polydactyly. Other associated anomalies may include cleft lip or palate, CNS malformations (occipital encephalocoele, Dandy-Walker and Arnold-Chiari malformations), fibrotic changes in the liver, micrognathia, hypopituitarism, webbed neck and clubbed foot.[4] The incidence of MGS is reported to be 1 in 15,000–400,000 births. It is more commonly reported from Finnish population, Belgians, Bedouin Kuwaitis and Ashkenazi Jews. Male and female are affected equally.[5] The basic pathology appears to be ciliopathy caused be defective function of cilia and flagella. Other diseases belonging to ciliopathy group include Bardet-Biedl syndrome, Alstrom syndrome and Joubert syndrome. The dysplastic kidneys lead to oligohydramnios and consequent pulmonary hypoplasia. The prognosis is bad and the condition is incompatible with life. The death may occur in-utero, immediately after birth or in some days. The

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longest survival reported in the literature is 4 months.[6] Since the affected children are not expected to survive beyond some days or months and since the chances of recurrence is 25% in every subsequent pregnancy (being an autosomal recessive disorder) the antenatal diagnosis is of para-mount importance. Antenatal Scans can reliably diagnose MGS if classical triad is kept in mind. Ini-tial presentation may include oligohydramnios in late first or early second trimester.[7] The presence of dysplastic or cystic kidneys in combination with oligohydramnios should prompt a radiologist to look for other associated anomalies. Though oligohydramnios may not be present in early scans presence of cystic dysplastic kidneys are a constant finding and must be looked for in cases particularly if there is a family history of MGS.[8] The kidneys initially have microscopic cysts which later enlarge to cause gross enlargement of both the kidneys. After the renal anomalies the most constant anomaly is occipital encephalocoele which is present in 70% to 80% foetuses affected with MGS.[9] Neural tube defects though usually cause increased serum alpha fetoprotein levels it may remain within normal range if the encephalocoele is covered by a membrane. In presence of cerebral en-cephalocaele and dysplastic kidney the diagnosis is almost certain if there is a family history other-wise addition of digital anomalies like polydactyly or syndactyly completes the triad and confirms the antenatal diagnosis of MGS. The past history of stillbirths or early neonatal deaths and history of consanguinity should be specifically asked in order to address the possibility of an earlier child with MGS.[10]

We are reporting the case of a woman who came to us for obstetric ultrasound in early second tri-mester for the first time. During scanning the fetal anomalies like occipital encephalocoele, polydactyly with syndactyly, and renal cystic dysplasia were found completing the triad of MGS.

CASE REPORT

A twenty-six year old female came to us for obstetric scan at 17 weeks of gestation for the first time. There was no history of consanguinity, abortions or stillbirths in the past. The woman has a 5 year old living issue. Early obstetric ultrasound or 13 weeks scan was not done. On ultrasound Av-erage gestational age was found to be 16 weeks 2 days and approximate fetal weight was 146 grams +/- 22grams .The ultrasound scan revealed bilateral enlarged dysplastic kidneys [Figure 1].

In addition to Bilateral dysplastic kidneys there was an abnormal soft tissue measuring 19x17 mm with cystic area adjacent to this defect in occipital area suggestive of occipital encephalocoele [Figure 2].

Presence of bilateral dysplastic kidneys and cerebral encephalocoele raised the suspicion of fetus having MGS and hence a careful digital examination was carried out which showed polydactyly and syndactyly confirming the diagnosis of MGS [Figure 3].

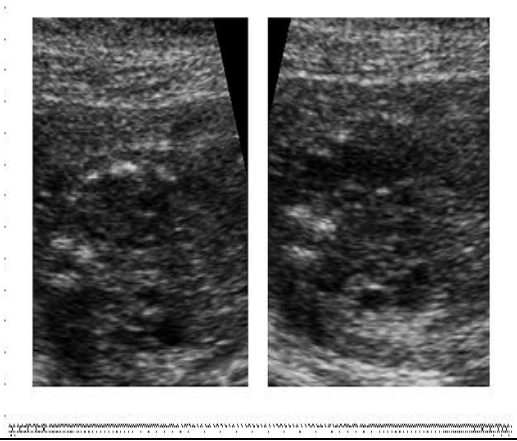

Figure 1: Bilateral dysplastic kidneys seen on the antenatal ultrasound.

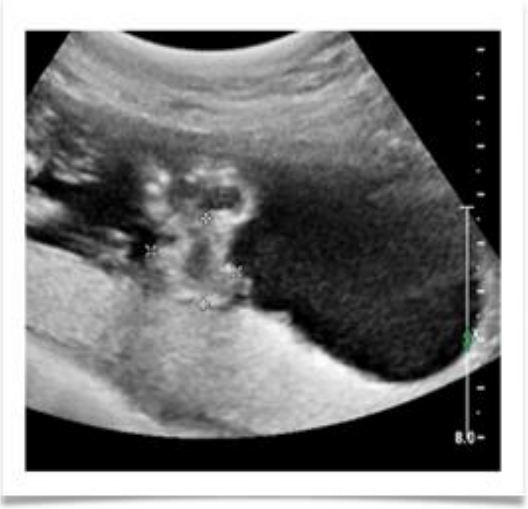

Figure 2: Occipital Encephalocoele noted on antenatal ultrasound.

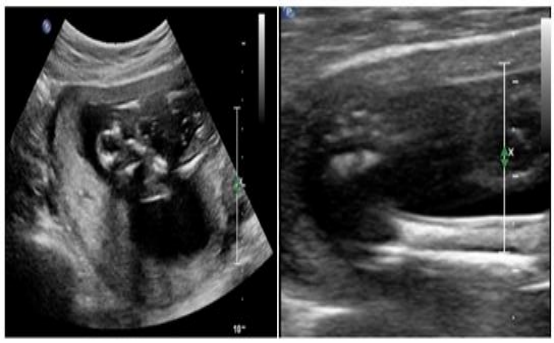

Figure 3: Micropthalmia (Left) and club foot (Right) were also found in the scan.

Club foot and micropthalmia was also present in addition to classical triad of cerebral encephalocoele, bilateral dysplastic kidneys and polydactyly.

In view of completion of triad of Meckel-Gruber syndrome parents were counseled about the condi-

tion and were referred back to gynecologist for further management.

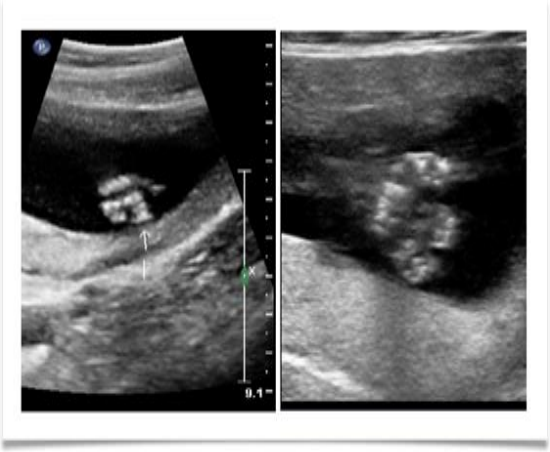

Figure 4: Antenatal Scan Showing Polydactyly (Left) and syndactyly (Right).

DISCUSSION

In 1822 Johann Friedrich Meckel first described the syndrome which consisted of occipital en-cephalocele, polycystic kidneys and polydactyly. In 1934 George B Gruber reported some familial cases with similar features and named it "dysencephalia splanchnocystica." Though Meckel and Gruber initially described features of this syndrome it was only in 2006 that Opitz et al critically reviewed MGS.[11] Though the incidence of MGS is 1 in 15,000–400,000 births it is known to oc-cur more commonly in Belgians and Finnish population, Bedouin Kuwaitis and Ashkenazi Jews. An interesting paper by young et al reported a very high incidence of MGS in Guajarati Indians. They concluded that the increased frequency of MGS in this particular community was due to consan-guinity and estimated the gene frequency in the particular ethnic population to be approximately 0.028.[12]

Being autosomal recessive disorder it affects males and females in equal frequency and the recur-rence rate is 25% (1 in 4). The diagnostic triad of MGS include occipital encephalocoele, cystic dys-plastic kidneys and polydactyly. Our case had all these findings. Other anomalies associated with MGS includes CNS anomalies (microcephaly, hydrocephalus, anencephaly, holoporencephaly etc), Orofacial anomalies (Cleft lip, cleft palate, micropthalmia and nasal hypoplasia), Skeletal anomalies (polydactyly, syndactyly, club foot and clinodactyly), cardiovascular (atrial septal defect, pulmo-nary stenosis and aortic coarctation), respiratory anomalies (lung hypoplasia), Renal anomalies (pol-ycystic kidneys, renal dysplasia, hypoplasia and horse shoe kidneys), Hepatic (fibrosis and ductal agenesis), ambiguous genitalia, cryptoorchidism and imperforate anus. Any combination of these anomalies may be present in fetus and can help in antenatal diagnosis.[13]

The antenatal diagnosis is important as MGS is invariably a lethal syndrome. If diagnosed early the parents can take an informed decision about continuation or termination of pregnancy. The first ultrasound finding in many cases is oligohydramnios which develops secondary to renal dysplasia. The presence of bilateral dysplastic kidney and oligohydramnios should prompt the radiologist to look for other anomalies associated with MGS namely occipital encephalocoele, syndactyly or poly-dactyly and Orofacial anomalies. It must also be remembered that in some cases oligohydramnios may not be present and absence of oligohydramnios does not exclude MGS. Though the early diag-nosis is desirable absence of anomalies in early obstetric scan doesn't rule out MGS and a follow up ultrasound scan is recommended at 20 weeks particularly in patients who are at the risk of recur-rence.[14]

Chorionic villous sampling at 14 weeks followed by molecular diagnosis can confirm MGS. It is im-portant that Chorionic villous sample be tested for all known mutations including but not limited to 17q21-24, 12q21.31-q21.33, 12q24.31 and 16q23.1 (MKS11). After confirmation of diagnosis ge-netic counseling is must and parents should be counseled about the risk of recurrence in subsequent pregnancies.[15]

CONCLUSION

Meckel Gruber syndrome is a rare autosomal recessive syndrome which is incompatible with life. Early antenatal diagnosis is crucial so as to provide parents with an option of safe termination of pregnancy in case they choose to do so. The triad of occipital encephalocoele, bilateral dysplastic kidneys and polydactyly in presence of a normal karyotype almost confirms the diagnosis. Defini-tive diagnosis depends upon chorionic villous sampling and molecular diagnosis.

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