A Distinctive Triad of Malformations of the Central Nervous System in the Meckel-Gruber Syndrome

Mamdouha Ahdab-Barmada, M.D. and Diana Claassen, M.D.

Abstract. A distinct triad of central nervous system (CNS) malformations (prosencephalic dysgenesis, occipital exencephalocele and rhombic roof dysgenesis) was present in seven cases of the Meckel-Gruber syndrome examined at autopsy. We compared our findings with those previously described. Microcephaly, sloping forehead, posterior occipital exencephalocele, cerebellar hypoplasia, Chiari malformation, hydrocephalus, polymicrogyria, arhinencephaly, holoprosencephaly and anencephaly constituted a broad spectrum of the reported CNS anomalies. Few reports contained a comprehensive description of the observed CNS malformations. In those reports, and in our cases, features of prosencephalic dysgenesis included agenesis of olfactory bulbs and tracts (arhinencephaly), hypoplasia of optic nerves and chiasm, agenesis of corpus callosum, fused thalami or complete holoprosencephaly. The occipital encephalocele has consisted of a displacement of rhombic roof elements, including caudal third ventricle, cerebellar vermis and fourth ventricle, extruded through an enlarged posterior fontanelle rather than through an occipital cranium bifidum and is thus more precisely labeled an encephalocele. Different degrees of dysgenesis of posterior fossa structures, described by some as a variant of Dandy-Walker cyst with features of a Chiari malformation, were often associated with this occipital encephalocele. This pattern of CNS anomalies represents a triad of malformations probably associated with defective ventral induction of the developing CNS by the prechordal mesoderm.

Key Words: Encephalocele; Exencephalocele; Holoprosencephaly; Meckel-Gruber Syndrome; Mesoderm, prechordal; Notochord; Rhombencephalon.

INTRODUCTION

Originally described by Meckel in 1822 (1), and labelled “Dysencephalia splanchnocystica” by Gruber (2), the nature of this syndrome was emphasized by Opitz and Howe in 1969 (3). Previous reports of typical cases had ignored the eponymous designation (4–6). It is a lethal autosomal recessive disorder characterized by an “impressive combination” (3) of clinical features including sloping forehead, posterior exencephalocele, polydactyly and polycystic kidneys. However, the criteria required for diagnosis (3, 7, 8) were present in other malformative syndromes. A broad spectrum of associated anomalies and clinical variations was recognized (9–14), including a few “fornes frustes” (15, 16). In search of the most characteristic “working definition” for the diagnosis of Meckel-Gruber syndrome (MGS), the presence of cystic dysplasia of the kidneys with at least two other “relevant” malformations of brain, heart, liver, genitalia or lip was suggested as most compatible with the observed variability of expression of the recessive gene (10). Other studies stressed fibrotic changes of the liver with bile-duct proliferation as a helpful diagnostic criterion (17, 18). Due to a lack of systematic examination of the central nervous system (CNS), some authors implied a spurious morphologic heterogeneity of CNS malformations in this syndrome. Although features of arhinencephaly were noted.
in six of the seven cases which had detailed neuropathologic examinations in the 59 cases of MGS collected by Salonen (19), the only consistent feature retained was an occipital encephalocoele.

We observed a constant pattern of CNS dysgenesis in seven autopsied cases of MGS, compared our findings with other reported CNS malformations in this syndrome and delineated a characteristic malformative triad. In this report we describe the consistent features of this CNS dysgenesis and propose that the malformative triad important for the diagnosis of MGS is: 1. prosencephalic dysgenesis (arhinencephaly-holoprosencephaly and related midline anomalies; 2. occipital exencephalocoele, an extrusion of the diencephalic-rhombencephalic dilated roof through the posterior fontanelle; 3. rhombic roof dysgenesis.

MATERIALS AND METHODS

Five infant girls and one boy with the diagnosis of Meckel-Gruber syndrome (MGS) were autopsied at Magee Womens Hospital (MWH), the obstetric and neonatal facility of the University of Pittsburgh. The diagnosis was suspected clinically and confirmed at autopsy in all cases. Neuropathological evaluations were done by the authors. Another boy (Case 6) was the sibling of Case 2 and was autopsied in Erie, PA. The findings were reviewed by the authors.

The central nervous system (CNS) was observed in situ by the authors in all six cases at the time of autopsy at MWH and further dissected and photographed following fixation by immersion in 10% buffered formalin or in Bouin's fixative for the therapeutic abortion cases for two weeks. Selected blocks were processed through paraffin embedding, sectioned at 6 to 10 micrometers, and stained with hematoxylin and eosin (H&E), Masson's trichrome, Nissl (cresyl violet) and myelin (luxolfast blue, Heidenhain-Woelcke) stains.

Case Reports
(All CNS Anomalies are Listed in Table 1)

Case 1: A white female was delivered by cesarean section at 37 weeks gestation because of fetal distress. The mother was 21 years old and this was her first pregnancy. Multiple ultrasound examinations during gestation had shown hydrocephalus, encephalocoele, polycystic kidneys, and severe oligohydramnios. The newborn baby weighed 2,330 g with crown-rump/crown-heel measurements of 31/41 cm. Apgar scores were 5 at one minute (min) and 6 at five min. She had immediate tracheal intubation because of respiratory distress. Biparietal diameter was nine cm, and she had a posterior occipital exencephalocoele measuring 3.5 × 2.5 × 2 cm. The sternum was short. Post axial polydactyly (sixth digit on all four extremities) and contractures of both upper and lower limbs were also present. The abdomen was distended. She died 22 hours (h) following birth. Autopsy: situs inversus totalis without splenic anomaly; cystic dysplastic kidneys with hypoplastic ureters and urinary bladder; bile duct proliferation with mild hepatic fibrosis; small cysts of the pancreas and hypoplastic dysmature lungs.

Case 2: This white female was therapeutically aborted (saline termination) at 22 weeks gestation because of elevated levels of alpha fetoprotein, abnormal outline of the fetal head on repeated ultrasound examinations and oligohydramnios. The mother was 29 years old, and had previously delivered a male infant (Case 6) with the MGS. The stillborn fetus had an occipital exencephalocoele, flattened nasal bridge, slanting eyes, low set ears, micrognathia, high arched palate, contractures of both upper and lower limbs, postaxial hexadactyly in all four extremities, a varus deformity of the feet, hypoplastic genitalia, and anal atresia. Autopsy: pulmonary hypoplasia; malrotation of intestines; high anorectal agenesis with rectovesical fistula; bicornuate uterus with persistent urogenital sinus and a single external orifice; hypoplastic-dysplastic cystic kidneys; bile duct proliferation with fibrosis and cystic changes in the liver.

Case 3: A 2,080 g white female was born at 34 weeks gestation to a 21 year old mother. There was oligohydramnios and an elevated alpha fetoprotein level at 27 weeks gestation. A normal female karyotype was demonstrated by amniocentesis. An ultrasound examination
had shown enlarged cystic kidneys and microcephaly two weeks before delivery. The infant
died one h after birth. She had a small head, two standard deviations below normal for age,
a sloping forehead, posteriorly rotated low set ears, an occipital exencephalocele, and poly-
dactyly of the feet (six toes) with club feet. Crown–rump/crown–heel measurements (32/41
cm) were small for age. Autopsy: pulmonary hypoplasia; cystic dysplastic kidneys; hepatome-
galy with periporal fibrosis and bile duct proliferation; non-fixed malrotated bowel.

Case 4: A 500 g white female was therapeutically aborted (saline termination) at 24 weeks
gestation. The mother was 32 years old, with a previous induced abortion and no live children.
There was oligohydramnios. An ultrasound examination at 20 weeks gestation had shown
microcephaly and cystic kidneys. The infant measured 22 cm in crown–rump and 31 cm in
crown–heel length. She was microcephalic with a sloping forehead, an occipital exencephaly,
bell-shaped thorax and rocker-bottom feet. There was no polydactyly. Autopsy: hypoplastic
lungs; malrotated, malfixed bowel; cystic dysplasia of kidneys; peripheral and lobular fibrosis
of the liver with excessive bile duct proliferation.

Case 5: This 150 g white female fetus was therapeutically aborted (saline termination) at
19 weeks gestation because of multiple anomalies noted on a routine sonogram. The mother
was 25 years old, with three previous normal pregnancies and deliveries. The fetus showed
microcephaly, hypotelorism, cleft palate, a three cm occipital exencephalocele, a short webbed
neck, a small chest, bilateral postaxial polydactyly of the hands and feet, and polysyndactyly
of the right foot. Autopsy: hypoplastic lungs; cystic and dysplastic kidneys; periporal hepatic
fibrosis with bile duct proliferation; polysplenia syndrome with left isomerism; complex con-
genital heart disease.

Case 6: Autopsied in Erie, PA, and the autopsy protocol was reviewed by the authors. A
2,875 g white baby boy was born at 36 weeks gestation to a 27 year old mother after a normal
pregnancy. He was delivered by cesarean section because of a large encephalocele. He died
three and one half h after birth. Multiple anomalies were present and included: a five cm
posterior occipital exencephalocele; distended abdomen with cystic kidneys; ambiguous gen-
italia with no external opening; a short webbed neck and polydactyly (bilateral hexadactyly,
hands and feet). Autopsy: hypoplastic lungs; cystic, dysplastic kidneys; absence of ureters,
urinary bladder, urethra and penis; nondescended hypoplastic testes; periporal hepatic fibro-
sis. Anomalies of the CNS were not described in great detail in the autopsy protocol, except
for the occipital exencephalocele (Table 1).

Case 7: A 2,410 g white male was delivered at 32 weeks gestation to a 14 year old primiparous
mother. Cesarean section was done for prolapsed umbilical cord. Ultrasound examination at
16 weeks; normal; repeat ultrasound at 32 weeks: oligohydramnios, microcystic kidneys,
hydrocephalus and a questionable posterior fossa cyst. Following delivery, the baby survived
day with marked respiratory distress. Autopsy: crown–rump length 32.5 cm; crown–heel
length 45.0 cm; Potter’s facies; hypoplastic lungs; enlarged, polycystic kidneys; periporal
hepatic fibrosis and bile duct proliferation.

RESULTS

Important CNS and facial anomalies are listed in Table 1 and grouped in small
clusters of related features.

Features of arhinencephaly or holoprosencephaly, with associated related midline
defects, such as agenesis of the corpus callosum and fused thalami (Fig. 1) were
present in all cases. Small hypoplastic optic nerves and tracts, sometimes associated
with microphthalmia, a dysmorphic hypothalamus, hypoplastic third ventricle, small
anterior lobe or absent anterior and posterior lobes of pituitary gland and hypoplastic
pineal gland were often seen.

Occipital exencephalocele was a constant feature in all seven cases. It consisted of
 herniation or extrusion of rhombic roof elements, cerebellar vermis, caudal third
ventricle and distended fourth ventricle, through a widened posterior fontanelle.
Medial occipital cortex was sometimes included in the sac formed by the dilated

CNS IN MECKEL-GRUBER SYNDROME

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<th>CNS and face anomalies</th>
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<td>Holoprosencephaly</td>
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<td>Fused thalami</td>
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<td>Hypoplasia, third ventricle</td>
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<td>2—Occipital exencephalocele</td>
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<td>3—Rhombic roof dysgenesis</td>
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<td>Absent brain stem tectum</td>
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<td>Agenesis-dysgenesis cerebellar vermis</td>
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<td>Periventricular and leptomeningeal heterotopia</td>
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caudal third ventricle. An adherent dural sac covered the extruded CNS elements. A small additional opening of the occipital bone (vascular foramen) was sometimes present two to three cm below the widened posterior fontanelle, but it did not contain herniated brain or meninges.

Anomalies of the rhombic roof were prominent. A large supracerebellar cyst, sometimes including the fourth ventricle with total agenesis of the cerebellar vermis, was a consistent finding, and often herniated through the widened posterior fontanelle (Fig. 2). These features are similar to the Dandy-Walker type of anomaly. However, the posterior fossa was small, funnel-shaped, and the brain stem flattened and elongated with different degrees of dysgenesis of cranial nerve nuclei and of cerebellum, reminiscent of the Chiari-type malformations. Aqueductal stenosis and hydrocephalus in Case 1 further illustrate such a link to the Chiari malformations.

Other anomalies included microcephaly with sloping forehead in Cases 2, 3, 4 and 5, while Cases 1, 6, and 7 had a normal size brain, and there was hydrocephalus in Case 1. Polymicrogyria, focal pachygyria, periventricular and leptomeningeal heterotopias reflected some degree of impairment in cerebral migration and differentiation and were prominent in some of the cases (Case 7).

Facial anomalies such as cleft lip and palate, high arched palate and hypotelorism observed in many of the cases (Table 1) are frequent accompaniments to the arhinencephaly-holoprosencephaly anomalies of forebrain development. Micrognathia may reflect brain stem dysgenesis or result from the oligohydramnios, in association with the Potter's syndrome facies. Similarly, limb contractures and foot deformities may be associated with oligohydramnios, or reflect a motor neuron disease such as observed with arthrogryposis multiplex congenita.

Fig. 1. (A) Coronal sections of cerebral hemispheres at the level of mid and caudal thalamus from Case 1. Arhinencephaly and holoprosencephaly were present rostrally, but two hemispheres are clearly seen caudal to the midthalamus in the above sections. Note ventricular dilatation, fusion of thalami and small third ventricle. (B) Coronal sections of cerebral hemispheres from Case 2; agenesis of corpus callosum, fused thalami, and hypoplasia of third ventricle.

DISCUSSION

A distinctive triad of central nervous system (CNS) malformations has been present in all cases of Meckel-Gruber syndrome (MGS) that we have examined at autopsy: 1. prosencephalic dysgenesis (arhinencephaly-holoprosencephaly and related midline cerebral anomalies); 2. occipital exencephalocele, an extrusion of the diencephalic-rhombencephalic dilated roof through a large posterior fontanelle (in contrast to encephalocele, which is the extrusion of similar elements from a true cranium bifidum); 3. rhombic roof dysgenesis with variable degrees of anomaly and deformation of posterior fossa structures reminiscent of changes in the Dandy-Walker and the Chiari-type malformations (Figs. 3 and 4).

Our analysis of the literature illustrates the same consistent pattern of CNS malformations (Table 2), as well as some paradoxical inconsistencies which probably result from the lack of detailed CNS examinations in many of the reports. Gruber (2) called attention to arhinencephaly (in the broadest sense of the term) as the major developmental anomaly of the CNS in this syndrome of diencephalia splanchnocystica. Only six of the 44 reviewed cases by Opitz and Howe (3) included detailed descriptions of the CNS malformations, with some degree of arhinencephaly in all
Fig. 2. (A) Skull of Case 2 with scalp reflected over the face (thin arrow), and a large posterior exencephalocele (large arrow) extended through a large posterior fontanelle (arrow heads). (B) Transverse section of brain stem at the level of mid-pons in Case 3 shows agenesis of cerebellar vermis, small dysplastic cerebellar hemispheres and herniation of rhombencephalic roof into the occipital exencephalocele (arrow). The fourth ventricle is small and not dilated, the pons is deformed and elongated. The malformation has associated features of the Dandy-Walker and Arnold-Chiari syndromes.

of these cases. Arhinencephaly with diencephalic and rhombencephalohar dysgenesis is present in cases described by Hsia et al (8), Miller and Selden (4), and Fried et al (15). A posterior occipital “encephalocele” was described in 25 of the 44 cases reviewed by Opitz and Howe (3) and in 53 of the 59 cases reported by Salonen (19). In all cases where a more detailed description was available, this “encephalocele” was extruded through the posterior fontanelle. Different degrees of occipital cranium bifidum were described in some of the cases: a small additional defect in the squamous portion of the occipital bone, or an extension of the defect through the occipital bone from the posterior fontanelle to the upper two cervical vertebrae (19–21). A small additional defect in the occipital bone may suggest a persistent “vascular foramen” while the extensive defect is reminiscent of what has been described as the Chiari type III malformation with related mesodermal and neural malformations of posterior fossa structures (22, 23). The association of brain stem anomalies of the Dandy-Walker or Chiari types with polycystic renal disease is encountered in many syndromes (24–25).

The three cases reported by Aleksic et al (27) are recorded as “an unusual set of anomalies” of the CNS, with arhinencephaly, a large occipital ventriculome, hypoplasia or agenesis of cerebellar vermis, and aqueductal stenosis. Furthermore, the cases of Ellis et al (28, 29) suggested features of the Chiari and Dandy-Walker malformations as important components of the Meckel-Gruber syndrome. In the two cases listed by Banker (30), the association of arthrogryposis with arhinencephaly and diencephalic and rhombencephalohar dysgenesis is mentioned. Other cases are described (31, 32) with only partial expression of the typical CNS dysgenesis and unusual chromosomal anomalies.

The high frequency of female involvement in the population we have described is not unusual, although less marked when large numbers of cases are reviewed. There were 62 females and 51 males in our review of the previous literature, whenever the sex of the affected infant was identified.
Fig. 3. Lateral view of the malformed brain of Case 3 with a diagrammatic representation of a sagittal section of this brain, illustrating the malformative triad: (1) Prosencephalic dysgenesis. (2) Posterior exencephalocele extruded through the posterior fontanelle. (3) Rhombic roof dysgenesis.

It appears that the clustering of CNS anomalies described with the Meckel-Gruber syndrome does represent not only the suggested, "unusual set of anomalies" (27), but a dysgenesis of closely related structures of the CNS. "Median cranioencephalic dysraphias and olfactogenital dysplasia" was described by DeMorsier (33) as a related clustering of CNS anomalies. Opitz and Gilbert (34) referred to "the midline as a developmental field," but included syndromes of ventral and tectal midline defects in such definitions. Agenesis of the corpus callosum was considered by Loeser and Alvord (35) to be a midline dysgenesis closely related but less severe than holoprosencephaly. More recent studies have included an array of midline dysgenetic syndromes.
Fig. 4. Case 7 midsagittal section of brain further illustrates the combination of prosencephalic and rhombencephalic dysgenesis: arhinencephaly with malformed hypothalamus, abnormal tectum and supracerebellar cyst communicating with third and fourth ventricles, and extrusion through an enlarged posterior fontanelle forming an occipital encephalocele.

as a “group sharing defects of midline prosencephalic growth” (36). Such dysgenetic alterations within midline structures of the prosencephalon have been linked to abnormal development of the prechordal mesoderm (37) or a faulty interaction between the notochordal plate and the neuroectoderm (38). A similar pathogenetic theory of the development of Chiari malformations implies a defective pontine flexure as the basic mechanism, related to a defective ventral induction of the notochord on the overlying neural tube (23, 38). Similarly, among other theories, the Dandy-Walker malformation and other more severe dysgeneses or ageneses of rhombic roof elements (39, 40) have been attributed to partial failure of formation of the rhombic lip from the alar plate. Impairment of the normal migration of neurons from the rhombic lip is linked to defective ventral induction, and results in a thick posterior medullary velum with distention of the fourth ventricle and deformity of the brain stem (38, 41).

Abnormal development of the prechordal mesoderm, or a faulty interaction between the notochordal plate and the overlying neuroectoderm, may be logical hypotheses to explain the pathogenesis of such apparently disparate midline dysgeneses. Interest in the inductive mechanisms associated with the notochord in embryonal development (42) has stimulated a series of investigations aimed at defining the components involved in inducing tissue interactions. Perinotochordal proteoglycans were reported to influence chondrogenesis in somites (43). A possible role for glycosaminoglycans in the genesis of CNS dysraphic states and associated mesodermal-
TABLE 2
Central Nervous System (CNS) Anomalies in Meckel-Gruber Syndrome Review of Literature

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<td>Small optic nerves</td>
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neural dysgenesis, has been suggested for other syndromes (44, 45). The role of extracellular matrix in development (46), the cell-matrix interaction in the embryo and their role in differentiation (47), and the array of “adhesion molecules” as regulators of cell-cell interactions (48, 49), have aided in understanding defective embryogenesis. In the Meckel-Gruber syndrome, related visceral analogies are suggested. The primary renal dysgenesis may represent a failure of interaction of metanephric duct and renal blastema, and the hepatic anomalies illustrate a lack of stromal-epithelial interaction (18). A defective gene may have affected a perinoto- chordal matrix substance with inductive action and thus led to this apparently disparate array of malformations.

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