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CASE REPORT

Tectocerebellar dysraphia with occipital encephalocele: a phenotypic variant of the TMEM231 gene mutation induced Joubert syndrome.

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Abstract

There are few reported cases of tectocerebellar dysraphia with occipital encephalocele (TCD-OE) in the literature. This malformation was first described by Padget and Lindburg in 1972 and consists of an occipital encephalocele, a cerebellar midline defect, inverted cerebellum, and deformity of the tectum. Occurrence is believed to be sporadic with a male predominance and a usually poor prognosis. We report a patient with brain MRI findings compatible with tectocerebellar dysraphia and occipital encephalocele. Additional features consistent with Joubert syndrome including deepened interpeduncular fossa, as well as elongated, thickened, and anteroposteriorly oriented superior cerebellar peduncles, were noted. The patient's evaluation also revealed a homozygous mutation of the TMEM231 gene, known to cause Meckel-Gruber and Joubert syndromes. Our case represents the first reported genetic confirmation that tectocerebellar dysraphia with occipital encephalocele is not a distinct nosological entity but likely a phenotypic variation of Joubert syndrome.

Keywords Tectocerebellar dysraphia · Occipital encephalocele · TMEM231 gene · Joubert syndrome · Meckel-Gruber syndrome

Introduction

There are few reported cases of tectocerebellar dysraphia with occipital encephalocele (TCD-OE) in the literature. This malformation was first described by Padget and Lindburg in 1972 and consists of an occipital encephalocele, a cerebellar midline defect, inverted cerebellum, and deformity of the tectum. Less consistent anomalies include posteriorly kinked brainstem, fusion of the thalami, aplasia of the mammillary bodies, callosal dysgenesis, abnormal cerebral gyral anatomy, bifid atlas, bifid occipital bone, and cervical hydromyelia [1]. Occurrence is believed to be sporadic with a male predominance and a usually poor prognosis [2]. We report a patient with brain MRI findings compatible with tectocerebellar dysraphia and occipital encephalocele, as well as findings of a molar tooth malformation, whose evaluation also revealed bilateral postaxial polydactyly of the hands and a homozygous mutation of the TMEM231 gene, known to cause Meckel-Gruber and Joubert syndromes [3–5].

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Case report

The patient is a baby boy born full term to consanguineous Saudi parents, with a prenatal ultrasound diagnosis of occipicervical encephalocele and ventriculomegaly. The neonatal course was complicated by recurrent episodes of desaturation and stridor secondary to laryngomalacia. The patient had seizures which were well controlled with phenobarbital. He also had congenital nystagmus. Ultrasound showed a normal liver and kidneys. There were small bilateral hydroceles due to patent processus vaginalis. Cardiac echo was normal. Brain MRI at 5 days of age (Fig. 1) revealed an occipitocervical meningocele

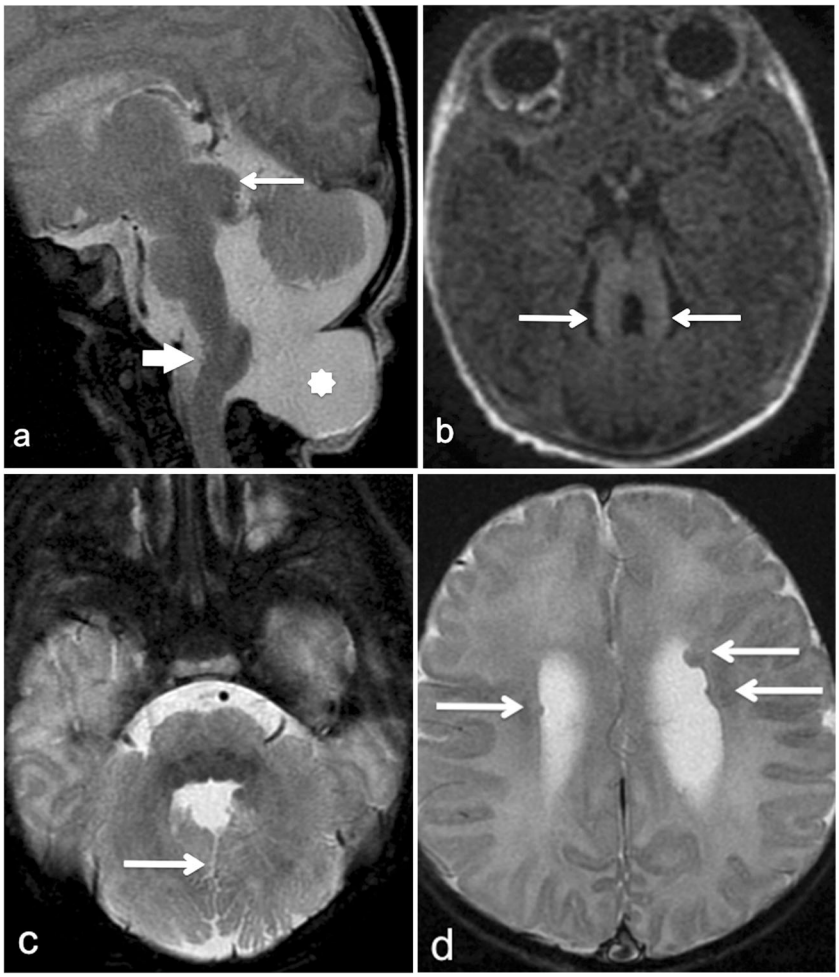

Fig. 1 Brain MRI at age 5 days. **a** Sagittal T2-weighted image demonstrates a midline inferior occipital bone defect with a meningocele sac containing CSF (asterisk). The tectum is dysmorphic and thick (long white arrow). There is mild kinking of the cervicomedullary junction (short white arrow). **b** Axial volumetric T1-weighted image shows thick elongated and anteroposteriorly oriented superior cerebellar peduncles (white arrows), a feature referred to as molar tooth malformation, characteristic of the Joubert spectrum brain malformations. **c** Axial T2-weighted image demonstrates a midline cleft (white arrow) separating the cerebellar hemispheres compatible with vermian hypoplasia and absence of the inferior midline vermis. **d** Axial T2-weighted image at the level of the lateral ventricles shows several small foci of subependymal nodular heterotopia along the walls of the lateral ventricles (white arrows), exhibiting similar signal characteristics to cortical gray matter

sac communicating with the fourth ventricle, a thick dysmorphic tectum as well as a midline cleft partially separating the cerebellar hemispheres, compatible with vermian hypoplasia and absence of the inferior midline vermis. There were features of a molar tooth malformation, with thick elongated and anteroposteriorly oriented superior cerebellar peduncles and a deep interpeduncular fossa. Mild kinking of the cervicomedullary junction and multiple small supratentorial foci of gray matter heterotopia were also noted. Hand radiographs showed bilateral postaxial polydactyly, surgically corrected at age 3 weeks. The patient also underwent Nissen funduplication and gastric tube insertion on the same date for swallowing dysfunction. The meningocele was repaired at 2 months of age. Genetic testing revealed a homozygous mutation of the TMEM231 gene (*TMEM231*:NM_001077416:exon5:c.824-11T>C). He was discharged at 3 months of age on oxygen therapy and gastric tube feeding.

Discussion

Although in their earliest neuropathological description of tectocerebellar dysraphia with occipital encephalocele, Friede et al. [2] separated this entity from Joubert syndrome as distinct disorders causing vermian dysgenesis, a recent report by Poretti et al. emphasized the overlap between these malformations [6]. Poretti et al. described a case of tectocerebellar dysraphia with occipital encephalocele associated with a molar tooth malformation, and confirmed lack of decussation of the superior cerebellar peduncles by diffusion

Table 1 Findings in reported cases of tectocerebellar dysraphism with occipital cephalocele. *SCP*, superior cerebellar peduncles; *DTI*, diffusion tensor tractography

	Patient age and sex	Reported findings
Timur et al. [10]	20 weeks gestation	Occipital encephalocele, inferior vermian agenesis, tectal beaking, large posterior fossa, mild ventriculomegaly
Poretti et al. [6]	4-year-old female	Occipital encephalocele, vermian hypoplasia, tectal thickening, large posterior fossa, elongated, thickened, horizontally oriented SCP, deep interpeduncular fossa (molar tooth malformation), cortical dysplasia, subependymal heterotopia, closed lip schizencephaly, absent decussation of the superior cerebellar peduncles at the pontomesencephalic junction on DTI
Agrawal et al. [11]	3-month-old boy	Occipital meningocele, vermian agenesis, dysplastic tectum, melanocytic nevus of the posterior neck, pectus excavatum
Anik et al. [12]	5-month-old girl	Vermian encephalocele, tectal beaking, partial inversion of the cerebellum. (questionable diagnosis, only mildly reduced vermian volume)
Krishnamurthy et al. [13]	7-month-old boy	Occipital encephalocele, aplasia of the cerebellar vermis, distorted tectum, thin corpus callosum, ventriculomegaly, bulky thalami and basal ganglia Double outlet right ventricle, ventricular septal defect, pulmonary stenosis, abdominal situs inversus
Dehdashti et al. [8]	9-month-old girl	Occipital cephalocele, extracranial and intracranial lipoma adherent to the tectum, cartilage separating extracranial from intracranial lipoma, stretched tectum and brainstem, absent vermis, elevated torcular, dermal sinus tract with blind ending in the lipoma
Komiyama et al. [7]	20-year old female	Occipital encephalocele, agenesis of the cerebellar vermis, elongated, thin, and horizontally orientated SCP, large lipoma and a cystic formation in the posterior fossa stretching the brainstem backwards and the tectum upwards, dysgenesis of the corpus callosum
Demaerel et al. [9]	3 years old	Occipital encephalocele, vermian agenesis, hypoplasia of the cerebellar hemispheres, thin and elongated SCP, lipoma in the posterior fossa deforming the tectum and stretching the brainstem backwards
	2 months old	Small occipital encephalocele, agenesis of the inferior vermis, enlargement and distortion of the fourth ventricle, rostral shifting of the fastigium, thickened and horizontally oriented SCP, enlarged and elongated tectum, severe hypoplasia of the corpus callosum
Friede and Boltshauser,[2]	8-year-old boy, autopsy description	Occipital encephalocele containing dysplastic cerebellum, severe vermian hypoplasia, hydrocephalus, narrow tectum, crowded posterior fossa, cerebellar tonsillar herniation, cervical hydromyelia, bifid atlas, short clivus, large foramen magnum and spinal canal, disproportion of the cerebral lobes (large occipital lobes), interdigitation of occipital gyri and herniation at the tentorial hiatus
	2-month-old boy, autopsy	Occipital encephalocele, severe vermian hypoplasia, stretched tectum, short falx, disproportion of the cerebral lobes (large occipital lobes), interdigitation of occipital gyri and herniation at the tentorial hiatus, elevated torcular, bilateral cerebellopontine angle cysts, dysgenesis of the mammillary bodies, fused thalami, midline defect of the occipital bone, absent olfactory tracts and bulbs, Pierre Robin syndrome, small VSD
Padget and Lindenberg, [1]	Male, autopsy	Occipital encephalocele, complete vermian agenesis, ventral extension of the cerebellar hemispheres, high torcular, lateral stumps of tectal plate (no tectum, no aqueduct), absent mamillary bodies with broad caudal lobe of tuber, cervicothoracic hydromyelia, fused occipital lobes with disproportion in size of cerebral lobes, fused thalami, subtotal atresia of the lateral ventricles, callosal agenesis

tractography. They also reviewed the MRI images of previously reported cases of tectocerebellar dysraphia with occipital encephalocele. They noted that the most definite cases of tectocerebellar dysraphia with occipital encephalocele, where the imaging features fulfilled all criteria for this malformation, also exhibited a molar tooth malformation, not reported by authors as the elongated appearance of the superior cerebellar peduncles was erroneously considered to be secondary to traction at the encephalocele site [7–9]. A more comprehensive review of previously reported cases of tectocerebellar dysraphia with occipital encephalocele is presented in Table 1. Unfortunately, in several of the reported cases, the images included do not allow one to evaluate for a molar tooth malformation [10–13].

Genetic testing was not available in previously reported cases of tectocerebellar dysraphia with occipital encephalocele, and this malformation was considered sporadic [2, 6, 8, 12, 13]. Our patient had a homozygous mutation of

the TMEM231 gene, a ciliary gene located on chromosome 16 (16q23.1, Fig. 2), known to cause Meckel-Gruber and Joubert syndromes [3–5]. These two disorders belong to the group of ciliopathies caused by mutation of ciliary genes. They share allelism, variable expressivity, and overlapping features. The primary cilium is an organelle which projects from the apical surface of the cell and acts as a receiver and transducer of chemosensory and mechanosensory signals. TMEM231 is a transmembrane protein localized at the ciliary membrane within the transition zone of the cilium and its mutation causes impaired intracellular signaling [14]. The correlation between the TMEM231 genetic mutation and the resulting phenotype being Joubert syndrome or Meckel-Gruber syndrome is not understood [5]. One possible explanation is the different strength of various alleles. It is possible that Meckel-Gruber causing alleles are stronger alleles which compromise ciliogenesis and result in a severe phenotype, while Joubert syndrome causing alleles spare ciliogenesis but alter ciliary membrane composition and thus ciliary signaling [15]. The homozygous mutation identified in our patient (*TMEM231*:NM_001077416:exon5:c.824-11T>C) has already been reported to be pathogenic in the Saudi population, causing aberrant splicing of the gene transcript [5]. Transmission is autosomal recessive [3]. There were no known similar cases in the patient's family (Fig. 3).

Joubert syndrome is defined by key clinical and imaging features. It presents clinically with oculomotor apraxia, breathing abnormalities, developmental delay, ataxia, and hypotonia. Its cardinal imaging feature is the molar tooth malformation. This represents a midbrain-hindbrain malformation including vermian hypoplasia and deepened interpeduncular fossa as well as thickened and elongated superior cerebellar peduncles due to lack of decussation of their fibers at the pontomesencephalic junction. Additional variably present features are fibrocystic kidney disease, congenital hepatic fibrosis, retinal degeneration, retinal colobomas, and polydactyly [3, 5, 16]. Meckel-Gruber syndrome represents the most severe end of the ciliopathy phenotypic spectrum, being fatal in the perinatal period. It is characterized by a clinical triad of occipital encephalocele, renal cystic dysplasia, and polydactyly [5]. An additional obligate feature of this syndrome is hepatic fibrosis. Central nervous system defects are an obligate feature of this disorder, most frequently in the form of occipital encephalocele. Renal cystic dysplasia is also a cardinal feature of the syndrome. The kidneys are characteristically markedly enlarged, causing massive enlargement of the abdomen. Postaxial polydactyly of the hands and feet is present in 70–80% of Meckel-Gruber syndrome patients [14]. Although some patients with Joubert syndrome may have polydactyly, hepatic fibrosis, and renal abnormalities, the clinical and imaging presentations of these two disorders remain quite distinct [5].

The presence of a molar tooth malformation in our patient along with the TMEM231 mutation is strong evidence that tectocerebellar dysraphia with occipital cephalocele is likely a variant phenotype of Joubert syndrome, as was previously

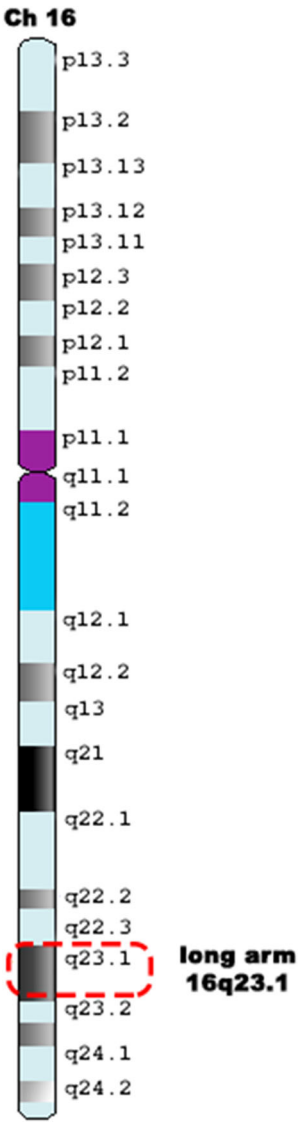

Fig. 2 Gene locus diagram of the TMEM231 gene

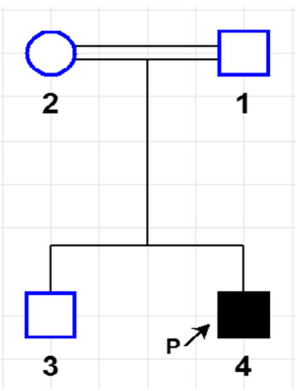

Fig. 3 Pedigree of the patient. P, patient

suggested by Poretti et al. [6]. The other manifestations of tectocerebellar dysraphia, including its basic features of tectal dysmorphism, vermian hypoplasia, and occipital cephalocele, all do occur in Joubert spectrum disorders [17]. Although more commonly seen with Meckel-Gruber syndrome, polydactyly is a rarely reported feature of tectocerebellar dysraphia with occipital encephalocele [18] and Joubert syndrome. Our patient had normal kidneys and liver ultrasound which does not support the diagnosis of Meckel-Gruber syndrome, as cystic renal dysplasia is an obligate feature of Meckel-Gruber syndrome [19].

The meningocele sac in the majority of cases of tectocerebellar dysraphia with occipital encephalocele contains CSF, as in our patient. There are reported cases of a lipoencephalocele [8] and vermian cephalocele [12].

Conclusion

We report a case of tectocerebellar dysraphia with occipital encephalocele where imaging revealed a molar tooth type malformation and genetic testing a homozygous mutation of the TMEM231 gene. This is the first case of tectocerebellar dysraphia where genetic testing and imaging results support that this entity is likely a phenotypic variation of Joubert spectrum disorders and not a separate nosological entity. In the presence of imaging findings compatible with tectocerebellar dysraphia with occipital encephalocele, a molar tooth malformation should always be sought.

Compliance with ethical standards

Conflict of interest The authors declare that that they have no conflict of interest.

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