MR Imaging Diagnosis of Diencephalic-Mesencephalic Junction Dysplasia in Fetuses with Developmental Ventriculomegaly


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ABSTRACT

SUMMARY: Diencephalic-mesencephalic junction dysplasia is a rare malformation characterized by a poorly defined junction between the diencephalon and the mesencephalon, associated with a characteristic butterfly-like contour of the midbrain (butterfly sign). This condition may be variably associated with other brain malformations, including callosal abnormalities and supratentorial ventricular dilation, and is a potential cause of developmental hydrocephalus. Here, we have reported 13 fetuses with second-trimester obstructive ventriculomegaly and MR features of diencephalic-mesencephalic junction dysplasia, correlating the fetal imaging with available pathology and/or postnatal data. The butterfly sign can be clearly detected on axial images on fetal MR imaging, thus allowing for the prenatal diagnosis of diencephalic-mesencephalic junction dysplasia, with possible implications for the surgical management of hydrocephalus and parental counseling.

ABBREVIATION: DMJ = diencephalic-mesencephalic junction

Diencephalic-mesencephalic junction (DMJ) dysplasia is a rare malformation characterized by a poorly defined junction between the diencephalon and the mesencephalon and associated with a characteristic butterfly-shaped contour of the midbrain on axial sections on MR imaging.1-3 This condition is included in a larger spectrum of DMJ anomalies, comprising forms that are recognizable in the axial (type A-DMJ anomalies, including DMJ dysplasia) or sagittal planes (type B-DMJ anomalies).3 DMJ anomalies may be variably associated with other brain malformations, including callosal abnormalities and supratentorial ventricular dilation. In the original report, massively enlarged lateral ventricles were appreciated in 2 patients with DMJ dysplasia.1 Thereafter, partial aqueductal stenosis was identified in 1 patient with DMJ dysplasia and prenatal onset of severe ventriculomegaly, suggesting a mixed obstructive and malformative cause of the hydrocephalus.5 The prenatal imaging features of DMJ have not been reported. Moreover, the relationship between DMJ anomalies and early developmental hydrocephalus remains unclear.

Several causes of developmental hydrocephalus have been described in fetuses and children, mostly associated with myelomeningocele, aqueductal obstruction, posterior fossa crowding, and cysts or cephaloceles.4-6 To the best of our knowledge, no imaging features of DMJ dysplasia have been described in fetuses with developmental ventriculomegaly. Here, we have reported the second-trimester prenatal MR imaging of 13 fetuses with moderate-to-severe obstructive ventriculomegaly presenting unequivocal features of DMJ dysplasia, and we correlated the imaging with available pathology and/or postnatal data.

CASE SERIES

This case series included 13 fetuses, referred to 3 pediatric institutions over a 10-year period (2005–2015) for fetal MR imaging because of second-trimester ultrasound findings of obstructive ventriculomegaly, in whom clear MR features of DMJ dysplasia were retrospectively detected. These cases were found by searching the fetal MR imaging data bases of the 3 centers for reports indicating obstructive ventriculomegaly, defined as bilateral atrial width > 12 mm with the hemisphere convexity reaching or almost reaching the skull inner surface, and with downward displacement of the fornix, without enlargement of the fourth ventricle. The DMJ dysplasia was not detected in the sonography examinations.
Prenatal and postnatal MR findings of DMJ dysplasia in a 23-week-old fetus (case #7). A, Axial T2-weighted image reveals abnormal contour of the midbrain with a deep ventral cleft (arrow), resulting in a butterfly-like appearance. B, Sagittal T2-weighted image demonstrates marked hypoplasia of the pons (thick arrow) and vermis, aqueductal stenosis, and mild kinking of the cervicomедullary junction (thin arrow). The interthalamic adhesion is enlarged and ventrally located (black arrowhead). C, Coronal T2-weighted image shows fusion between the midbrain and thalami (asterisks) as well as moderate supratentorial ventriculomegaly.

FIG 1. DMJ dysplasia in a 28-week-old fetus (case #9). A, Axial T2-weighted image reveals fusion of the hypothalamus and midbrain (asterisk), enlargement of the dorsoventral axis of the midbrain, and a ventral midbrain cleft (arrow) resulting in a butterfly-like appearance. B, Sagittal T2-weighted image demonstrates partial callosal agenesis (black arrow) associated with hypoplasia of the pons (empty arrow) and vermis and mild kinking of the cervicomедullary junction (white arrowhead). Note that the cerebral aqueduct is not visible. The interthalamic adhesion is enlarged and ventrally located (black arrowhead). C, Coronal T2-weighted image shows fusion between the midbrain and thalami (asterisks) as well as moderate supratentorial ventriculomegaly.
Griffiths et al. demonstrated a 17% risk of finding other brain abnormalities in fetuses with ventriculomegaly. The role of MR imaging in detecting brain abnormalities in fetuses with ventriculomegaly is well established. Conversely, DMJ dysplasia is probably rare, though it may be underestimated in cases without ventriculomegaly. More recently, Barzilay et al. showed that pressure in the third ventricle is higher when the interthalamic adhesion is located close to the cerebral aqueduct. A recent computational study on CSF dynamics demonstrated that pressure in the third ventricle is higher when the interthalamic adhesion is located close to the cerebral aqueduct. Developmental forms of hydrocephalus often have multiple points of obstruction. In the present series, cerebral aqueduct stenosis was confirmed in all cases with postnatal MR imaging or autopsy. Moreover, the cerebral aqueduct was scarcely visible in most fetuses of our series, suggesting that aqueductal stenosis could be the main cause of obstructive ventriculomegaly. Of note, the identification of the lumen of the cerebral aqueduct on MR imaging may not always be reliable in the early gestational weeks, often requiring follow-up studies for confirmation. Interestingly, in most of the present fetuses, the interthalamic adhesion was additionally enlarged and caudally displaced. The location of the interthalamic adhesion is highly variable in humans, but in most people, it lies at the center or in the anterior upper quadrant of the third ventricle, whereas it is located in the posterior inferior quadrant in fewer than 1% of cases. A recent computational study on CSF dynamics demonstrated that pressure in the third ventricle is higher when the interthalamic adhesion is located close to the cerebral aqueduct. Partial or complete aqueductal stenosis associated with alterations of CSF flow dynamics within the third ventricle and abnormal WM development might thus explain the ventriculomegaly in these fetuses. In addition, the interthalamic adhesion hypertrophy is an important dysmorphic feature reported in several brain malformations, including Chiari II malformation, L1 syndrome with X-linked hydrocephalus, and 6q terminal deletion syndrome. Notably, marked interthalamic adhesion hypertrophy may overlap with diencephalosynapsis, a rare malformation designating a complete or partial fusion of the thalami associated with secondary reduction of the lumen of the third ventricle, and with rhombencephalosynapsis.

Interestingly, all our presented fetuses were males, suggesting a possible X-linked inheritance pattern. Neuropathologic data from 138 fetuses and neonates genetically tested for X-linked and seizures. So far, no causative genes have been linked to this condition. On imaging, DMJ dysplasia is characterized by a poorly defined junction between the dienencephalon and the mesencephalon and by a ventral cleft contiguous with the third ventricle, producing a characteristic butterfly-shaped contour of the midbrain on axial images. Notably, MR imaging identified the butterfly sign and the abnormal relation between the midbrain and thalamic mass already at 20–21 gestational weeks in 6 fetuses of this series. Nonetheless, if not carefully sought, this finding may be overlooked, especially in the early gestational weeks. Therefore, to improve the detection rate of DMJ anomalies in earlier gestational stages, fetal MR imaging must be technically adequate, with perfectly oriented axial planes, and should not be hampered by fetal motion artifacts.

Developmental forms of hydrocephalus often have multiple points of obstruction. In the present series, cerebral aqueduct stenosis was confirmed in all cases with postnatal MR imaging or autopsy. Moreover, the cerebral aqueduct was scarcely visible in most fetuses of our series, suggesting that aqueductal stenosis could be the main cause of obstructive ventriculomegaly. Of note, the identification of the lumen of the cerebral aqueduct on MR imaging may not always be reliable in the early gestational weeks, often requiring follow-up studies for confirmation. Interestingly, in most of the present fetuses, the interthalamic adhesion was additionally enlarged and caudally displaced. The location of the interthalamic adhesion is highly variable in humans, but in most people, it lies at the center or in the anterior upper quadrant of the third ventricle, whereas it is located in the posterior inferior quadrant in fewer than 1% of cases. A recent computational study on CSF dynamics demonstrated that pressure in the third ventricle is higher when the interthalamic adhesion is located close to the cerebral aqueduct. Partial or complete aqueductal stenosis associated with alterations of CSF flow dynamics within the third ventricle and abnormal WM development might thus explain the ventriculomegaly in these fetuses. In addition, the interthalamic adhesion hypertrophy is an important dysmorphic feature reported in several brain malformations, including Chiari II malformation, L1 syndrome with X-linked hydrocephalus, and 6q terminal deletion syndrome. Notably, marked interthalamic adhesion hypertrophy may overlap with diencephalosynapsis, a rare malformation designating a complete or partial fusion of the thalami associated with secondary reduction of the lumen of the third ventricle, and with rhombencephalosynapsis.

Interestingly, all our presented fetuses were males, suggesting a possible X-linked inheritance pattern. Neuropathologic data from 138 fetuses and neonates genetically tested for X-linked
hydrocephalus showed that 56 subjects (42%) harbored L1CAM gene mutations, and the remaining fetuses (58%) were classified into 4 distinct subgroups: 1) "L1-like" syndrome, including fetuses with no L1CAM mutations, but exhibiting characteristics of L1 syndrome (20%); 2) aqueductal atresia/forking spectrum, often associated with midbrain-hindbrain dorsoventral patterning defects (27%); 3) hydrocephalus associated with polymalformative syndromes, such as VACTERL-H (9%); and 4) hydrocephalus associated with isolated CNS malformations (44%). The L1CAM gene (Xq28) encodes a highly conserved type 1 transmembrane protein of the immunoglobulin superfamily that plays important roles in neuronal adhesion, neuronal migration, axonal growth, pathfinding, and fasciculation as well as in the development of the ventricular system and cerebellum. On imaging, L1 syndrome with X-linked hydrocephalus is usually characterized by bi- or triventricular dilation, aqueductal stenosis, enlarged quadrigeminal plate, interthalamic adhesion hypertrophy, and vermian hypoplasia. Intriguingly, most of the fetuses in our series showed phenotypic and imaging characteristics similar to L1CAM-mutated fetuses. Moreover, postnatal MR imaging with DTI revealed corticospinal tract abnormalities in 2 cases, likely corresponding to the agenesis/fragmentation of the corticospinal tracts described in neuropathology cases of L1 and L1-like syndromes. Unfortunately, because of the lack of L1CAM genetic analysis in the present cases, we cannot establish whether DMJ dysplasia is caused by L1CAM mutations or if it belongs to the L1-like spectrum. Moreover, data on fetal MR features of L1 or L1-like syndrome are not available in the literature. DMJ features are likely to occur on a different genetic basis, and studies on genotype-phenotype correlation are definitively needed.

Finally, we observed pontine hypoplasia and small cerebellar vermis in most of the present fetuses, variably associated with moderate brain stem kinking. The differential diagnosis of prenatal ventriculomegaly and brain stem kinking has been recently widened to include several brain malformations, such as congenital muscular dystrophies, X-linked hydrocephalus caused by L1CAM mutations, microcephaly with lissencephaly and mid-hindbrain involvement, and tubulointerstitial. Taken together, these data indicate that a kinked brain stem is not a pathognomonic finding, but more likely an indicator of severe neurodysgenesis arising early in gestation and often associated with developmental hydrocephalus.

The main limitation of our report is the lack of extensive genetic testing and histology investigation in all cases with pregnancy termination. Moreover, the possibility that fetal DMJ dysplasia cases without developmental obstructive ventriculomegaly may have been missed in our prenatal imaging search has to be taken into account.

In conclusion, a butterfly-shaped contour of the midbrain along with an abnormal spatial relation between the midbrain and thalamic mass may be detected on axial and sagittal sections, respectively, thus allowing an early prenatal diagnosis of DMJ dysplasia in fetuses with proximal obstructive ventriculomegaly. Among the rare causes of developmental hydrocephalus, DMJ dysplasia is likely to be an underestimated condition and seems to share phenotypic features with the L1 and L1-like syndromes. Further studies on larger fetal populations with genotype-phenotype correlations are needed to clarify the causes, pathophysiology, and prevalence of DMJ dysplasia in the fetal population.

Disclosures: Andrea Rossi—UNRELATED: Consultancy: Bracco Imaging Italia Srl.

REFERENCES

10. Šamra KA, Cooper HS. Radiology of the massa intermedia. Radiology 1968;91:1124–28 CrossRef Medline