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Diencephalon-Mesencephalon Dysplasia, with Dysplastic Basal Ganglia, and Midline Fusion, a Case Report of Novel Appearances

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Abstract

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 on axial Magnetic resonance imaging (MRI) sections (butterfly sign). This condition may be variably associated with other brain malformations, including callosal abnormalities and supratentorial developmental hydrocephalus. We report one newborn with third-trimester fetal ultrasound (US) showing ventriculomegaly. After full term delivery, the baby had microcephaly and generalized hypotonia, and MRI undertaken at age of 5 days, showed features of diencephalic-mesencephalic junction dysplasia (DMJD). The hypothalamic-midbrain fusion and midbrain butterfly sign could have been seen on fetal MRI, thus allowing for the prenatal diagnosis of DMJD, with implications for the surgical management of hydrocephalus and parental counseling.

Keywords: DMJ (Diencephalic-Mesencephalic Junction); Hypothalamus; Midbrain; Ventriculomegaly

Case Report

A female baby, product of full-term normal delivery presented with developmental delay, microcephaly, truncal and appendicular hypotonia, spastic quadriparesis and normal face. Her third trimester intrauterine US showed ventriculomegaly and pineal region cyst. MRI Head was undertaken at age of 5 days for further evaluation, and showed dysplastic midbrain, elongated antero-posteriorly and rostro-caudally, with anterior midline cleft continuous with the third ventricle, resultant abnormal anteroposterior elongation of vestibulocochlear nerves, and abnormal orientation of inner ear structures, abnormal dysplastic basal ganglia, fused thalami poorly demarcated from hypothalamic structures with large massa intermedia, hypoplastic bilateral hippocampi. We herein report constellation of imaging findings of diencephalon mesencephalon dysplasia, with novel association of midline fusion, and abnormal dysplastic basal ganglia. Medical history, neurological findings, and brain imaging studies were presented (Figure 1 and 2).

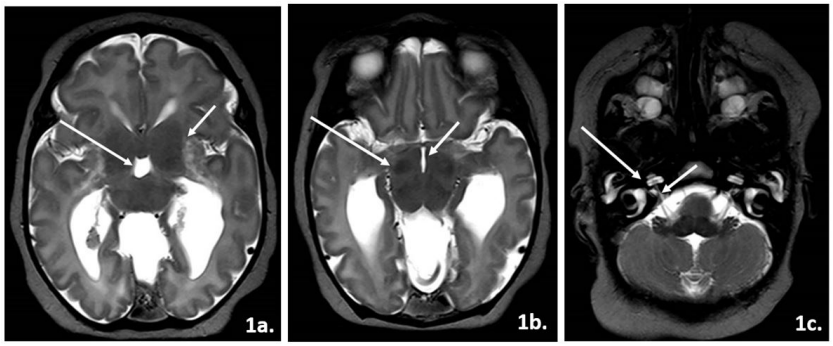

Figure 1: Axial MRI Image **(A)** At the Level of the Midbrain Showing Dysplastic Midbrain, Elongated Anteroposteriorly (Long Arrow), with Anterior Midline Cleft (Short Arrow), Axial MRI Image at a Higher Level; **(B)** Showing the Midline Midbrain Cleft Continuous with third Ventricle (Long Arrow) Giving the Characteristic 'Butterfly Sign' , Fusion of Thalami and Hypothalamic Structures, with Abnormal Dysplastic Fused Basal Ganglia (Short Arrow), Axial MRI Image at Lower Pontine Level; **(C)** Showing Resultant Abnormal Anteroposterior Elongation of Vestibulocochlear Nerves, and Abnormal Orientation of Inner Ear Structures

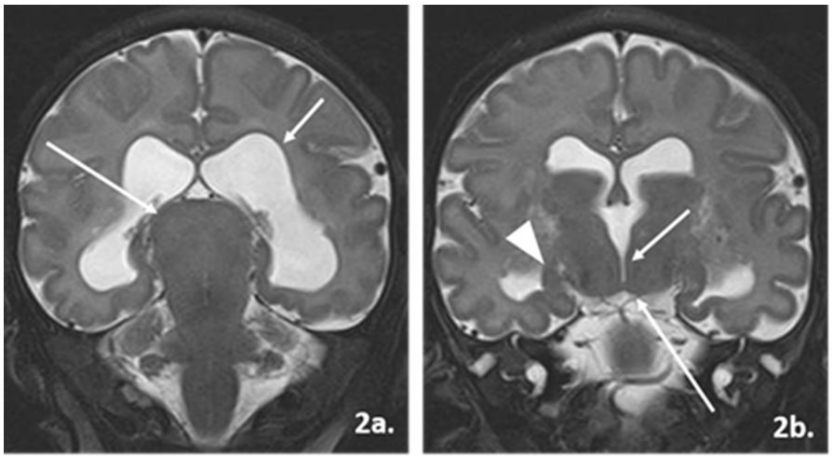

Figure 2: Coronal MRI Image at the Level of Body of Lateral Ventricles **(A)** Showing Thickening and Elongation of the Midbrain in the Rostro-Caudal Axis (Long Arrow), and Moderate Ventriculomegaly (Short Arrow), and Coronal MRI Image at the Level of Frontal Horns of Lateral Ventricles; **(B)** Showing the Midline Midbrain Cleft Continuous Superiorly with the Third Ventricle (Short Arrow), Dysplastic Hypothalamic Structures Poorly Demarcated from Thalami (Long Arrow), and Hypoplastic Hippocampi (Arrowhead)

Introduction

Midbrain–hindbrain malformations (MHMs) are a rare heterogeneous group of structural posterior fossa abnormalities. They can be caused either by embryogenic disruptions or genetic mutations. The structural heterogeneity of MHMs classifications is a based on wide spectrum of clinical manifestations, morphological pathologies, embryological and genetic defects. This structural difference in MHMs can be used in correlation with clinical symptoms to estimate the possible impact of morphological changes on a patients' prognosis and mortality.

Diencephalic–mesencephalic junction dysplasia (DMJD) is a very rare MHM caused by early anteroposterior patterning defect of the neural tube [1-3].

During embryogenesis, with induction of a combination of signals, an early regionalization and patterning of the neural tube occur along the anterior–posterior (the rostral–caudal) axis, leading to the formation of a series of three anatomically defined vesicles at its rostral end, the prosencephalon (forebrain), mesencephalon (midbrain) and rhombencephalon (hindbrain). Subsequently, the prosencephalon divides into rostral telencephalon (cerebrum) and caudal diencephalon (thalami), whereas the rhombencephalon divides into the rostral metencephalon (pons and cerebellum) and caudal myelencephalon (medulla oblongata) [1,2].

The diencephalic-mesencephalic junction (DMJ) and the mesencephalic- rhombencephalic junction (MRJ) act as important signaling centers during encephalon embryonic development, and this 'organizing activity' was named the isthmic organizer (IsO) [1,2].

The DMJ, like the MRJ is probably formed under the genetic influence of secreted fibroblast growth factor 8 (FGF8), which regulates the anterior–posterior expression of the engrailed (En) and Paired box (Pax) transcription factors.

Impaired secretion of FGF8 will lead to impaired regulation of the anterior–posterior expression of the engrailed (En) and Paired box (Pax) transcription factors, resulting in shifts of the DMJ boundary caudally (more Pax6) or rostrally (more En2 and En3), whereas combined loss of both En and Pax leads to complete loss of midbrain identity with fusion of the forebrain and the hindbrain primordia. Experimentally, similar changes of DMJ dysplasia were observed in mice by overexpression of Pax6 or underexpression of En1/Pax2 in the anterior mesencephalon [4,5].

Discussion

There are mainly two types of DMJD, type-A which exhibits neurological symptoms during the first months of a patient's life, and usually follows a severe course [6], and the MRI scans show complete hypothalamic-mesencephalic fusion, with midbrain elongation on axial scans and ventral midbrain cleft (the butterfly sign) [7], and type-B where neurological symptoms appear later, often in adulthood, with mild and slowly progressive course, and the MRI scans show incomplete hypothalamic-mesencephalic fusion [8].

Our index case represents a type-A DMJD, presenting immediately after birth with severe appendicular and axial hypotonia, and showed on MRI extension of the third ventricle and other diencephalic structures into the upper part of a thickened midbrain.

Zaki *et al*., [6], were the first to describe 6 patients of type A DMJD with a novel characteristic brain malformation at the level of the diencephalic–mesencephalic junction. The neurological and general symptoms in their patients began at the first months of life, the neurological examination showed severe cognitive impairment, spastic quadriparesis, truncal axial hypotonia, and suffered

from epileptic seizures. Brain MRI in their cases demonstrated BMJD with a characteristic "butterfly" like contour of the midbrain on axial sections, additional imaging features included variable degrees of supratentorial ventricular dilatation, corpus callosum hypoplasia, agenesis or extreme thinning, and basal ganglia abnormalities ranging from absent, hypoplastic, dysmorphic, or fused. Other findings that were seen on MRI scans were partial agenesis of cerebral hemispheres and schizencephaly [6,7]. Those children with type A BMJD usually had post- natal progressive microcephaly and often died in the age of few months or years [6,7].

On the contrary type-B of DMJD is more difficult to recognize than type-A, the symptoms are mild and progress in a slow manner, patients may present with pyramidal tract signs, speech and gait disturbances, psychomotor excitation, or tonic-clonic seizures [7,8]. The MRI scans in those patients may show hypoplastic corpus callosum, hemispheric hypoplasia with white matter signal abnormalities, and small hippocampus [7,8].

J Madry *et al.*, [8] described a type B BMJD in a 66-year- old man who suffered from very mild and slow progression of neurological symptoms which became evident in his sixties, and his MRI scans were typical for type-B of DMJD.

Children with type-A DMJD described by Zaki *et al*., were from three consanguineous Egyptian families with possible autosomal recessive inheritance. Despite exome sequencing in these affected individuals, no obvious candidate gene has emerged.

Our case was sporadic, from non-consanguineous parents. Given the caudal shift of the DMJD and the interplay between the development of the DMJ and the MRJ, one might anticipate associated patterning defects of the midbrain–hindbrain boundary. It is therefore relevant that the affected individuals with DMJD to show cerebellar vermis hypoplasia [6].

Imaging findings in our index case included thickening and elongation of the midbrain on the rostro-caudal axis, with dysplastic morphology of both ventral and dorsal midbrain enlarged in dorso-ventral axis, a deeper than normal interpeduncular fossa, a midline cleft contiguous with the third ventricle, giving the characteristic 'butterfly sign' on axial scans described in DMJD. A poorly defined junction between the thalamus and hypothalamic structures (diencephalon) and brain stem (mesencephalon). The third ventricle appeared surrounded by fused thalami posteriorly and large Massa intermedia anteriorly, dysplastic poorly defined basal ganglia differentiation, absent anterior limb of internal capsule, poorly formed hippocampi, and moderate ventriculomegaly.

Conclusion

Diencephalic–mesencephalic junction dysplasia (DMJD) is a very rare midbrain-hindbrain malformation (MHM) caused by early anteroposterior patterning defect of neural tube, where imaging and clinical severity usually represents a continuous spectrum. We report a case of type A-DMD presenting at birth with severe neurological disability, where MRI showed characteristic features of DMJD, associated ventriculomegaly, along with novel description of association of midline fusion, and abnormal dysplastic basal ganglia.

These findings could have been seen on fetal MRI allowing for the prenatal diagnosis of type-A DMJD, with implications for the surgical management of hydrocephalus and parental counseling.

References

1. Barkovich AJ, Millen KJ, Dobyns WB (2007) A developmental classification of malformations of the brainstem. Ann Neurol 62: 625-39.

2. Barkovich AJ, Millen KJ, Dobyns WB (2009) A developmental and genetic classification for midbrain–hindbrain malformations. Brain 132: 3199-230.

3. Doherty D, Millen KJ, Barkovich AJ (2013) Midbrain and hindbrain malformations: advances in clinical diagnosis, imaging, and genetics. Lancet Neurol 12: 381-93.

4. Nakamura H, Watanabe Y (2005) Isthmus organizer and regionalization of the mesencephalon and metencephalon. Int J Dev Biol 49: 231-5.

5. Scholpp S, Lohs C, Brand M (2003) Engrailed and Fgf8 act synergistically to maintain the boundary between diencephalon and mesencephalon. Development 130: 4881-93.

6. Zaki MS, Saalem SN, Dobyns WB, Barkovich AJ, Bartsch H, et al. (2012) Diencephalic– mesencephalic junction dysplasia: a novel recessive brain malformation. Brain 135: 2416-27.

7. Severino M, Tortora D, Pistorio A, Ramenghi LA, Napoli F (2016) Expanding the spectrum of congenital anomalies of the diencephalic-mesencephalic junction. Neuroradiology 58: 33-4.

8. Razek A, Khalek AA, Mauricio C (2016) Magnetic Resonance Imaging of Malformations of Midbrain-Hindbrain. J Comput Assist Tomogr 40: 14-25.