ISSN 2563-9218

CASE REPORT

Diencephalic-Mesencephalic Junction Dysplasia: A Case Report and Overview of What is Known so far

Patricia Piazza Rafful[1*], Mareen Sarah Kraus[2]

Rafful PP, Kraus MS. Diencephalic-Mesencephalic Junction Dysplasia: A Case Report and Overview of What is Known so far. Int J Biomed Clin Anal. 2023;3(1):38-49.

Abstract

Background: Diencephalic-Mesencephalic Junction Dysplasia (DMJD) is a rare and recently newly described forebrain-midbrain malformation involving the upper aspect of the brainstem and resulting in an abnormal regionalization of the diencephalon and mesencephalon level. The fingerprint of DMJD is the pathognomonic butterfly-like appearance of the midbrain seen on the axial plane of brain magnetic resonance imaging (MRI). Initially, only two types of diencephalon-mesencephalon continuity were defined: type A describes the continuity of the hypothalamus with the mesencephalon, and type B a parenchymal band between the thalamus and the superior surface of the midbrain. However, DMJD classification continues to expand, and recently, type C was described as showing a complete continuity of the thalamus and midbrain. In this paper, we refer to mesencephalon and midbrain as the anatomical marker of the topmost part of the brainstem, and those terms are used interchangeably in the text.

Methodology: PubMed database search for the exact words "diencephalic-mesencephalic junction dysplasia" and "DMJD" yielded 12 relevant publications. A showcase of an original rare type C DMJD was performed.

Objective: The purpose of this article is to present a brief comprehensive illustration/elucidation of the physiopathology of neural tube regionalization to facilitate the understanding of DMJD malformation; to present an updated overview of recent publications involving imaging findings, genetics, and clinical concerns; and to show an original fetal case of type C DJMD. The aim is to increase awareness of DMJD and strengthen clinical suspicion, especially since early diagnosis is primarily based on imaging.

Key Words: *Diencephalic-Mesencephalic Junction Dysplasia (DMJD); Brain malformation; Posterior fossa; Magnetic resonance; Butterfly-like sign*

[1]Neuropediatric Radiologist, Roberts Center for Pediatric Research, Children's Hospital of Philadelphia, 734 Schuylkill Ave Philadelphia, United States

[2]Faculty Member, Department of Diagnostic Imaging, IWK Health Centre, Dalhousie University, 5980 University Ave #5850, Halifax, NS B3K 6R8, Canada

[*]Corresponding author: Patricia Piazza Rafful, Neuropediatric Radiologist, Roberts Center for Pediatric Research, Children's Hospital of Philadelphia,734 Schuylkill Ave Philadelphia, United States, Tel: 267 5213048; E-mail: raffulp@chop.edu

Received: February 17, 2023, Accepted: March 09, 2023, Published: May 26, 2023

Introduction

Diencephalic-Mesencephalic Junction Dysplasia (DMJD) is a very rare and underestimated posterior fossa malformation first described in 2012 by Zaki et al., in which the rostro-caudal and dorso-ventral regionalization of the neural tube fails to define the boundaries between the rostral and ventral aspects of the brainstem, leading to a dysmorphic midbrain featuring an enlarged mesencephalon, that appears contiguous with the thalamus [1-3]. During development, mid-hindbrain growth occurs predominantly in the rostro-caudal and dorso-ventral axis.

Neuromeres along the neural tube are organized into molecular regions with different specializations, a preparation for neuron differentiation, neuronal migration, and function. A key involved signaling center known as isthmus organizer (IO) is situated at the midbrain-hindbrain boundary - with the posterior commissure as an anatomical landmark [4] - and is involved in this regionalization process by controlling the molecular signaling of Wnt and Fgf8, which are responsible for the rostro-caudal regional identity of the midbrain, rhombomere 1, and rhombomere 2 (the latter corresponds to the hindbrain level) [5-7] Wnt signaling is important for Fgf8 expression in rhombomere 1 which will generate tissue with the characteristics of an isthmus organizer [4,7]

The mesencephalon is defined by the molecular expression of En1/Pax2 and Otx2. Rostrally, the diencephalon is defined by the expression of Pax6; and caudally the metencephalon is defined by the expression of Gbx2. Diencephalic-mesencephalic boundary formation is determined by the repressive interaction between Pax 6 (diencephalon) and En1/Pax2 (mesencephalon) [4,8]. The mesencephalon-metencephalon boundary is defined by the repressive interaction between Otx2 (mesencephalon) and Gbx2 (metencephalon) [4]. In the dorso-ventral axis, dorsalization occurs with the expression of bone morphogenic protein (BMP), while ventralization pattern is induced by sonic hedgehog (Shh); thus dorso-ventral pattern depends on the amount (gradient) of dorsalization and ventralization factors [5] (Figure 1).

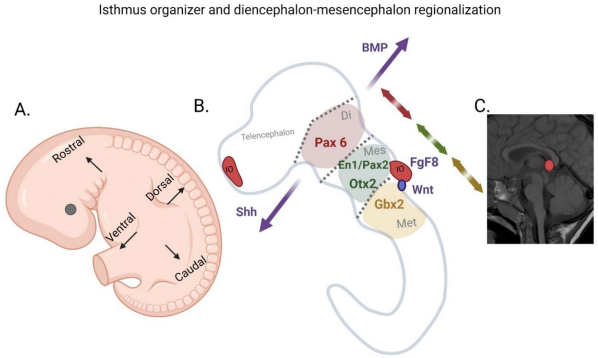

Figure 1) *A sketch of the directional axis of the fetal body. (A) A sketch of the primordium vesicles and important molecular signaling pathways in a sagittal plane. Two isthmus organizers (IO) are responsible to control transcription factors of the neuro primordium; one is located in the rostral top of the forebrain, and the other in the junction between the mid- and hindbrain (red oval circles in Image B). Wnt signaling regulates the expression of Fgf8 in the IO, which is responsible for maintaining the regionalization of the vesicles in the neural primordium during development. (B) MRI T1 weighted sagittal plane of the posterior fossa showing the anatomical correlation of the isthmus organizer at the level of the posterior commissure (red dot), that marks the boundary between the diencephalon and mesencephalon (red circle). (C) (Di=diencephalon; Mes=mesencephalon; Met=metencephalon). Image B is based on [4].*

Morphologic abnormality of diencephalic-mesencephalic junction (DMJ) is a consequence of the impairment in regionalization of the diencephalon, rhombomere 1, and rhombomere 2, leading to hypothalamic-mesencephalic continuity seen in most severe cases; or incomplete separation between thalamic and midbrain in less severe cases [2]. Because imbalances of the rostro-caudal and dorso-

ventral axis can impact, and/or overlap with the boundaries of adjacent structures of the posterior fossa, a precise assessment to evaluate the size and morphology of vicinity structures including midbrain tegmentum and tectum, cerebellar peduncles, dorsal and ventral pons, vermis and cerebellum is crucial [2,5], as this can help in differentiating DMJD from other posterior fossa abnormalities such as Joubert's syndrome and related ciliopathy disorders, horizontal gaze palsy and progressive scoliosis, pontine tegmental cap dysplasia, rhombencephalosynapsis, and pontocerebellar hypoplasia [5,9].

A key imaging feature of DMJD is the butterfly-like contour of the midbrain best seen on axial plane of magnetic resonance imaging (MRI), which represents the continuity of the hypothalamus with the midbrain, resulting in shortening of the rostro-caudal axis and elongation of the dorso-ventral midbrain, and poorly defined boundaries between the hypothalamus and midbrain [1,2]. At the level of the inferior colliculus, a deep dorso-ventral cleft in the anterior midbrain gives the final pathognomonic imaging appearance (the butterfly-like sign) and the cleft communicating continuously with the third ventricle. The optic recess of the third ventricle can be elongated in the dorso-ventral direction and can be seen at the same level as the midbrain cleft [1,2,6].

To date, three types of DMJD patterns have been described based on the anatomic level of the diencephalon involvement (hypothalamus or thalamus), and the degree of nonseparation between the diencephalon-mesencephalon, including type A with hypothalamic-mesencephalic continuity; type B with incomplete thalamic-mesencephalic cleavage [2]; type C with complete or near complete thalamic-midbrain union [10] (Figure 2).

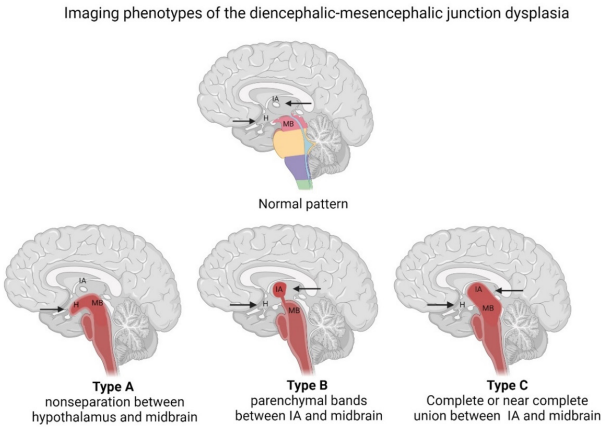

Figure 2) *Demonstration of the differences between the three types of Diencephalic-mesencephalic junction dysplasia (DMJD): Type A refers to the continuity between the hypothalamus and midbrain; Type B refers to a parenchymal band between the interthalamic adhesion/ thalamus and the superior surface of the midbrain; and Type C refers to a complete/or near complete continuity between the thalamus and the midbrain. (IA= interthalamic adhesion).*

In addition, an association with congenital hydrocephalus has been described mainly in male fetuses, and a possible x-linked inheritance was suggested in initial publications [2] and later proven to be associated with the L1 syndrome, a type of x-linked hydrocephalus [10,11]. However, so far, only three adult cases with type B DMJD were reported in the literature to date [12-14].

Much attention has been drawn to DMJD type A, reported in infants. Clinically, type A DMJD presents postnatally as progressive microcephaly with bitemporal narrowing, severe cognitive delay, motor spasticity, hyperreflexia, ataxia, impairment of fine motor skills, language development, and cranial nerve findings such as strabismus and dysphagia [15]. Imaging findings of DMJD type A are better appreciated on axial MRI planes as a result of the nonseparation between the hypothalamus and the midbrain resulting in a caudal shift of the diencephalic-mesencephalic junction, emulating the pathognomonic butterfly-like sign with a ventral midbrain cleft [1]. In a larger

series of 33 patients with types A, B and C DMJD pattern, the vermis and brainstem were found to be small or normal in size [15]. In another study with 13 patients with DMJD pattern types A and B, 6 patients had pons hypoplasia, 3 cerebellar hypoplasia, and 11 kinking of the brainstem [2]. Other brain congenital abnormalities were found in association with DMJD type A including gray matter heterotopia, open-lip schizencephaly, corpus callosum dysgenesis, basal ganglia hypoplasia, dysmorphic and fused basal ganglia, absent olfactory bulbs, and abnormal cortico spinal tract (CST) which abruptly arrests at the level of the pons seen on DTI tractography [2].

Lately, a subset of DMJD types A and B was found to present with hydrocephalus, as a consequence of severe dysmorphism of the midbrain dorso-ventral pattern [10], leading to aqueductal stenosis. The amount of ventricular dilatation can lead to supratentorial brain thinning which is an important feature to raise suspicion for the DMJD recognition on fetal MRI because the latter is usually motivated by abnormal ventricular findings on ultrasound, which has low accuracy for brainstem abnormalities recognition. Of note, the abnormal butterfly-like contour of the midbrain can be seen on fetal MRI as early as gestation week 18 [3,10]. Additionally, an interthalamic adhesion was found to be enlarged and inferiorly displaced in those fetuses with hydrocephaly, which may contribute to cerebrospinal fluid flow obstruction into the cerebral aqueduct.

Exact gene mutation is still under investigation, and some new associations have been described. A recent publication reported an association of bi-allelic loss of function variants of gene *protocadherin-12 (PCDH12)* with type A DMJD after performing whole body exome sequencing in 8 families with high risks for genetic disorders (i.e. consanguineous parents, known recessive diseases in familial members) [15]. *PCDH12* is part of a *protocadherin* superfamily encoding a large glycoprotein, originally found in cell-to-cell junctions of the endothelium to promote cell adhesion. *PCDH12* was also found to have an important role in neurite outgrowth through neuronal progenitor cells. Other pathogenic variants of the *protocadherin* superfamily have been identified in clinically similar presentations such as epilepsy with mental retardation disease, autism, microcephaly, seizures, and spasticity with brain calcification [15].

L1CAM gene encodes for the L1 cell adhesion molecule, a membrane glycoprotein mediating cell-to-cell adhesion at the cell surface. Previous publications of fetuses harboring *L1CAM* mutation show a similar DMJD pattern of the midbrain, with the pathognomonic butterfly-like contour. L1 syndrome is a rare form of x-linked congenital hydrocephalus secondary to aqueduct stenosis. Clinically, it is associated with severe clinical findings including mental retardation, aphasia, shuffling gait, and adducted thumbs (MASA). Other L1 syndrome imaging findings comprise corpus callosum agenesis, enlarged quadrigeminal plate, interthalamic adhesion hypertrophy, and vermian hypoplasia [11]. These findings suggest a possible contribution of *L1CAM* mutation to DMJD abnormality [10,11]. In one cohort of 33 patients with type A, B, and C DMJD pattern, a microcephaly panel was performed: qin one case presenting DMJD type C, a pathogenic variant of the *VRK* serine/threonine kinase 1 (*VRK1*) was found, consistent with an autosomal recessive *VRK-1*-related disorder, that might be another genetic association leading to the DMJD pattern [10] (NIH Medline plus https://medlineplus.gov/genetics/gene/vrk1/).

Fox head box A2 (*FOXA2*) mutations at 20p11.2 chromosome were associated with midline development defects such as diencephalosynapsis and mesencephalonsynapsis, and also shares imaging similarities with DMJD pattern. Other imaging features comprises obstructive hydrocephalus, corpus callosum agenesis, absent anterior pituitary and ectopic posterior pituitary, and cervicomedullary kinking [16-18].

Methodology

We performed a literature search using an important digital database repository for scientific publications (PubMed). Keyword search for "diencephalic-mesencephalic junction dysplasia" and "DMJD" was performed with no filters – especially no time lime. PubMed uncovered 15 publications. Of those 15, we deemed 12 publications to contain relevant information on DMJD imaging, genetics and clinical findings – these are included in of the literature overview Table 1; the remaining three publications were publications not dedicated to DMJD and/or without relevant information.

TABLE 1
Literature overview of 12 papers on DMJD malformation

Author, publication type	Sample size	DMJD Imaging Description	Associations	Clinical findings	Genetic findings	Learning point
Zaki et al., 2015 Original Paper [1]	6 children - 3 consanguineous families	Nonseparation of the hypothalamus and midbrain, midbrain with a ventral cleft- butterfly-like pattern (axial plane)	Hydrocephalus, hypoplasia to complete agenesis of the corpus callosum, lack of identifiable CST	Facial dysmorphism, severe cognitive impairment, spastic quadriparesis, central hypotonia, unexplained fever, seizures	None	Detection of a novel brain malformation
Severino et al.; 2016 Original paper [2]	12 children	DMJD subtypes A and B description: **Type A:** continuity between hypothalamus and ventral midbrain (abnormal contour), variable midbrain ventral cleft (some with butterfly-like sign in axial plane) **Type B:** incomplete cleavage with parenchymal band between thalamus and midbrain (sagittal plane).	**Type A:** MCD, CCD, basal ganglia malformation, variable degree of brainstem and cerebellar hypoplasia, cervical-medullary kinking. Variable ventricular enlargement (aqueduct stenosis). Premature termination of the CST at the level of the pons (tractography) **Type B:** moderate enlargement of the lateral ventricles (aqueduct stenosis), mild brainstem, and vermian hypoplasia.	Hypothalamic dysfunction (unexplained fevers, vasomotor instabilities, sleep disorders)	None	Differentiation into subtype A and B
Severino et al., 2017 Original paper [3]	13 male fetuses with ventriculomegaly	Butterfly-like sign (with cleft) in all prenatal cases, the abnormal anterior position of the interthalamic adhesion, aqueduct stenosis, corticomedullary kinking	MCD, CCD, pontine hypoplasia, and small cerebellar vermis, variable brainstem kinking.	none	Suggested *L1CAM* gene (a type of x-linked hydrocephalus)	Consider DMJD in a fetal investigation for ventriculomegaly; concerns about underestimation of DMJD malformation in fetuses without hydrocephalus.

Madry et al., 2017 Case report [12]	An adult case of DMJD type B	Butterfly-like sign	none	Disorder of speech fluency and articulation, gradual hearing loss, mild cognitive impairment, minor right hemiparesis, involuntary trunk movements and abnormal gait	none	An adult case of type b
Guemez-Gamboa et al., 2018 Original paper [15]	8 families with whole exome analysis	with midbrain cleft (butterfly-like sign)	Microcephaly thinned CC, ventriculomegaly, and subtle brain calcifications (mimicking congenital infections). Note: abnormal white matter tracts, and defective neurite growth found in NPCs derived from affected individuals.	Facial dysmorphisms, profound psychomotor delay); ataxia, autistic features, poor outcome due to brainstem malformation, cranial nerve findings (strabismus, dysphagia)	All patients positive for biallelic mutations in the nonclustered *protocadherin-12 (PCDH12)* gene	DMJD should be added to the spectrum of *PCDH12*-related disorders
Dines et al., 2019 Original paper [16]	A newborn with proximal 20p11.2 deletion (*FOXA2* gene*)*	continuity of the hypothalamus and inferior thalamus (mesencephalosynapsis)	Congenital nasal pyriform aperture stenosis, single-center incisor, severe hydrocephalus, aqueduct stenosis, absent pituitary stalk, and gland, "J" shaped sella, absent septum pellucidum, fused fornix	Macrocephaly, inverted nipples, low-set ears, arachnodactyly, micrognathia. Hormone deficiencies (ACTH, GH, TSH), cardiac abnormalities	proximal 20p11.2 deletion (*FOXA2* gene*)*	Expanding the phenotype of *FOXA2* deletion
N Shah, 2019 Letter to the Editors [18]	A prenatal ultrasound at 23 gestational weeks	DMJD type A, dorsoventral elongated midbrain with midline cleft (butterfly-like sign). Confirmed by postnatal MRI	Severe hydrocephalus, aqueduct stenosis,	Mother had two prior male stillbirths	none	DMJD diagnosed on ultrasound; useful in low-resource settings. Important factors for recognition: clear amniotic-tissue interface, gestational age (second trimester), good maternal tissue quality (low BMI)
Lawrence et al., 2020 Original paper [10]	Prenatal imaging of 33 fetuses	**Description of new type C DMJD**: complete/near complete midbrain thalamic continuity	Aqueduct stenosis, ventriculomegaly, CCD, MCD, normal or small brainstem or cerebellum. Parenchymal calcifications in type A DMJD	Postnatal Seizures, developmental delay, hypotonia, spasticity	Four cases positive for *L1CAM* mutation; two pathogenic variants of *VRK1*- gene in one case (DMJD type c)	Description of new image phenotype (type C); DMJD can be identified on fetal MRI as early as gestational week 18; most cases type B (less severe clinical phenotype); type A seen as clinically most severe impairment

Moreno-Esteban et al., 2020 Case report [13]	an adult case of DMJD type B	pathognomonic butterfly-like sign of the midbrain, with a midline cleft, enlargement o thalami	Small posterior fossa with downward displacement of the pons and medulla oblongata, leading to partial obliteration of the pontocerebellar cistern; CC hypoplasia, and thin cerebral peduncles.	Depressive mood, cognitive/ language impairment (semantically and phonetically), emotional lability, irritability, apathy, progressive dysphagia, and strabismus	none	Second adult DMJ type B in the literature. Progressive symptoms around age 60
Mehta, et al, 2020 Case report [14]	An adult case of DMJD type B	classic butterfly-like sign	Small posterior fossa, association with Chiari 1 and hydrocephalus	Cough-induced headaches, worse with Valsalva maneuver	none	Adult case with Chiari 1 and hydrocephalus association
Accogli et al., 2021 Original paper [11]	10 fetal with *L1CAM* mutations	2 DMJD imaging patterns of *L1CAM* mutations: Pattern 1: DMJD (butterfly-like sign) type A and B, diencepalosynapsis, CCD. Variable aqueduct stenosis, severe obstructive hydrocephalus, cerebellar vermis hypoplasia, pontine hypoplasia Pattern 2: CCD, mild-moderate ventricular dilatation, reduced white matter, pontine hypoplasia, normal/ absent interthalamic mass	L1CAM syndrome encompasses x-linked hydrocephalus, aqueduct stenosis, MASA syndrome (intellectual disability, spasticity, abducted thumbs)	N/A	*L1CAM* mutation	Prenatal identification of *L1CAM* mutation pattern for timely counseling, concerning undiagnosed brainstem malformation in prenatal US
Jacobs et al., 2023 Original paper [17]	16 fetal cases with orbit or orbital abnormalities	DMJD	Globe and orbital abnormalities including hypertelorism, persistent fetal vasculature, retinopathy, glaucoma, microphthalmia, anophthalmia	N/A	N/A	100% globe or orbital abnormalities

DMJD: Diencephalic-Mesencephalic Cortical Dysplasia; CST: Corticospinal Tract; PCDH12: Protocadherin-12 Gene; L1CAM: L1 Cell Adhesion Molecule; MCD: Malformation of Cortical Development; CCD: Corpus Callosum Dysgenesis; CC: Corpus Callosum; N/A: Non-Applicable, BMI: Body Mass Index

Case Study

Our case shows MRI of a male fetus at 26 weeks of gestation, ordered to evaluate for hydrocephalus after a prenatal ultrasound raised suspicion for cerebral abnormalities in the anatomy screen at 20 weeks. The parents were non-consanguineous, and this was their first child. MRI findings were positive for the non-cleavage between the thalamus and midbrain, with a thick and undefined interthalamic adhesion seen on the sagittal plane, consistent with DMJD type C. The hypothalamus appeared slightly thicker and on axial plane, a partial union of the ventral aspect of the thalamus with the hypothalamus was noted in the midline. Also, the cerebral aqueduct was not visible at the midbrain level and the inlet of the fourth ventricle was narrowed. Severe hydrocephalus was noted with dilatation of the lateral ventricles and importantly, thinning of the supratentorial brain with concordant less severe dilatation of the third ventricle. In our case, the corpus callosum was severely thinned and a mild cervico-medullary kinking was noted. Otherwise, no other posterior fossa abnormality was identified. Vermis and cerebellum were within normal morphology and size. The orbits appeared anatomical with normal morphology and distance, with no hyper or hypotelorism (Figure 3).

A ventral cleft was appreciated within the anteroposterior midbrain, subtle deeper, and continuous with the third ventricle. We presumed that the classic butterfly-like sign depends on the degree of the involvement of the hypothalamus, which will lead to the dorsoventral elongation with a deep midline cleft, that can be striking as first described in 2012 [1], or less characteristic if the midbrain cleft is subtle deeper as reported in other series and as seen in our case [3,10] (Figure 4).

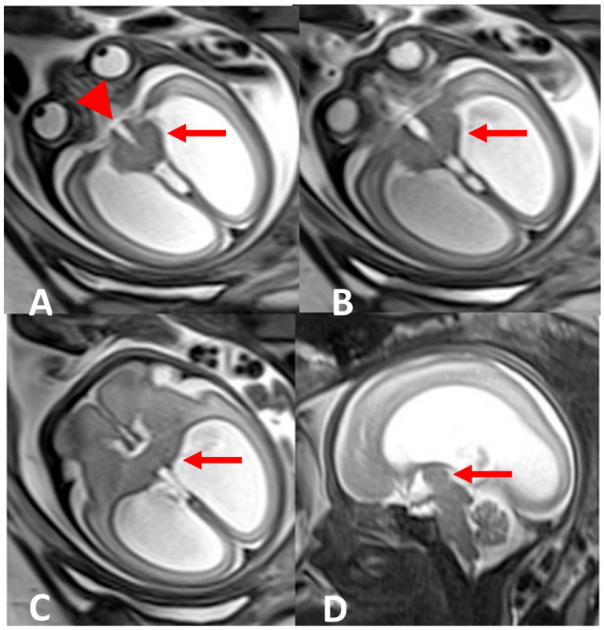

Figure 3) *Inuterine T2 MRI sequences of a male fetus at 26 weeks of gestation in axial (A, B, C) and sagittal plane. Imaging shows an abnormal midbrain contour with thick cerebral pedicles (arrows in A and B) and a mild midline cleft that is not as deep as the classic pathognomonic butterfly-like sign (arrowhead in A). The mild midline cleft is continuous with the third ventricle (A and B). Superiorly, the thalami are fused in the midline (arrow in C). The interthalamic adhesion is thickened and poorly defined (arrow in D), and there is a complete continuity between the thalami/ interthalamic adhesion and the midbrain (D), characterizing DMJD type C. There is aqueduct stenosis and severe hydrocephalus with thinning of the supratentorial brain on the sagittal plane (A-D). No other associated abnormality was found in the posterior fossa, globes, or orbits. No malformation of cortical development was seen in this case.*

Figure 4) *Demonstration of abnormal midbrain and cleft of a fetus in prenatal T2 MRI sequence. There is elongation of the midbrain and subtle depth of the midbrain cleft in the axial plane in keeping with type C DMJD (images A and B, midbrain highlighted in blue). Image C shows a visual reproduction of possible midbrain clefts and presumable depth variations in an axial plane, that are believed to coincide with the type of DMJD. Data from previous publications indicates that the pathognomonic butterfly-like sign with a deep cleft is not a constant finding for all DMJD types, most frequently described in type A; whilst subtle deep cleft has been inconsistently reported in thalamus-midbrain continuity (types B and C).*

Discussion

When summarizing the results of the gathered information from these 12 selected scientific publications, it clearly crystalizes the extreme rarity of DMDJ pattern with the largest patient cohort being of 33 patients, extracted from a large institutional digital radiology database of 1,744,302 individual patients from 2008 to 2020 using the search term "diencephalic-mesencephalic" and subsequently using the search terms "fetal" and "aqueduct stenosis" [10].

Initially, in 2012, no associated gene culprit was found of DMJD, however, in most recent publications, four gene mutations have shown associations with DMJD or DMJD imaging patterns, including *L1CAM, PCDH12* gene*, VRK1* and *FOXA2* [3,10,11,15,16]. *PCDH12* is related to neurite overgrowth and *L1CAM* plays a role in the neuronal migration and organization of neurons and the outgrowth of axons (MedLine Plus Website), whereas *VRK1* gene has an important role in regulating a transcription factor for p53 protein. P53 protein is essential in the repair of damaged DNA, it regulates cell division, and prevents the formation of cancerous tumors (Medline Plus website/NIH). *FOXA2* encodes for a DNA-binding protein mainly expressed in liver tissue, initially related to biliary atresia but also found in midline brain defects [16].

To date, three phenotypes with subtypes of DMJD have been described (types A, B, and C), but not all of them present the pathognomonic butterfly-like sign seen on axial MRI at the midbrain level: some have a dysmorphic dorso-ventral elongated midbrain without the deep midline cleft, and others present with a parenchymal band between the thalamus and the superior surface of the midbrain which is better appreciated on sagittal planes [1,2,10].

It has been suggested that type B DMJD is the most common pattern and the one with a better prognosis concerning the child's development and neurological thriving. The most profound impairment was found in type A DMJD with severe cognitive delay, microcephaly, cranial nerve impairment, and hypothalamic signs including autonomic instabilities [10]. It is uncertain where type C DMJD impairment sits relative to the other DMJD types; whether it has poorer or better outcomes [10].

The three adult cases found in literature were reported as type B DMJD. Revising the published figures/images from two adult cases [12,13], a complete or nearly complete union between thalamus/interthalamic adhesion and the midbrain were noted, similar to type C DMJD. No hydrocephalus was seen in those two cases. Of note, the classification of type C was reported later in 2020, after the publication of the adult cases. Clinically, both cases reported gradual symptoms of cranial nerve abnormalities, including diplopia, deafness, dysphagia, and speech problems [12,13], which may conclude that type C has a better outcome after all. A third case was described as type B with cough-induced headaches in adulthood, hydrocephalus and association with Chiari type I deformity [14].

Regardless of the phenotype, good quality imaging of the axial and sagittal planes of fetal MRI are critical to properly appreciate this intricate anatomy involving the hypothalamus, thalamus, midbrain and the impairment regionalization of these structures [10]. Similarly, the acknowledgment of imaging characteristics of a dysmorphic diencephalon-mesencephalon should raise the suspicious of DMJD in fetal MRI examination, primarily ordered for the evaluation of hydrocephalus

and aqueduct stenosis, concerning the differentiation between genetic disorder and congenital infectious disease. If DMJD is suspected, a possible association with the L1 syndrome would allow early parental counseling [11]. In addition, DMJD with obstructive hydrocephalus could preclude planning for endoscopic third ventriculostomy postnatally [3]. Other important imaging findings are brain calcifications in children with type A DMJD that harbor the mutation in the *PCDH12* gene, which can mimic congenital infection, making an active search for the butterfly-like sign and /or diencephalon-mesencephalon dysmorphism even more important. In early pregnancy with DMJD, the ventricles might be within normal range, the aqueduct might still be visible during the first trimester and early second trimester, whilst the neurostructures and the midbrain are still developing. This might be a silent period that all radiologists should be aware of the proper indicate subsequent examinations in high-risk cases (i.e. consanguinity, a prior child with DMJD) [3,10]. Of note, DMJD not always presents with hydrocephalus, and in these cases the early diagnosis using fetal MRI might be delayed, relying only on the abnormal morphology of the diencephalon-midbrain, which might be an explanation for possible underestimation of DMJD [3].

Globe and orbital findings in fetuses with DMJD were found in 100% of a cohort of 16 DMJD cases; and hypertelorism was the most common finding with an interocular distance measuring 2 standard deviations above the mean for gestational age. Other less common findings were persistent fetal vasculature, retinopathy, glaucoma, microphthalmia, and anophthalmia [17]. So far, no abnormal imaging involving the internal ear has been reported in association with the DMJD pattern.

Prenatal ultrasound is the standard imaging methodology for fetal screening. However, the detection of brain malformation involving the brainstem can be challenging, especially at 20 weeks of gestation. Nevertheless, one case report showed a type A DMJD diagnosis on prenatal ultrasound with obstructive hydrocephalus at 25 gestational weeks, which was supported by MRI [18]. The midbrain butterfly-like sign was visualized in two dimensional images in a low axial plane at the level of the orbits, thalamus and lateral ventricles. The factors that enable the demonstration of the abnormality was related to a controlled ultrasound setting (Fetal Medicine Department), a clear amniotic-tissue interface during the 2nd trimester, and good maternal scan window (low body mass index) [18]. This can be of value in settings where MRI is not promptly available. Nonetheless, international consensus is needed on when to best perform prenatal ultrasound to ensure also when neurocerebral alterations can be picked up accordingly and an early third trimester scan might be the best way forward, such as performed in most european countries.

DMJD pattern can be found concomitant with malformation of cortical development, particularly callosal dysgenesis, and radiologists should be aware of the variety of neurodevelopmental impairment associations to rigorously search for additional imaging findings [1-3,10,11,15]. Furthermore, the DMJD pattern was proven not to be related to a single gene mutation, but rather as a part of a complex biological pathway that involves neurite growth and neuron specification, which favors the possibility of a more diffuse defect. Nonetheless, further investigation is needed to address the neurodevelopmental granularity involving DMJD patterns and its radiological features, as well as its clinical manifestations and prognostication.

Conclusion

DMJD is a rare malformation involving the diencephalon-mesencephalon junction with three distinct key imaging types (Types A, B, and C) with diverse prognoses. Increased risk for DMJD have children born from consanguineous parents and family members with autosomal recessive diseases, and possible x-linked diseases. Hydrocephalus and aqueduct stenosis can be associated with severe type A DMJD and might not be visible in the first and early second trimester, therefore subsequent examinations should be performed in a high-risk setting. Parenchymal calcifications can be seen in type A DMJD mimicking congenital infection. Neuroradiologists should be aware of those challenges to improve diagnosis. Type B is the most common pattern, and is associated with a better prognosis when compared to type A.

Diagnosis of DMJD is primarily made by brain MRI or fetal MRI as early as 18 weeks of gestation. Prenatal ultrasound diagnosis can be an option in places where fetal MRI is not available, and further investigation is needed to settle when to best perform prenatal ultrasound if DMJD is suspected, and a late second or early third trimester scan might ensure brainstem structural alterations to be properly recognized. So far, four DMJD associated genetic abnormalities have been reported (mutation in *PCDH12*, *L1CAM*, *VRK1* and *FOXA2* genes).

Globe and orbital findings in fetuses with DMJD are believed to coincide with hypertelorism being the most common abnormality. Other globe findings include persistent fetal vasculature, retinopathy, glaucoma, microphthalmia, and anophthalmia and those abnormal features in a fetal MRI should raise suspicion for an association with the DMDJ pattern.

References

1. Zaki MS, Saleem SN, Dobyns WB, et al. Diencephalic-mesencephalic junction dysplasia: a novel recessive brain malformation. Brain. 2012;135:2416-27.
2. Severino M, Tortora D, Pistorio A, et al. Expanding the spectrum of congenital anomalies of the diencephalic-mesencephalic junction. Neuroradiology. 2016;58:33-44.
3. Severino M, Righini A, Tortora D, et al. MR Imaging diagnosis of diencephalic-mesencephalic junction dysplasia in fetuses with developmental ventriculomegaly. Am J Neuroradiol. 2017;38:1643-6.
4. Nakamura H, Watanabe Y. Isthmus organizer and regionalization of the mesencephalon and metencephalon. Int J Dev Biol. 2005;49:231-5.
5. Barkovich AJ, Millen KJ, Dobyns WB. A developmental and genetic classification for midbrain-hindbrain malformations. Brain. 2009;132:3199-230.
6. Barkovich AJ, Millen KJ, Dobyns WB. A developmental classification of malformations of the brainstem. Ann Neurol. 2007;62:625-39.
7. Canning CA, Lee L, Irving C, et al. Sustained interactive Wnt and FGF signaling is required to maintain isthmic identity. Dev Biol. 2007;305:276-86.
8. Abdel Razek AA, Castillo M. Magnetic Resonance Imaging of malformations of midbrain-hindbrain. J Comput Assist Tomogr. 2016;40:14-25.
9. Barkovich AJ. Developmental disorders of the midbrain and hindbrain. Front Neuroanat. 2012;6:7.
10. Lawrence AK, Whitehead MT, Kruszka P, et al. Prenatal diagnosis of diencephalic-mesencephalic junction dysplasia: fetal magnetic resonance imaging phenotypes, genetic diagnoses, and outcomes. Prenat Diagn. 2021;41:778-90.

11. Accogli A, Goergen S, Izzo G, et al. L1CAM variants cause two distinct imaging phenotypes on fetal MRI. Ann Clin Transl Neurol. 2021;8:2004-12.

12. Mądry J, Szlufik S, Koziorowski D, et al. The patient with mild diencephalic-mesencephalic junction dysplasia - case report and review of literature. Neurol Neurochir Pol. 2017;51:514-8.

13. Moreno-Estébanez A, Martínez MF, González TG-P, et al. Type B diencephalic-mesencephalic junction dysplasia, a congenital brainstem malformation that may be silent until adulthood: a case report. Neurol Sci. 2020;41:2293-6.

14. Mehta DG, Swanson JW. Type-B diencephalic-mesencephalic junction dysplasia initially presented with secondary cough-induced headaches: a case report. Headache. 2020;60:2600-2.

15. Guemez-Gamboa A, Çağlayan AO, Stanley V, et al. Loss of protocadherin-12 leads to diencephalic-mesencephalic junction dysplasia syndrome. Ann Neurol. 2018;84:638-47.

16. Dines JN, Liu YJ, Neufeld-Kaiser W, et al. Expanding phenotype with severe midline brain anomalies and missense variant supports a causal role for FOXA2 in 20p11.2 deletion syndrome. Am J Med Genet A. 2019;179:1783-90.

17. Jacobs E, Whitehead MT. Clinical spectrum of orbital and ocular abnormalities on fetal MRI. Pediatr Radiol. 2023;53:121-30.

18. Shah N. Prenatal ultrasound signs of diencephalic-mesencephalic junction dysplasia. Ultrasound Obstet Gynecol. 2019;54:416-7.