

Minireview

Human malformations of the midbrain and hindbrain: review and proposed classification scheme

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Abstract

Although a great deal of interest in the genetics and etiology of cerebral, particularly forebrain, malformations has been generated in the past decade, relatively little is known about the basis of congenital malformations of the structures of the posterior fossa, namely the midbrain, cerebellum, pons, and medulla. In this review, we present a classification scheme for malformations of the midbrain and hindbrain based on their embryologic derivation, highlight four of the conditions associated with such abnormalities, and describe the genetics, prognosis, and recurrence risks for each. We describe several disorders in addition to Joubert syndrome with the distinctive radiologic sign known as the “molar tooth sign,” comprised of midbrain and hindbrain malformations. We discuss Dandy–Walker malformation, its classical definition, and the surprisingly good outcome in the absence of other brain malformations. We consider the heterogeneous entity of cerebellar vermis hypoplasia and describe the recently identified gene associated with an X-linked form of this condition. Finally, the pontocerebellar hypoplasias are discussed in the context of their generally progressive degenerative and severe course, and the differential diagnosis is emphasized. We anticipate that as imaging technologies improve, differentiation of the various disorders should aid in efforts to identify the causative genes.

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Introduction

While significant progress has been made in recent years in our understanding of forebrain development and malformations, much less attention has been given to the midbrain and hindbrain. These are the posterior fossa structures that comprise the brainstem, which consists of the midbrain, pons, and medulla, as well as the cerebellum and related cerebrospinal fluid (CSF) spaces including the aqueduct of Sylvius, 4th ventricle, and the foramina of Luschka and Magendie, comprising the lateral and medial outflow tracts, respectively [1]. The embryologic development of these structures is complex, beginning at about 3 weeks gestation and continuing until 20 months of postnatal life for complete

cellular differentiation of the cerebellar layers in humans [2]. These structures are primarily derivatives of the primitive hindbrain or rhombencephalon, with the cerebellum derived from the most rostral segment of the hindbrain (rhombomere 1), the pons from the rostral half of the hindbrain (the metencephalon), and the medulla from the lower half of the hindbrain (the myelencephalon). Further details are available in the accompanying review by Chizhikov and Millen [3]. In contrast, the midbrain is derived from the mesencephalon.

Malformations of the posterior fossa have been recognized much more frequently during the past decade or more, based on rapid advances in technology. The first imaging modality to identify these malformations was pneumoencephalography, where air injected into the CSF spaces of the brain could identify displaced, occluded, or dysplastic structures. With the advent of computerized tomography (CT), and more recently,

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magnetic resonance imaging (MRI), the resolution of cranial structures including the mid-hindbrain regions has improved greatly [4]. However, with improved brain imaging technologies has arisen perplexing problems of categorization and syndrome delineation, as more subtle structural anomalies can now be identified, often of uncertain significance. In fact, the ability to predict the degree of motor and cognitive impairment based on the gross appearance of brain images has been problematic. Cerebellar symptoms such as ataxia and motor incoordination or brainstem impairment have been equally difficult to prognosticate. Even more challenging has been the prenatal identification of a posterior fossa malformation, with resultant inability to accurately predict the outcome, often resulting in poorly informed decisions regarding pregnancy termination [5]. Several different classification schemes for malformations of posterior fossa structures have been proposed [2,4,6,7]. However, none of these approaches consistently relates malformations to the embryological structures involved.

In this review, we present our preferred classification scheme, which is based as much as possible on the

embryologic derivation of midbrain and hindbrain structures (Table 1). Although a comprehensive summary of all posterior fossa malformations included in this scheme is beyond the scope of this mini-review, we choose to focus on four of the relatively more common malformations, and those in which there has been considerable confusion regarding delineation and/or prognosis. Our emphasis is on abnormalities that primarily affect only the midbrain and/or hindbrain, although supratentorial structural abnormalities and cerebral dysfunction may also be a component. We will highlight four malformations that primarily involve posterior fossa structures: the molar tooth sign (MTS) and associated mid-hindbrain malformations that occur in Joubert and related syndromes; Dandy–Walker malformation (DWM); cerebellar vermis hypoplasia and dysplasia (CVH); and pontocerebellar hypoplasias (PCH). We will discuss the structural manifestations seen on MRI, the clinical features, the inheritance and causative genes (if known), the prognosis, and recurrence risks for each of these conditions (Table 2).

Table 1
Classification scheme for malformations of mid-hindbrain development

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- *Malformations of both midbrain and hindbrain*
 - Brainstem-cerebellar hypoplasia-dysplasia
 - Chiari II malformations
 - Cobblestone LIS with mid-hindbrain malformation
 - **Molar tooth sign associated malformations**
 - **Joubert syndrome**
 - **JSRD, including Senior–Löken and COACH**
 - Rhombencephalosynapsis
 - *Malformations affecting predominantly the midbrain*
 - *Malformations affecting predominantly the cerebellum and derivatives (Rh1)*
 - Focal cerebellar hypoplasia (focal or hemispheric)
 - Paleocerebellar hypoplasia (vermis predominantly affected, brainstem often mildly hypoplastic)
 - **Dandy–Walker malformation**
 - **Cerebellar vermis hypoplasia, isolated**
 - CVH with periventricular nodular heterotopia
 - CVH with cortical malformations (LIS, PMG)
 - Neocerebellar hypoplasia (hemispheres and vermis affected, predominantly granule cell hypoplasia)
 - *Malformations affecting predominantly the lower hindbrain (Rh2–Rh8)*
 - Chiari I malformations
 - Cranial nerve and nuclear aplasias
 - Möbius syndrome
 - Duane retraction syndrome
 - *Posterior fossa abnormalities*
 - Abnormal fluid collections
 - Arachnoid cyst
 - Blake's pouch cyst
 - Mega-cisterna magna
 - Abnormal bone and brain structure
 - *Malformations associated with prenatal onset degeneration*
 - **Ponto-cerebellar hypoplasia (hypoplasia and prenatal onset atrophy)**
 - **PCH type 1, PCH type 2, PCH type 3**
 - Congenital disorders of glycosylation (CDG)
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Conditions that are in bold indicate those featured in this review.

CDG, congenital disorders of glycosylation; COACH, Cerebellar vermis hypoplasia, Oligophrenia, Ataxia, Coloboma, and Hepatic fibrosis; CVH, cerebellar vermis hypoplasia; JSRD, Joubert syndrome and related disorders; LIS, lissencephaly; PCH, pontocerebellar hypoplasia; PMG, polymicrogyria; Rh, rhombomere.

Table 2
Genetic basis, prognosis, and recurrence risks of midbrain–hindbrain malformations

Condition	Features	Inheritance	Loci/genes	Prognosis ^a	Differential Diagnosis/ Management	Recurrence risk
Molar tooth sign (MTS) and associated malformation disorders						
Classic Joubert syndrome	Hypotonia, DD/MR, OMA, apnea/tachypnea, ataxia, (polydactyly)	AR	9q34, others	Variable; mild to severe MR, visual impairment	See text	25%
JS-LCA-like	JS plus retinal dystrophy (flat ERG), and severe visual impairment	AR	?	Similar to JS	See text; interventions for blindness	25%
Dekaban–Arima	JS plus cystic dysplastic kidneys	AR	?	Often die of neonatal apnea or renal failure	Monitor for renal complications	25%
COACH	JS plus ocular coloboma and hepatic fibrosis	AR	?	Require hepatic transplant	Monitor for liver failure	25%
Senior–Löken	Retinal dystrophy and juvenile-onset NPHP, (JS features)	AR	2q13 (<i>NPHP1</i>) ^b 3q22 1p36 (<i>NPHP4</i>) ^b	Onset of ESRD at 8–12 years; often need renal transplant	Monitor for renal failure; interventions for retinal dystrophy/visual loss	25%
OFD VI	JS plus polydactyly (mesaxial), midline oral clefts, tongue tumors	AR	?	Variable	See text	25%
Dandy–Walker malformation (DWM)						
Classic	CVH, cystic dilatation of 4th ventricle, elevated torcula, (hydrocephalus)	Sporadic	?	Generally good if no associated anomalies	Karyotype; shunting for symptomatic HC	~1–5%
Other	Classic DWM plus other structural	Chromosomal, syndromic	Multiple	Depends on underlying abnormality	Karyotype; shunting for symptomatic HC	Variable
Cerebellar vermis hypoplasia (CVH)						
X-linked	CVH, retrocerebellar cyst, hypotonia, spasticity, seizures, (hydrocephalus), (sex reversal)	XL	Xq12 (<i>OPHN1</i>) Others?	Generally poor; carrier females often have milder or variable symptoms	Karyotype; mutational analysis may be available on a research basis	50% overall (assumes females affected)
Other		AR?	?	Variable	Karyotype	25% ?
Posterior fossa fluid collections	Non-communicating membrane-enclosed cyst; normal cerebellum; (ataxia), (hydrocephalus)	Unknown	?	Generally good; may have MR if supratentorial malformations	Symptomatic	Unknown
Pontocerebellar hypoplasia (PCH)						
PCH-1	Spinal muscular atrophy, respiratory insufficiency, contractures	AR	?	Poor, degenerative course with death within 1 year	Initial workup to exclude CDG (see below)	25%
PCH-2	Progressive microcephaly, dyskinesia, poor feeding, seizures	AR	?	Generally poor, degenerative course with death within first decade	Initial workup to exclude CDG (see below)	25%

Table 2 (continued)

Condition	Features	Inheritance	Loci/genes	Prognosis ^a	Differential Diagnosis/ Management	Recurrence risk
PCH-3	Progressive microcephaly, seizures, spasticity, (optic atrophy)	AR	7q11-21	Generally poor, variable degenerative course	Initial workup to exclude CDG (see below)	25%
Congenital disorders of glycosylation (CDG)	PCH Hypotonia, dysmorphic facies, strabismus, inverted nipples, lipodystrophy; (hepatic fibrosis); (TCP)	AR	Ia: 16p13 (<i>PMM2</i>) Ib: 15q22 (<i>MPI</i>) Ic: 1p22.3 (<i>ALG6</i>) Id: 3q27(<i>ALG3</i>) others	Variable	Serum transferrin isoelectric focusing for type I CDG	25%

See text for references.

Features in parentheses are variable for that condition.

Abbreviations: *ALG3*, Man(5)GlcNAc(2)-PP-dolichyl mannosyltransferase; *ALG6*, Man(9)GlcNAc(2)-PP-Dol α -1,3-glucosyltransferase; AR, autosomal recessive; DD/MR, developmental delays/mental retardation; ESRD, end-stage renal disease; HC, hydrocephalus; JS, Joubert syndrome; LCA, Leber congenital amaurosis; *MPI*, Mannosephosphate isomerase; NPHP, nephronophthisis; *NPHPI*, nephrocystin; *NPHP4*, nephroretinin; OMA, oculomotor apraxia; *OPHN1*, Oligophrenin-1; *PMM2*, phosphomannomutase 2; TCP, thrombocytopenia; XL, X-linked.

^a All of these entities are associated with some degree of mental retardation except for classic DWM and posterior fossa fluid collections.

^b Although mutations in these 2 genes have been identified in individuals with Senior-Löken syndrome, the molar tooth sign and other features of JS have not been confirmed in individuals with these mutations.

Embryology and classification scheme

The available methods of classifying congenital malformations of the posterior fossa all have limitations, in part because of poor understanding of the molecular basis of human midbrain and hindbrain development. Some schemes emphasize categorization on an anatomical basis, such as midline versus hemispheric cerebellar changes or abnormalities of cerebellar foliation and fissuration [2,7,8]. While anatomic landmarks can be very helpful for delineating the abnormal structures that correspond to radiologic findings, these artificial separations may fail to recognize the broad developmental effects from a single gene or environmental factor. Other classification schemes focus on known causes of pontine and/or cerebellar hypoplasia (e.g., teratogens, chromosomal anomalies, metabolic derangements) [7], but in the majority of cases, knowledge of etiology is limited or non-existent. A more recent classification system based on radiological findings on MRI proposes to group cerebellar malformations into two broad categories distinguished by hypoplasia versus dysplasia [4], but in our experience, this distinction can be difficult in practice. Although each of these approaches has merit, no single classification system has adequately addressed the variety of posterior fossa malformations in a consistently useful manner. Here we present a framework for classification that is based on the embryologic derivation of the involved structures, which we hope will be amenable to revisions as knowledge advances.

The development of the posterior fossa begins shortly after neural tube closure when the primary brain vesicles

(prosencephalon, mesencephalon, and rhombencephalon) form along the anterior–posterior axis of the developing brain [1]. Between 3 and 5 weeks gestation, the neural tube bends at the cranial and cervical flexures and the rhombencephalon subdivides into 8 rhombomeres [2]. Soon thereafter, the pontine flexure forms between the metencephalon (the future pons and cerebellum) and the myelencephalon (the future medulla oblongata). The isthmus develops at the junction of the mesencephalon and metencephalon and serves as an organizing center for both the midbrain and the structures of rhombomere 1 (Rh1), which will develop into the pons ventrally and cerebellum dorsally (see [3] for a review of the analogous process in the developing mouse brain and a summary of the genes known to regulate this patterning process). The lateral flare at the pontine flexure creates the 4th ventricle, the roof of which develops into the cerebellum. Between 6 and 7 weeks gestation, the flocculonodular lobe (archicerebellum) and dentate nuclei of the cerebellum form. The remainder of the cerebellum develops in a rostro-caudal manner, with the more rostral regions remaining in the midline and giving rise to the midline vermis, while more caudal regions move laterally due to forces exerted by the pontine flexure and give rise to the cerebellar hemispheres. The vermis (paleocerebellum) develops and becomes fully foliated by 4 months gestation, while development of the large cerebellar hemispheres (neocerebellum) lags behind that of the vermis by 30–60 days [1]. Postnatally, proliferation of the cellular components of the cerebellum continues, with completion of the foliation pattern by 7 months of life [9] and final migration, proliferation, and arborization

of cerebellar neurons by about 20 months of life [10]. The caudal rhombomeres (Rh2–Rh8) develop into the pons and medulla oblongata and form the nuclei of cranial nerves 5–10 [1,11]. The adult appearance and identification of posterior fossa structures is illustrated in Fig. 1.

An embryologic approach to classifying mid-hind-brain malformations is presented in Table 1. Conditions known to affect derivatives of both the mesencephalon and rhombencephalon are included in the first category. Within the group of brainstem-cerebellar hypoplasia-dysplasias is the extremely rare condition of complete cerebellar agenesis as well as more common forms of hypoplasia with diffuse and often severe brainstem (including pontine) involvement. The most common posterior fossa anomaly is the Chiari group of malformations in which the brainstem and cerebellar tonsils are displaced downward through the foramen magnum [12]. Type II Chiari malformations associated with meningocele are the most prevalent, and other brain anomalies, such as beaking of the tectum or roof of the midbrain, are common [12]. Conditions with cobblestone lissencephaly and mid-hindbrain abnormalities with cerebellar hypoplasia include autosomal recessive disorders that are often associated with congenital muscular dystrophy and ocular anomalies such as muscle–eye–brain disease, Walker–Warburg syndrome, and Fukuyama congenital muscular dystrophy [13]. Malformations comprising the molar tooth sign are reviewed below. Rhombencephalosynapsis is a rare anomaly characterized by absence or severe dysgenesis

of the cerebellar vermis with fusion of the cerebellar hemispheres, peduncles, and dentate nuclei; variable features include fusion of the midbrain colliculi, hydrocephalus, absence of the corpus callosum, and/or septum pellucidum, and other midline structural brain malformations [14–16].

Although we are not aware of isolated midbrain malformations, this category is included for theoretical purposes. Malformations affecting predominantly the cerebellum and derivatives of dorsal rhombomere 1 include the heterogeneous group of focal cerebellar hypoplasias, which will not be addressed further. Malformations affecting the paleocerebellum, with vermis greater than hemispheric involvement, include Dandy–Walker malformation and cerebellar vermis hypoplasia, both discussed in detail below. CVH can also be seen in association with supratentorial anomalies including periventricular nodular heterotopia, lissencephaly, or polymicrogyria, some of which have known genetic causes and are discussed elsewhere [17,18]. Some forms of cerebellar hypoplasia affect the vermis and hemispheres equally with the appearance of shrunken folia and prominent fissures due to a failure of granule cell proliferation [2].

Chiari type I malformations consisting of hindbrain herniation through the foramen magnum and rarely, other structural anomalies, are included in the category of predominantly lower hindbrain malformations and often present with symptoms of headache and cranial nerve impingement in adulthood [12]. Few other isolated malformations of the lower hindbrain, derived from the

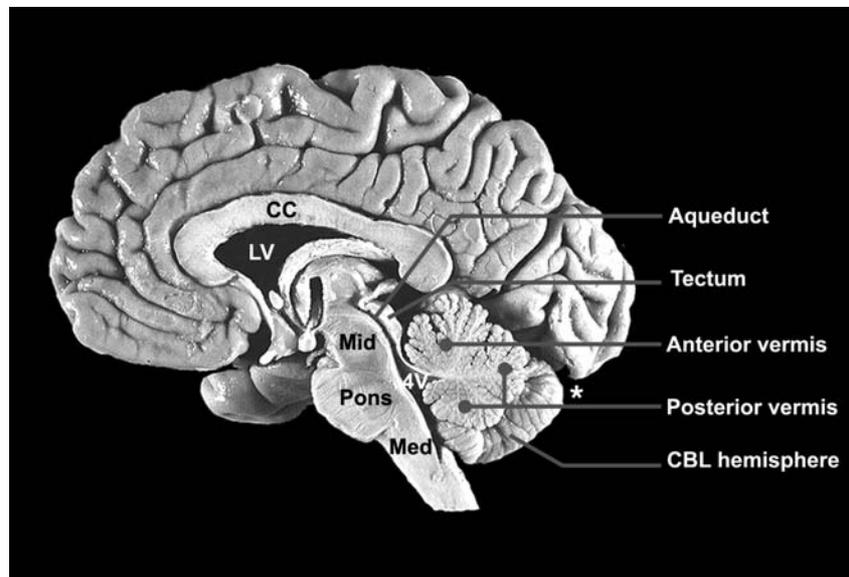


Fig. 1. Midsagittal view of a fixed normal brain with major posterior fossa structures and other anatomical landmarks indicated. The torcula represents the confluence of sinuses at the posterior midline that is not actually visible in this fixed specimen, but its position is indicated by an asterisk. Note that the lateral cerebellar hemisphere is visible behind the midline cerebellar vermis, and is often present on MRI slices that are not precisely at the midline. Aqueduct, aqueduct of Sylvius; CC, corpus callosum; CBL, cerebellum; LV, lateral ventricle; 4V, 4th ventricle; Mid, midbrain; Med, medulla. Photograph provided courtesy of the University of Washington Digital Anatomist Program.

myelencephalon, have been described. One exception is Möbius syndrome, in which aplasias of cranial nerves 6 and 7 result in facial nerve and lateral gaze palsy [19]. Another cranial nerve anomaly is implicated in Duane retraction syndrome, in which abnormal oculomotor movements occur during attempts at eye adduction [20].

The embryologic scheme breaks down in trying to describe abnormalities of the posterior fossa spaces surrounding the brainstem and cerebellum. An arachnoid cyst is a collection of CSF encased within a pia-arachnoid layer and not associated with abnormalities of the cerebellum or brainstem, although by mass effect may cause compression of these structures [1]. One of the well-known conditions associated with an abnormal retrocerebellar fluid collection is mega-cisterna magna, with normal size and position of the cerebellum, including its vermis, and normal 4th ventricle. This can be an incidental finding, but may be associated with hydrocephalus or mental retardation when cerebral anomalies are present [2]. In our experience, mega-cisterna magna and cerebellar vermis hypoplasia may be difficult to distinguish. We have frequently seen cerebral dysgenesis associated with cerebellar vermis hypoplasia, but rarely with mega-cisterna magna. A Blake's pouch cyst is a closely related malformation with a controversial definition and etiology [4].

The final category encompasses the group of pontocerebellar hypoplasias with a developmental pattern

more consistent with the prenatal onset of degeneration. Although the initial patterning may have been normal, these hindbrain structures demonstrate a failure of normal development at birth with progressive atrophy apparent on serial imaging [21]. Several of these conditions are metabolic in nature and these are reviewed below.

Common mid-hindbrain malformations

Molar tooth sign (MTS) and associated mid-hindbrain malformation disorders

Joubert syndrome (JS) is the best known and probably most common syndrome associated with the molar tooth sign (MTS). JS has been defined on the basis of clinical features which include hypotonia in infancy with later development of ataxia, developmental delays/mental retardation, an abnormal breathing pattern characterized by alternating tachypnea and apnea, abnormal eye movements typified by oculomotor apraxia, and the presence of the MTS on cranial MRI [22,23]. The MTS is a distinctive finding of hypoplasia/dysplasia of the cerebellar vermis with accompanying brainstem abnormalities visualized on axial images through the isthmus that resembles a tooth (Fig. 2) [24]. It is comprised of an abnormally deep interpeduncular fossa,

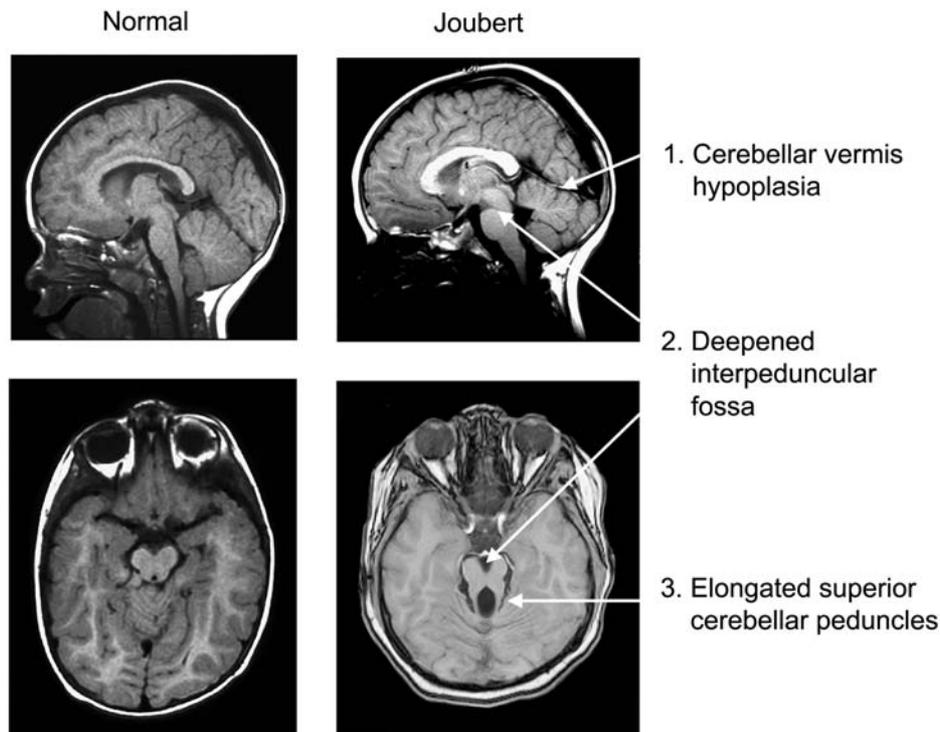


Fig. 2. The molar tooth sign (MTS) and associated mid-hindbrain malformation. Comparison of a normal brain in midsagittal view (top) and axial view (bottom) with that of a child with Joubert syndrome indicating the 3 components that comprise the molar tooth sign, shown in the axial image in the lower right panel.

hypoplasia of the cerebellar vermis, and prominent, straight, and thickened superior cerebellar peduncles [25]. In fact, the cerebellar vermis on mid-sagittal view often has a “kinked” appearance and severe hypoplasia and/or aplasia, with enlargement of the 4th ventricle [26]; these aspects of this complex malformation are not fully appreciated on views used to identify the MTS, and we therefore use “MTS-associated malformation” to describe the complete abnormality seen in JS. An enlarged posterior fossa fluid collection has been identified in about 10% of patients, but in contrast to DWM, the brainstem dimensions are abnormal [26]. JS is an autosomal recessive condition with an estimated prevalence of approximately 1:100,000 [27]. This likely represents an underestimate, as many children who had cranial imaging before description of the MTS in 1997 may not have been properly diagnosed, and many radiologists fail to identify the MTS even today (MAP, unpublished data). The French-Canadian family first described in 1969 by Joubert and colleagues has been traced to a founder who immigrated to Quebec from France in the 1600s [28,29]. One locus for JS has been mapped to 9q34 in two consanguineous Arabian families from Oman [30], but failure of other families to show linkage to this region underscores the genetic heterogeneity in JS [31].

Clinical heterogeneity

JS is notable for both intrafamilial and interfamilial phenotypic variability. In the original pedigree of four affected siblings, there were significant differences in cerebellar findings: two had hypoplasia of the posterior inferior cerebellar vermis, a third had complete agenesis of the cerebellar vermis, and a fourth had complete agenesis of the cerebellar vermis and an occipital meningoencephalocele [28]. Discordant phenotypes were observed in a set of monozygotic twins with Joubert syndrome; both had the MTS on MRI, but anatomic, neurologic, and developmental findings differed greatly [32]. Although some infants have died of apneic episodes, in general, the breathing abnormalities improve with age and may completely disappear [25,33]. Cognitive abilities are variable, ranging from severe mental retardation to normal, but most commonly in the moderately retarded range. Seizures and behavioral problems within the autism spectrum disorder have been described [34].

A variety of other features that have been identified in children with JS include retinal dystrophy, renal disease, ocular colobomas, hepatic fibrosis, and polydactyly [22,35]. The retinal disease consists of a pigmentary retinopathy indistinguishable from classic retinitis pigmentosa; it can occasionally have severe neonatal onset with congenital blindness and attenuated or extinguished electroretinogram studies (ERG) [36]. Pendular rotatory nystagmus is common but does not always

predict the development of retinopathy. Many children with JS demonstrate horizontal nystagmus at birth that improves with age. Oculomotor apraxia is often identified in childhood as jerky eye movements [37]. Colobomas can involve the iris and/or the retina. The renal disease in JS is variable, although the most common manifestation is cystic dysplasia of the kidneys, which is visualized on renal ultrasound as small cysts in the cortical and corticomedullary regions [22,37]. A distinctive renal condition found in some children with JS is juvenile nephronophthisis, or medullary cystic kidney disease, with progression to end-stage renal disease [36,37]. Renal ultrasound changes occur late in the disease, which can develop during childhood and early adolescence, necessitating vigilance to make a prompt diagnosis [37]. At least two genes for nephronophthisis have been isolated, but surveys have failed to identify the common *NPHP1* deletion in patients described as having a form of JS with nephronophthisis [38]. Some individuals with juvenile nephronophthisis and oculomotor apraxia with cerebellar vermis hypoplasia have been reported to have mutations in the *NPHP1* gene [39], although details of cranial imaging are limited, and the MTS-associated malformation has not been confirmed. Hepatic fibrosis has been seen in JS, and may be associated with cystic dysplastic kidneys or nephronophthisis [36]. Polydactyly can be unilateral or bilateral, and is often postaxial although preaxial polydactyly of the toes is also frequently reported [22]. CNS malformations in addition to the molar tooth sign can include occipital encephaloceles, and rarely, polymicrogyria, which may represent a unique subtype [40].

Other MTS-associated syndromes

The MTS-associated malformation has been described in at least 6 conditions, including “classic” JS, and the classification system is still evolving [35,36,40,41] (see Table 2). Many of these conditions fall within the spectrum of cerebello-oculo-renal disorders with established or presumed autosomal recessive inheritance, and at least a subset of individuals given one of these diagnoses demonstrates the MTS [36,40]. Some patients have severe retinal dysplasia with congenital blindness that resembles Leber congenital amaurosis (Fig. 3A). Others have Dekaban–Arima syndrome, a severe condition with retinopathy and cystic dysplastic kidneys [42]; COACH syndrome (Cerebellar vermis hypoplasia, **O**ligophrenia, **A**taxia, **C**oloboma, and **H**epatic fibrosis) [43,44]; or Senior–Löken syndrome (SLS; retinopathy and juvenile-onset nephronophthisis; Fig. 3B) [45,46]. Oral–Facial–Digital syndrome type VI (OFD VI) includes cerebellar vermis hypoplasia, oral frenula, tongue hamartomas, and midline cleft lip, as well as the distinctive feature of central polydactyly with a Y-shaped metacarpal [47], and the MTS-associated

malformation has been observed in at least one case (Fig. 3C) [40]. These conditions that have in common the molar tooth sign and the neurological features of JS have been termed “Joubert syndrome and related disorders (JSRD)” [40,48].

Management in MTS-associated malformation syndromes

Given the clinical heterogeneity in JSRD, the diagnostic and management issues for children with a suspected diagnosis are complex. The workup should

include a genetics referral to evaluate the family history for consanguinity and physical examination for manifestations of polydactyly and tongue abnormalities suggestive of OFD VI. A peripheral blood karyotype is recommended to exclude chromosomal disorders but is likely to be normal. Neurologic evaluation should include a high-resolution MRI to identify the MTS-associated malformation, polysomnogram to identify infants at risk for apnea, and swallowing studies and EEG as necessary. Developmental testing is mandatory to optimize educational performance. Ophthalmologic evaluation should include examination for colobomas and



Fig. 3. The molar tooth sign (MTS) and associated mid-hindbrain malformation is seen in multiple different conditions. (A) Joubert with Leber congenital amaurosis-like syndrome. This 15-month boy has a flat ERG and pigmentary changes with impaired visual tracking and postaxial polydactyly of the left foot, with evidence of the molar tooth sign on axial MRI. [LR01-201] (B) Senior-Löken syndrome. This boy at 10 months of age (left panel) and at 9 years of age (middle panel) has evidence of the MTS on MR image. He exhibited blindness by 2 months of age with retinal dystrophy and has severe mental retardation. He developed kidney failure due to nephronophthisis necessitating renal transplant. [DP97-030] (C) Oral-Facial-Digital syndrome type VI (OFD VI). The left panel shows a male infant with tongue papules and midline notching of the upper lip. Hands demonstrate preaxial, mesaxial, and postaxial polydactyly (middle panel). The molar tooth is visualized on MR images (right panel). [DP90-009]. Several of these images have been published in [36,40], and are reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

retinal dystrophy, with specialized ERG and related studies as indicated. Since there is currently no ability to predict which children will develop renal complications, we recommend annual renal ultrasound examinations with renal function analysis to include urinalysis for specific gravity, BUN and creatinine, and complete blood count. Annual liver function tests and examination for hepatic enlargement are also recommended [48].

Dandy–Walker malformation (DWM)

The Dandy–Walker malformation was first described in 1887 by Sutton [49] and was further characterized by Dandy and Blackfan in 1914 and Taggart and Walker in 1942 [50,51]. The key components of this malformation include hypoplasia of the cerebellar vermis and cystic dilatation of the 4th ventricle. The 4th ventricle communicates with a retrocerebellar cyst that may cause enlargement of the posterior fossa and elevation of the tentorium, seen on imaging studies as elevation of the torcula or confluence of the sinuses (Fig. 4). A third, variable component of DWM is communicating hydrocephalus with enlarged lateral ventricles. This condition often presents with macrocephaly in the neonatal period, and infants may come to medical attention because of hydrocephalus, developmental delay, or ataxia [52]. Some asymptomatic adults have been found to have the malformation incidentally [53,54]. A number of related conditions often designated “Dandy–Walker variants” have been described. Despite over a century of experience with DWM, our understanding of the etiology, classification, outcomes and underlying biology of this and related malformations remains limited. Given the confusion in the medical literature, the management and counseling given to families regarding a prenatal or postnatal diagnosis of “DWM” is, in our experience, frequently incorrect.

DWM is a relatively common malformation, occurring in at least 1 in 5000 liveborn infants (personal communication with Metropolitan Atlanta Congenital Defects Program, Centers for Disease Control and Prevention). DWM has been proposed to represent 4% of cases of hydrocephalus, with an estimated incidence of as high as 1/2500 to 1/3500 births [55]. In fact, DWM has been reported in a wide variety of chromosomal anomalies, including trisomy 18 as well as trisomy 9 and trisomy 13; triploidy; 45,X; partial duplication of 5p, 8p, 8q, and 11q; and deletion of 2q, 3q, and 6p (reviewed in [5,56,57]). DWM has also been described in many different genetic syndromes, many of which are autosomal recessive in inheritance, including the Meckel–Gruber and Walker–Warburg syndromes [56–58]. However, some of these syndromes, specifically Meckel–Gruber and Walker–Warburg syndromes, have complex mid-hindbrain malformations that are unlikely to represent classic DWM. For example, pathological examination

in Walker–Warburg syndrome shows that the entire brainstem and cerebellum are hypoplastic with striking dysplasia on microscopic exam [59]. Some surveys suggest that environmental factors, including prenatal exposure to teratogens such as rubella or alcohol, are associated with DWM [57,60].

Heterogeneity of DWM

Many groups have tried to define DWM in a consistent manner, utilizing in addition to the core criteria of cerebellar vermis hypoplasia and cystic enlargement of the 4th ventricle, other features that may include elevation of the roof of the posterior fossa (the tentorium cerebelli and torcula), enlargement of the posterior fossa, stenosis of the outflow tracts of the 4th ventricle, and hydrocephalus with increased intracranial pressure (see reviews by [52,61–71]). In these series, presentation has almost always been in infancy or early childhood due to hydrocephalus in at least 80% of subjects. We suspect that this is due in part to a bias of ascertainment in neurosurgical series, as fewer of the patients we have ascertained have had hydrocephalus. The authors of the series noted above found that associated malformations, generally central nervous system in origin (including occipital encephalocele, polymicrogyria, and heterotopia), are present in 29–48% of individuals with DWM. A significant proportion (~10–17%) of children with DWM have agenesis or dysgenesis of the corpus callosum [61,64,65,69,71]. While we have not yet reviewed our personal series in detail, our anecdotal experience indicates that other brain malformations, including complex malformations such as cobblestone lissencephaly, are more common with isolated cerebellar vermis hypoplasia (see below) than with typical DWM except for agenesis of the corpus callosum, which may be even more common than the previous literature suggests [4]. Other non-CNS anomalies with an increased frequency in DWM include congenital heart disease, cleft lip and/or palate, and neural tube defects [57]. A recurring association of DWM with facial hemangiomas has been noted and described under the acronym PHACE syndrome (P_osterior fossa brain malformations, H_emangiomas, A_rterial anomalies, C_oarctation of the aorta and cardiac defects, and E_ye abnormalities) [72].

For the purposes of this review and to clarify an often perplexing body of literature, we prefer to distinguish “true” DWM from three other related entities that are often confused with DWM. As classically defined, “true” DWM consists of cerebellar vermis hypoplasia with upward vermis rotation and often elevation of the torcula, an enlarged 4th ventricle which extends posteriorly as a retrocerebellar cyst, and hydrocephalus which is present in ~50–80% of subjects (Fig. 4). The second group consists of malformations with less severe cerebellar vermis hypoplasia, less notable or absent upward rotation of the

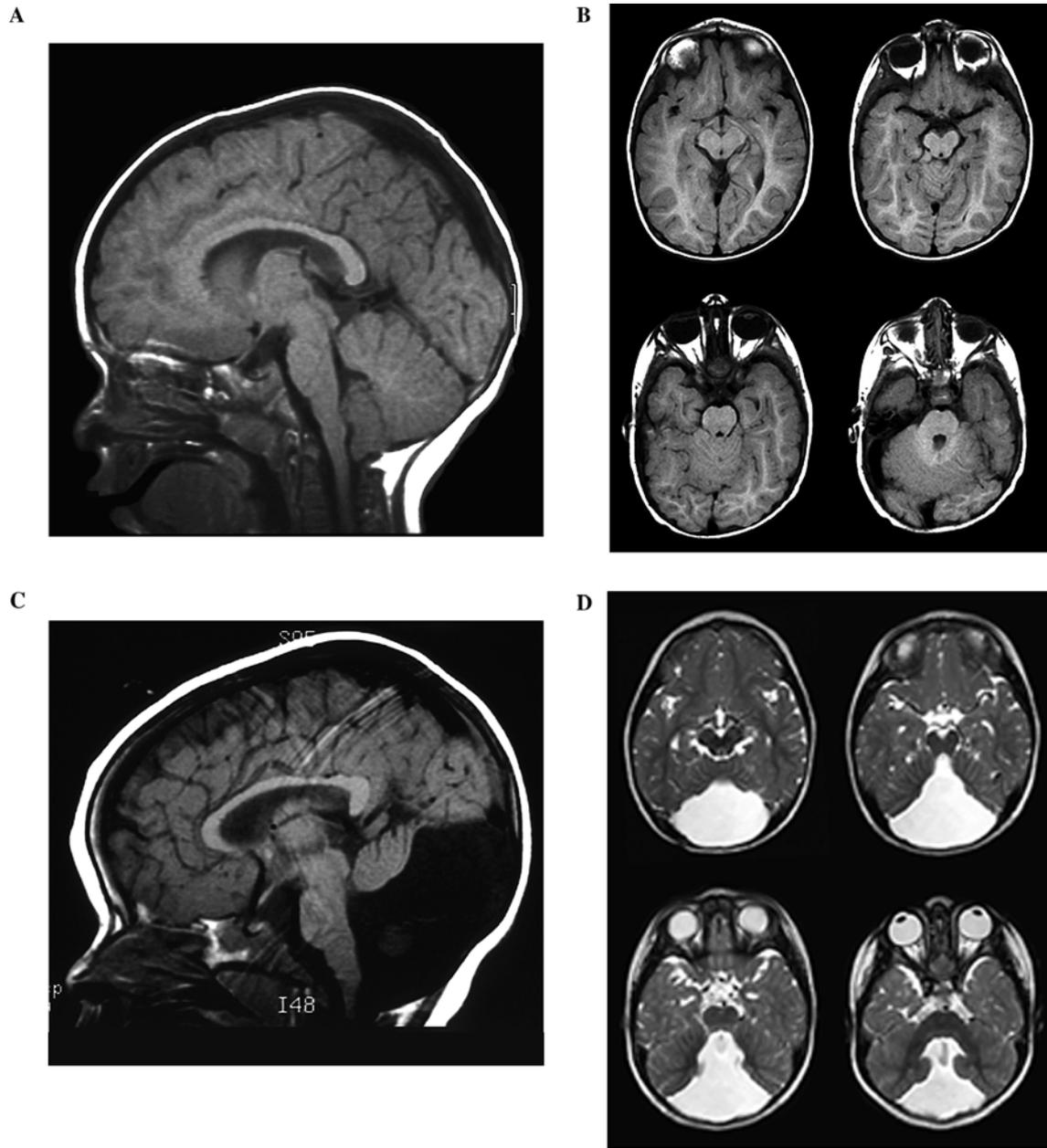


Fig. 4. Normal subject in comparison to subject with classic Dandy–Walker malformation (DWM). (A) Midsagittal view of brain of a normal subject. (B) Serial axial T1 MR images show normal posterior fossa, progressing from superior (upper left) to inferior (lower right). The 4th ventricle is visible as a dark space on the lower right panel. [DP98-029] (C) Midsagittal image of a 17-month-old girl with DWM. Note the elevated torcula, at the posterior junction of the occipital lobe and the infratentorial space. The upwardly rotated, hypoplastic cerebellar vermis is visible. (D) Serial axial T2 MR images of this child demonstrate the large, contrast-enhanced retrocerebellar space adjacent to the hypoplastic vermis. [LR01-276].

vermis, and generally smaller posterior fossa fluid collections. These are often categorized as “Dandy–Walker variants,” although we are not convinced that these malformations comprise part of the same spectrum as true DWM, at least in the majority of cases. We recommend abandoning the term “Dandy–Walker variant” given its variable definitions, lack of specificity, and confusion with classic DWM. A third group consists of diffuse cerebellar hypoplasia involving the vermis and hemispheres, usually with prominent hypoplasia of the brainstem as

well. The brainstem and cerebellar malformation seen in Walker–Warburg syndrome [59] is a good example of this group, included in the category of conditions affecting both midbrain and hindbrain in Table 1. Finally, some patients with large posterior fossa fluid collections, but with entirely normal size of the cerebellar vermis and hemispheres, are diagnosed as having DWM. This group may be divided into mega-cisterna magna and Blake’s pouch cyst [4]. The former is lined by arachnoid and the latter by ependyma, a distinction that cannot be

determined by conventional MRI. Thus, differentiation may not be possible without specialized imaging studies. In general, the outcome for this group of anomalies is better than for malformations with actual cerebellar hypoplasia [2,62,73].

Clinical course and outcome

Infants with “true” DWM often present in the neonatal period with macrocephaly, occipital cephaloceles, and/or hydrocephalus [52]. For those with severe obstructive hydrocephalus, multiple congenital anomalies, and/or other severe CNS anomalies such as porencephaly, the mortality is high. Apnea and seizures (up to 25% in one series [64]) are seen in a significant proportion of children with DWM, although developmental delay and mental retardation are highly variable (see below). On physical exam, these infants tend to have congenital hypotonia and may later develop spasticity [69]. Ataxia and nystagmus are seen in many, but cerebellar signs are variable and may not be present [64]. Many subjects (32% in one series) were diagnosed after the age of 6 months, due to increasing head circumference and/or symptoms of elevated intracranial pressure such as lethargy, vomiting, and irritability; however, 83% of these had normal intellect and essentially normal motor function [69]. There are reports of DWM diagnosed incidentally after cranial imaging studies performed for other indications [53,54].

The treatment of DWM has been a subject of great controversy. In early series, based on the belief that the hydrocephalus was due to obstruction of the foramina of Luschka and Magendie, surgery involved excision of the posterior fossa membranes to create unobstructed flow of CSF, with resultant poor outcomes [61,71]. Subsequent treatment by either direct shunting of the lateral ventricles, shunting of the posterior fossa cyst, or both, to relieve symptomatic hydrocephalus has met with mixed success, in part due to the intrinsic complications associated with shunt malfunction [61,64,65,69,71,74]. Although it has been proposed that return of normal cerebellar architecture by shunting the cyst is associated with good functional outcome [65,69], other authors suggest that the measured volume of cerebellum is not significantly changed by cyst shunting and advocate ventriculoperitoneal shunting as the best approach to relieve increased intracranial pressure [64].

Cognitive outcomes in DWM series vary widely. In early reports, DWM was associated with a high mortality rate of almost 50% [70], but more recent reports suggest that classic DWM does not carry such a dire prognosis. A summary of 7 references reveals that of 224 subjects with DWM, 61 died, for a 27% mortality rate [52,64,65,68–71]. Although one report suggests that 71% of subjects had an IQ less than 83 [71], a survey of six

references published between 1980 and 1995 reveals an IQ of greater than 80 in 47% of subjects [64,65,68–71]. In fact, the distribution of intelligence scores appears to be bimodal, suggesting that there may be two distinct groups included in these surveys: those with normal cognition (47%), and those with severe impairment (IQ <55), which represented 35% of the cohort. Those with mild MR (IQ 56–79) represented only 18% of the group. We speculate that some of the children with severe outcome in these reports may have had diffuse brainstem-cerebellar hypoplasia or other similar malformations, rather than typical DWM. Several authors have noted an improved outcome for DWM in the absence of major congenital anomalies [65,69].

Cerebellar vermis hypoplasia/dysplasia (CVH)

In contrast to DWM, cerebellar vermis hypoplasia in our classification scheme is associated with normal position of the cerebellar vermis relative to the brainstem or minimal upward rotation due to a mildly enlarged 4th ventricle, without elevation of the tentorium cerebelli (Figs. 5A and B). The retrocerebellar fluid collection (not technically a cyst) is generally smaller than that seen in true DWM, but does communicate directly with the 4th ventricle, as in DWM. These conditions are rare, but are likely to be underdiagnosed and often misdiagnosed as “Dandy–Walker variant,” a term whose usage we and others do not advocate [2]. Another term often confused with CVH is “mega cisterna magna,” a term whose usage should be reserved for a large posterior fossa fluid collection in the presence of a normal cerebellum including vermis. The heterogeneity in these conditions is quite broad, reflecting the lack of knowledge of specific etiologies for CVH. In some cases, the cerebellar vermis is poorly formed or architecturally abnormal, and the appearance is more dysplastic than hypoplastic [4] (WBD, unpublished data). There may be associated abnormalities of the central nervous system, and less commonly, other organ systems.

X-linked CVH

Several families in which multiple males are affected with CVH appear to follow X-linked inheritance [75]. In one large 4-generation family, the males exhibited severe mental retardation, hypotonia with evolution to spasticity and contractures, choreoathetosis, seizures, and coarse facial features [76]. In another family, two sons demonstrated significant dysplasia of the cerebellar vermis, as did their more mildly affected mother, presumably a carrier for this condition (WBD, unpublished data). Recently, mutations of the oligophrenin-1 gene (*OPHN1*) at Xq12, previously associated with X-linked mental retardation, have been identified in affected

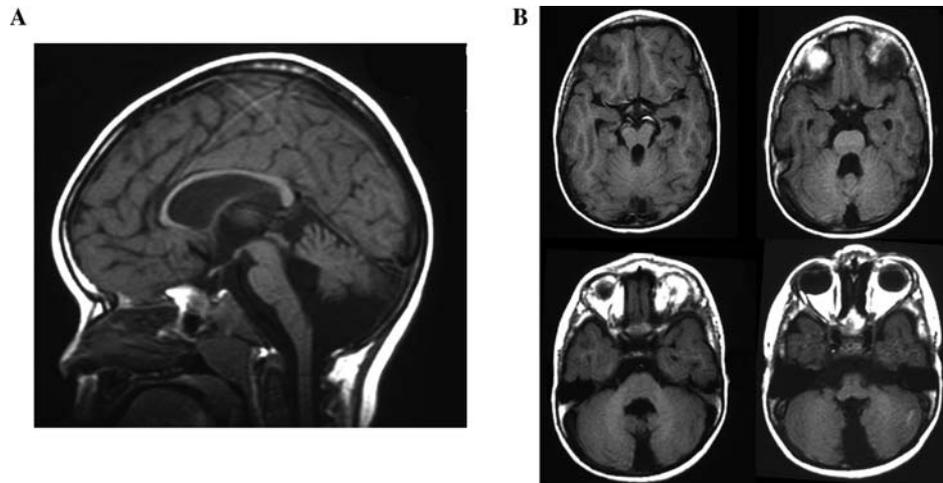


Fig. 5. Cerebellar vermis hypoplasia (CVH) in an almost 4-year-old subject with significant cognitive impairment. (A) Midsagittal view of brain with hypoplastic cerebellar vermis and increased retrocerebellar cerebrospinal fluid but normal placement of the torcula. (B) Serial axial T1 MR images from superior to inferior cuts through the posterior fossa. The 4th ventricle communicates with the posterior fossa fluid space. There is absence of the molar tooth sign. In the upper right panel, mild dysplasia of the cerebellar vermis is evident with diagonal rather than horizontal sulci. [LR02-019a2].

males from several families with mental retardation and cerebellar vermis hypoplasia [77]. In at least one family, affected males with an *OPHN1* mutation also exhibited undescended testes, scrotal hypoplasia, and micropenis [78]. Since the *OPHN1* gene is adjacent to the androgen receptor (*AR*) gene, and several 46,XY “females” with complete androgen insensitivity, CVH, and mental retardation have demonstrated a large deletion at Xq12 encompassing both genes, it is worthwhile to obtain a karyotype on all children with CVH and mental retardation [79]. Other X-linked genes associated with CVH are likely to exist as well, and several autosomal recessive forms have been proposed [2].

Other CVH syndromes

Several presumably different conditions that share the feature of CVH have been described, and the genetic basis for the majority of them is unknown. Many appear to be sporadic in inheritance, although recurrence in siblings has been described. One example of presumably autosomal recessive inheritance has been observed in male and female siblings with CVH and porencephaly (WBD, unpublished data); both had moderate to severe mental retardation. Some families with an autosomal recessive form of severe congenital microcephaly associated with a simplified gyral pattern and brainstem and cerebellar hypoplasia have a metabolic disorder characterized as 2-ketoglutaric aciduria [80].

A number of genetic syndromes with primarily vermis hypoplasia have been described [7]. Cogan syndrome is sporadic or familial oculomotor apraxia (delay in initiation of saccades), with motor delays and ataxia, associated with CVH [81]. Cerebellar vermis hypoplasia has also been described in autosomal recessive condi-

tions that include Marden–Walker and oto-palato-digital syndromes (reviewed in [21]). Cerebellar hypoplasia involving primarily the vermis has been associated with lissencephaly (LCH); at least 3 genes, including *LIS1*, *DCX/XLIS*, and *RELN* are responsible for the autosomal dominant, X-linked, and autosomal recessive forms, respectively, of LCH (reviewed in [17]). In these conditions, the malformation of the cerebral cortex is generally the most striking finding, but the cerebellar involvement serves as a reminder of the role of neuronal migration in the development of the cerebellum as well. The spectrum of anomalies associated with pan-cerebellar hypoplasia involving the hemispheres as well as vermis is outside the scope of this review, but has been described in other references [2,7].

Prognosis in CVH

Although the clinical heterogeneity in CVH is broad, in general, the prognosis for individuals with this and related conditions is often worse than for classic DWM in our experience, although the literature is conflicting in this regard. The majority of males with X-linked CVH have at least moderate mental retardation, and many also have seizures and spasticity [77]. Variable symptoms ranging from normal to mild mental retardation and early dementia have been described in carrier females, presumably related to the severity of the underlying mutation in *OPHN1* and degree of X-inactivation. For those children with CVH and more severe brain malformations such as lissencephaly or Walker–Warburg syndrome, the outcome is poor, and may not be compatible with long-term survival [17,59] (WBD, unpublished data). Ironically, the more dramatic appearance of the posterior fossa abnormality seen on the

MRI scans from children with classic DWM is often associated with a better cognitive outcome than those with the milder MRI changes of CVH. This is an important point, and conflicts with some current practice, especially regarding prenatal counseling (see below).

Prenatal diagnosis of DWM and CVH and their recurrence risks

The prenatal diagnosis of DWM is problematic for several reasons. First and foremost, prenatal imaging studies cannot reliably differentiate between true DWM and CVH, or between these and other mid-hindbrain malformations more generally. Although the cisterna magna can be visualized in approximately 95% of fetuses between 15 and 25 weeks gestation, determination of pathological significance can be difficult in cases where there is mild dilatation, or when the improper transducer angle through the posterior fossa gives the false appearance of an enlarged cisterna magna [5,82]. There are many examples of a prenatal diagnosis of DWM that has impacted prenatal and postnatal management of an affected fetus [83–86]. In one survey of 33 fetuses exhibiting an enlarged cisterna magna, 55% were found to have a chromosomal abnormality associated with a poor prognosis and were either electively terminated or died at birth or soon thereafter [5]. However, concerns have been raised that early diagnosis will lead to termination of pregnancies that may have had normal cognitive and motor development. In this same study, the fetuses with more dramatic ventricular enlargement were less likely to have a chromosomal abnormality and more likely to have classic DWM with a reasonably good prognosis, than those with milder posterior fossa abnormalities detected prenatally but associated with more severe outcomes [5].

Recurrence risks in DWM and CVH are variable and depend on the underlying etiology. For some chromosomal disorders, there may be risks to have a second affected child if a parent is a balanced translocation carrier. For those with a syndromic form of DWM or CVH associated with a known mode of inheritance, the Mendelian risks of having another affected child are applicable (e.g., 25% for a condition with autosomal recessive inheritance) [58]. For true DWM, however, the vast majority appears to be sporadic, with low recurrence risk. In a review of 98 siblings of children with DWM reported in the medical literature, Murray et al. [57] found only one familial recurrence of the condition, for an empiric risk of 1–5%. No imaging data were presented, so we cannot evaluate whether this represented true DWM or CVH according to our classification. In contrast, we have personally evaluated three families in whom several affected boys had CVH; using recurrence risks developed for true DWM could lead to inappropriate reassurance regarding the risk to future children.

Pontocerebellar hypoplasia (PCH)

Conditions described as pontocerebellar hypoplasia are more accurately termed pontocerebellar *atrophies* due to the appearance on serial brain imaging studies, which show progressive atrophy of the ventral pons and often the inferior olivary nuclei, cerebellar vermis, and hemispheres. Supratentorial atrophic changes include enlargement of the ventricles and extra-axial CSF spaces, widened cerebral sulci, and thinning of white matter and corpus callosum [87]. Clinically, they have prenatal onset of neurological abnormalities, and postnatal severe developmental delay, mental retardation, and often a seemingly neurodegenerative course [21]. In our personal experience, the progressive MRI changes are easier to document than actual clinical regression. In most subtypes, including all subtypes described below, the outcome is very poor. Surprisingly, we have seen a few children with a less severe course, including several sets of twins in which only one was affected [87].

Although the term “infantile olivopontocerebellar atrophy” has been applied to this group, this leads to confusion with the adult-onset spinocerebellar ataxia conditions [88]. Like CVH, the forms of PCH are individually very rare conditions, with less than 20 published cases [21,89]. However, given the autosomal recessive inheritance proposed for all forms described to date, these conditions have increased incidence among inbred populations due to presumed founder effects [90,91]. Although a uniform classification system for the PCH syndromes has not been established, at least 3 forms have been defined on clinical and pathologic features (WBD, unpublished data). Further refinement of this scheme awaits identification of causative genes.

PCH1 with spinal muscular atrophy

PCH1 is characterized by neonatal respiratory insufficiency, often with ventilator dependency and congenital contractures consistent with arthrogryposis. The clinical course is characterized by bulbar dysfunction, feeding and respiratory problems, and death generally within the first year of life [21]. MRI findings include hypoplastic brainstem and cerebellum (Figs. 6A and B). Degeneration of the anterior horn cells of the spinal cord resemble spinal muscular atrophy (SMA) histologically, and the muscle biopsy shows atrophy secondary to neurogenic changes [92,93]. In spite of the resemblance to SMA, linkage to the *SMN1* gene at 5q12 that causes classical SMA has been excluded, and no affected individuals have had mutations in *SMN1* [93].

PCH2 with dyskinesia

In PCH2, the neonatal presentation is of marked microcephaly and absence of normal swallow and

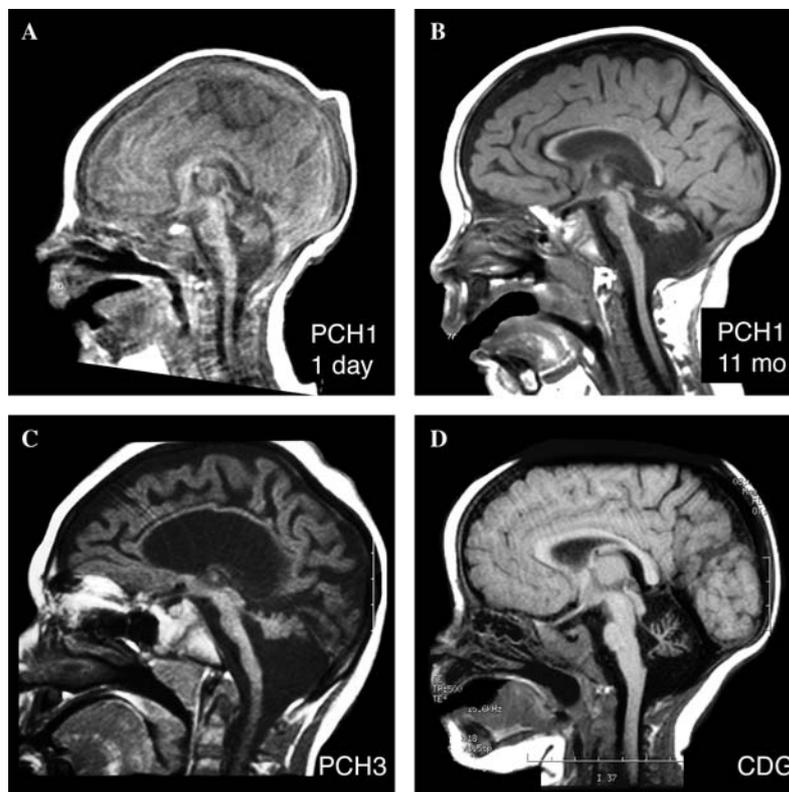


Fig. 6. Pontocerebellar hypoplasia (PCH) in PCH1, PCH3, and a congenital disorder of glycosylation. (A) Midsagittal view of a 1-day-old infant with PCH type 1 associated with symptoms of spinal muscular atrophy showing progression to more dramatic atrophy of pons and cerebellum by 11 months of age (B). [DR00-025] (C) Midsagittal view of the brain of a 3-year-old female with PCH type 3 showing atrophy of cerebellum and brainstem, especially the pons. Cerebral atrophy and thinning of the corpus callosum are present. This case has been published in [87]. [DP93-011a1] (D) Midsagittal view of 9-month-old female with a diagnosis of a type I congenital disorder of glycosylation and demonstration of PCH. [DR00-064].

feeding ability. The microcephaly is progressive, and generalized epilepsy with marked chorea has onset within the first few months of life that evolves into dystonia in later childhood [90]. Most affected children die within the first decade of life. Imaging reveals atrophy of ventral pons and cerebellar hemispheres and vermis with progressive subcortical atrophy [90]. Spinal anterior horn cells are normal, differentiating this condition from PCH1. There are several reports of less severe variants, and the suggestion of heterogeneity in PCH2. No genes have been mapped for this autosomal recessive condition.

PCH3 without dyskinesia

We are using “PCH3” to designate the condition reported in a consanguineous family from Oman with 3 affected children [91]. An Iranian family probably had the same disorder [87]. In infancy, these children exhibited hypotonia with head circumference in the low-normal range. They developed progressive microcephaly and limb spasticity with a generalized seizure disorder. They have severe mental retardation with inability to crawl, sit unsupported, or walk. One child is alive at age 12 years, and one sibling died at 6 years from a respi-

ratory illness. The children resemble PCH2 in their progressive microcephaly and MRI findings of atrophy of the cerebellum, brainstem, and cerebrum (Fig. 6C), but can be distinguished by the absence of extrapyramidal, choreiform movements, and presence of optic atrophy in at least one of the children [91]. This condition represents the first PCH locus to be mapped, with a multipoint lod score of 3.23 at 7q11-21 in this family [91].

Other syndromes

PCH has been described in other metabolic disorders that include infantile neuroaxonal dystrophy (Seitelberger disease) [94], mitochondrial defects, and PEHO syndrome (progressive encephalopathy with edema, hypsarrhythmia, and optic atrophy) (reviewed in [7]). One of the most important disorders in the differential diagnosis is the group of congenital disorders of glycosylation (CDG), previously known as carbohydrate-deficient glycoprotein syndromes (Fig. 6D). These autosomal recessive conditions are characterized by failure to thrive in infancy and later neurological impairment with hypotonia, ataxia, and peripheral neuropathy. Dysmorphic facial features, strabismus,

inverted nipples, and lipodystrophy with abnormal fat distribution are typical, although the manifestations are highly variable [95]. MRI changes are most often pontocerebellar atrophy, and later, cerebral atrophy. The diagnosis of type I CDG is established by isoelectric focusing of serum sialotransferrin, showing inadequate glycosylation of this secretory glycoprotein [96]. At least one form presents with predominantly gastrointestinal symptoms of a protein-losing enteropathy and liver fibrosis and may be amenable to dietary supplementation [97]. These conditions are inherited in an autosomal recessive manner, and the loci and genetic defects have been established for at least 4 subtypes. It has been recommended that all children with evidence of PCH be screened for type I CDG by transferrin isoelectric focusing [21].

Conclusions

We have provided an overview of some of the major categories of posterior fossa malformations, as well as their outcomes and genetic bases (summarized in Tables 1 and 2). Given the scope of this review, we have provided only a cursory discussion of the metabolic conditions often associated with hindbrain abnormalities and many of the brain malformation syndromes in which cerebellar involvement is only a part of the entire process, such as the cobblestone lissencephaly conditions and congenital muscular dystrophies. In focusing on the four entities of MTS-associated malformations, DWM, CVH, and PCH, we have attempted to provide an update on disorders in which clinical heterogeneity and inconsistent classification schemes have resulted in great confusion. The most crucial element for accurate diagnosis is the quality of MRI scans obtained, and serial imaging may be necessary to confirm the diagnosis in some cases, such as the PCH disorders. In contrast to many conditions in which the severity of MRI findings correlates with prognosis, this does not appear to be the case for classic DWM without cerebral involvement; a large posterior fossa cyst does not necessarily portend a severe cognitive deficit. In fact, among the conditions with enlarged posterior fossa fluid collections, classic DWM probably has the best outcome overall, with CVH and MTS-associated conditions in the moderate range of severity, and the progressive PCH conditions and some forms of CVH associated with severe impairment. It is notable that supposedly isolated posterior fossa anomalies have been identified in children with cognitive impairment, providing further evidence for the role of the cerebellum and perhaps other hindbrain structures in higher cortical function and language acquisition [2]. As the causative genes for these conditions are identified, and the understanding of the development of posterior

fossa structures is clarified, no doubt enhanced by observations in model organisms such as the mouse, we anticipate that the classification and clinical delineation of mid-hindbrain malformations will continue to evolve.

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