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Midbrain-Hindbrain Malformations: Advances in Clinical Diagnosis, Imaging, and Genetics

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Abstract

Historically, the midbrain and hindbrain (MBHB) have been considered “support staff” for the cerebrum, which has typically been acknowledged as the most important part of the brain. Radiologists and pathologists did not regularly examine these structures, also known as the brainstem and cerebellum, because they are small and difficult to remove without damage. With recent improvements in neuroimaging, neuropathology and neurogenetics, many developmental disorders of the MBHB have emerged as significant causes of neurodevelopmental dysfunction. This review provides an overview of MBHB disorders important to clinicians and developmental biologists. A basic understanding of MBHB embryology is essential to understanding the malformations that occur in MBHB structures; therefore, a brief embryology review is provided, as is a review of MBHB anatomy as assessed by MRI, and an approach to MRI analysis of the individual structures. Clinical features common to many MBHB disorders are presented, followed by a more in depth summary of the clinical presentations, MRI features and genetic causes of many common, and some less common, malformations. Research advances that may change how we treat these patients in the future are briefly discussed. The information provided in this review will improve the clinical acumen of the practicing neurologist in regard to malformations of the MBHB, while at the same time adding to their understanding of brainstem and cerebellar development, genetics, and function.

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Search Strategy: We searched all PubMed records through December 2012 with keywords for MBHB malformation anatomic features (cerebellar hypoplasia, cerebellar dysplasia, pontocerebellar hypoplasia, brainstem dysgenesis, molar tooth sign, rhombencephalosynapsis, pontine tegmental cap dysplasia), syndromes (PHACE, PHACES, Gómez-López-Hernández, Chudley-McCullough, Joubert, Walker-Warburg, Duane retraction, Duane radial ray, Athabaskan brainstem dysgenesis, Bosley-Salih-Alorainy, Moebius), disorders (Dandy-Walker, congenital disorders of glycosylation, dystroglycanopathy, Muscle-eye-brain disease, Fukuyama muscular dystrophy, Horizontal Gaze Palsy and Progressive Scoliosis) and selected genes (*RELN*, *VLDLR*, *TSEN**, *PTF1A*, *CASK*, *CHMP1A*, tubulins, *OPHN1*). Due to the breadth of this review, we did not perform comprehensive literature searches, and selected articles that made substantial contributions to the clinical description (including natural history), identified genetic causes, and/or described treatment. We apologize for not being able to cite all publications relating to MBHB malformations due to space constraints.

Additional resources: GeneReviews <http://www.ncbi.nlm.nih.gov/sites/GeneTests/review?db=GeneTests>
Online Mendelian Inheritance in Man www.omim.org

Introduction

Recent advances in genetic and neuroimaging technology have promoted enormous progress in the understanding of midbrain and hindbrain (MBHB) malformations.¹ Combining modern imaging with cutting edge genetic techniques has provided heretofore unimaginable clarity to the wide spectrum of developmental disorders affecting the MBHB. While many of these disorders result from inherited mutations, a number are caused by mutations that occur *de novo* in the affected individual, and are therefore not inherited. Great strides have also been made in understanding the mechanisms underlying normal and abnormal MBHB development using animal models such as mouse, chicken and zebrafish. These combined advances are poised to yield better diagnostic testing, and hopefully, more specific and effective treatments in the future.

The MBHB develops abnormally in many disorders, so this review focuses on congenital conditions in which the MBHB is predominantly affected and where progress has been made in the diagnosis and/or genetics. We omit MBHB disorders due to *in utero* insults, forebrain disorders secondarily affecting the MBHB, progressive disorders with onset after birth, and neural tube defects. In addition, later onset and acquired disorders that result in cerebellar atrophy have been reviewed elsewhere^{2,3} and are not covered. For comprehensive classification of MBHB malformations, see Barkovich et al. 2007⁴ and Barkovich et al. 2009.⁵

This review begins with a summary of basic MBHB embryology and developmental genetics that provides a framework for descriptions of the clinical features and causes of human MBHB malformations. A neuroimaging approach to the MBHB is then suggested to aid in the detection of subtle abnormalities. Finally, the clinico-radiologic features of a series of conceptually and clinically important MBHB malformations are described.

Basic embryology of the MBHB

After neural tube formation and segmentation into brain regions (fore-, mid- and hind-brain) and spinal cord, neurons of the MBHB are mostly generated in the neuroepithelium that lines the walls of the 4th ventricle (Fig 1). In the developing midbrain, neurons are generated from the ventricular zone and primarily migrate radially to form the tectum dorsally, and substantia nigra, red nuclei and cranial motor nerves 3 and 4, ventrally.

The cerebellum arises from the dorsal anterior hindbrain (rhombomere 1), and most neurons are generated in two distinct germinal matrices: 1) the dorsal- and rostral-most portion of the rhombic lip, which generates neuronal precursors that develop into glutamatergic neurons (cerebellar granule neurons and others), and 2) the adjacent dorsal ventricular zone, which generates cerebellar GABAergic neurons (Purkinje cells (PCs) and others). Although *ATOHI* (formerly called *MATH1*) and *PTF1A* are critical for defining these germinal zones, most genes required for cerebellar development remain to be identified.^{6,7} After generation in the rhombic lip, granule cells migrate tangentially to form a transient external granular layer (EGL) on the outside of the developing cerebellar hemisphere.⁸ The EGL is a secondary germinal zone, as immature granule cells undergo many cycles of mitosis (under the influence of sonic hedgehog, a mitogen secreted by underlying developing PCs), while

migrating over the enlarging cerebellum. As EGL progenitors differentiate into granule neurons, they migrate inwards to form the internal granular layer (IGL) located under the developing PCs. In humans, this process continues into the second postnatal year. Concurrently, GABAergic PCs are generated in the ventricular zone and migrate along radial glial processes into the cerebellar anlage, where they form an array of PC clusters under the EGL.⁹ Reelin, secreted by the EGL, binds to receptors on the PC processes, reducing PC-PC adhesion and allowing the cell clusters to string out into long parasagittal stripes, which form the skeleton of the mature cerebellum.¹⁰⁻¹²

In the posterior hindbrain, the lower rhombic lip is a germinal zone distinct from the upper rhombic lip. It does not contribute to the cerebellum, instead producing the neurons that migrate to form the precerebellar nuclei (pontine, pontine reticulotegmental nuclei, inferior olivary nuclei, external cuneate, and lateral reticular), all of which are directly connected to the cerebellum at an early developmental stage and maintain connections as the structures grow and mature.¹³ Development of the upper and lower rhombic lips is regulated by overlapping sets of genes, disruption of which can cause both cerebellar and brainstem defects, reinforcing the developmental interdependence of these structures.

Clinical features of MBHB malformations

Little population-based data on the prevalence of MBHB malformations exists, due to the uncommonness of these disorders and substantial under-recognition on brain imaging studies. The postnatal prevalence of Dandy-Walker malformation has been estimated to be $\sim 1/30,000$ ¹⁴ and $1/5,000$ ¹⁵. A prenatal prevalence of $\sim 1/10,000$ was estimated from a large birth defects registry in the United Kingdom.¹⁶

Clinical classification of MBHB disorders is important to provide accurate prognostic and recurrence risk information, as well as guide further evaluation and medical management. In addition, a clinical diagnosis can lead to identification of a genetic cause that can then be used for prenatal diagnosis and carrier testing. The utility of a given diagnostic category rests on whether it can be used to predict outcome, response to treatment and/or underlying cause. Given the overlapping clinical and imaging features of MBHB malformations, correct classification requires a holistic approach that integrates history, physical examination, imaging and laboratory testing.

Due to the widespread use of prenatal ultrasound and MRI to evaluate the fetal brain, MBHB malformations are frequently diagnosed before birth, although the sensitivity and specificity of prenatal imaging for MBHB malformations are unknown.¹⁷⁻²⁰ Prenatal ultrasound can identify cerebellar hypoplasia, abnormal fluid collections in the posterior fossa or poor delineation of posterior fossa landmarks. Further evaluation during the pregnancy can involve fetal MRI, genetic amniocentesis, cell free fetal DNA testing and evaluation for in utero infection. If work-up during the pregnancy does not identify a specific etiology, postnatal examination, imaging and laboratory testing are often revealing.

Postnatal presentation of patients with MBHB malformations is typically non-specific; features include hypotonia, motor delay, nystagmus, and decreased visual attention (Table 1). More severely affected patients can present with apnea, feeding difficulties, aspiration,

spasticity, lack of developmental progress or seizures. Signs of cranial neuropathy, such as abnormal eye movements, ptosis, facial palsy, hearing impairment (with consequent speech delay) and facial/corneal anesthesia, may also be observed. Ophthalmologic evaluation may reveal chorioretinal coloboma or retinal dystrophy in a subset of patients with Joubert syndrome (JS), a variety of structural eye abnormalities in patients with cobblestone malformations, or eye movement abnormalities. Cognitive impairment is common, but not universal, and autistic features are also observed.²¹ The range of neurodevelopmental outcome is broad. Mildly affected patients may have relatively isolated cranial nerve dysfunction, as in Duane retraction syndrome and horizontal gaze palsy with progressive scoliosis.

While these common features related to cerebellar and brainstem dysfunction help identify patients with MBHB malformations and prompt brain imaging, idiosyncratic features can help differentiate between specific diagnoses (Table 2 and sections below). For instance, alternating tachypnea/apnea, polydactyly, coloboma, and/or progressive retinal, kidney or liver disease can be seen in some, but not all, patients with JS. Most patients with rhombencephalosynapsis have persistent head-shaking, often in a figure-of-eight pattern; others have scalp alopecia, trigeminal anesthesia and hyperactivity. Extreme prematurity or intrauterine infection can point to a non-genetic cause; however, these are usually diagnoses of exclusion. Laboratory evaluation can also help differentiate patients: elevated creatine kinase in patients with cobblestone malformations, abnormal transferrin glycosylation in CDGS, elevated glucose and absent insulin in patients with *PTF1A*-related cerebellar and pancreatic agenesis.

Imaging Approach to MBHB malformations

Many physicians are comfortable with looking at images of the cerebral hemispheres and have worked out an approach to analyzing CT and MRI scans that allows them to detect significant abnormalities without missing any important features. The MBHB has always been more difficult to image than supratentorial structures, requiring a modified approach to evaluating the images. The MBHB is composed of the brainstem and the cerebellum. The brainstem is composed of the midbrain, derived from the embryonic mesencephalon, the pons, formed from the rostral part of the rhombencephalon (the metencephalon), and the medulla, formed from the caudal part of the rhombencephalon (myelencephalon). The cerebellum, which is a dorsal extension of the rostral rhombencephalon, is composed of the medial/midline vermis and the bilateral hemispheres. It is best to start by looking at the midline sagittal image (Fig 2A), which allows an overall estimate of the size of the posterior fossa in addition to detailed views of the brainstem, the fourth ventricle and the cerebellar vermis. The posterior margin of the brainstem from the distal aqueduct to the obex should be nearly straight. The fastigium of the fourth ventricle should be just below the mid-point of the ventral pons. As an approximation, the cranio-caudal size (height) of the vermis on this image should be equal to the distance from the intercollicular sulcus of the midbrain tectum to the obex. The vermis is divided into three sections by the primary and prepymidal fissures (Fig 2A, arrows). These sections are approximately equal in size, with the anterior vermis (the portion anterior to the primary fissure) being largest and the middle section typically the smallest. The rostrocaudal length of the ventral pons at its largest point should

be approximately double the size of the midbrain from the anteromedial most point of the midbrain on this image to the third ventricle; the latter is equal to the distance from the anterior-posterior level of the obex to the inferior margin of the ventral pons. The cerebellar hemispheres are characterized on coronal images by fissures that radiate towards the cerebellar nuclei; this is best seen on images at the level of the vermician nodulus (Fig 2B). The cerebellar peduncles should be evaluated for size, contour, and location (Fig 2C-D). On axial images, the hemispheric folia of the inferior half of the cerebellum are seen to course parallel to the calvarium (Fig 2D).

Specific Malformations

Predominantly Cerebellar Malformations

Cerebellar hypoplasia has many causes including chromosomal disorders, specific genetic syndromes, and prenatal disruptions. The vermis and both hemispheres may be equally small or may be hypoplastic in any combination. Pontine hypoplasia and midbrain malformation are typically, but not invariably, associated.

Dandy-Walker Malformation—Perhaps the most common MBHB malformation is Dandy-Walker malformation (DWM MIM 220200). Although variably defined in the literature since the term was first coined by Benda in 1954,²² this heterogeneous disorder is defined by a hypoplastic (and commonly counterclockwise rotated) vermis, an enlarged fourth ventricle, and an enlarged posterior fossa with an elevated torcular (Fig 3B). Typically, the cerebellar hemispheres are less affected than the vermis, and the brainstem is normal to moderately hypoplastic. Subsets of patients have other brain findings such as agenesis of the corpus callosum and hydrocephalus. DWM can be isolated, part of a defined syndrome or associated with extra-CNS malformations that do not fit with a known condition (summarized in Poretti et al. 2012).²³ Detailed evaluation of brain imaging is important to 1) distinguish DWM from more benign entities such as persistent Blake pouch cyst, in which a normal vermis is rotated counterclockwise by the cyst, and 2) identify mass-effect that might result in obstructive hydrocephalus. Midsagittal thin slices (0.5 mm) using high-resolution steady state MRI sequences (CISS, FIESTA) best demonstrate the level of obstructed CSF flow, if present; axial or coronal images can demonstrate the abnormal membranes of arachnoid cysts (although most cysts cause no clinically significant abnormality).

Developmental outcome spans a wide range, with additional malformations and/or cerebellar vermis dysplasia likely to be associated with more severe impairment.²⁴ A substantial subset of patients requires shunting for hydrocephalus, and a smaller subset has seizures. Empirically, the recurrence risk is low.²⁵ Although few genetic causes have been identified, one cause, loss of *FOXC1* function, has led to the hypothesis that cerebellar and posterior skull development are linked through inductive interactions between the mesenchyme and rhombic lip.²⁶

Lissencephaly and cerebellar hypoplasia—Cerebellar hypoplasia may be found in patients with cerebral malformations in the lissencephaly spectrum, caused by defects in the RELN pathway or microtubule function. The RELN pathway is incompletely understood

and it is likely that some, perhaps many, patients with cerebellar hypoplasia have defects in this pathway. Reported patients with *RELN* mutations have pachygyria and minimal foliation of a very hypoplastic cerebellum, vermis worse than hemispheres (Fig 3C and 4A).²⁷⁻³⁰ Profound developmental disability, microcephaly, sloping forehead, seizures, and congenital lymphedema have also been reported in these patients. In contrast, patients with mutations in *VLDLR* have a simplified, mildly pachygyric cerebral cortex and milder cerebellar hypoplasia with some degree of cerebellar foliation.^{31, 32} *RELN* signaling, via the *VLDLR* and *APOER2* receptors and *DAB1* effector, is important for dispersion of Purkinje cells from their clumped configuration during early cerebellar formation.¹²

The “tubulinopathies” are caused by mutations in genes involved in microtubule formation and function. The spectrum of phenotypes associated with mutations in *TUBA1A*, *TUBA8*, *TUBB2B*, *TUBB3* and *TUBB5* ranges from isolated congenital fibrosis of the extraocular muscles to severe intellectual disability, quadriplegic cerebral palsy, seizures, cranial neuropathies and hydrocephalus.³³⁻³⁸ Imaging features include cortical dysgenesis (lissencephaly or polymicrogyria), malformation of cranial nerves and basal ganglia, often with cerebellar and pontine hypoplasia, as well as defects in the corpus callosum, anterior commissure and internal capsule (Fig 3D). Dysmorphic features are infrequently reported,³⁹ and remarkably, other organ systems are not affected. While most occurrences are sporadic and due to *de novo* mutations, recurrences have been reported due to germline mosaicism and autosomal recessive inheritance.³⁶

Other cerebellar hypoplasias—While the cause of cerebellar hypoplasia remains unknown in many patients, a number of other rare cerebellar hypoplasia disorders deserve mention. Cerebellar hypoplasia, ventriculomegaly, intellectual disability, seizures and mildly dysmorphic facial features are characteristic in males and occasional females with mutations in the X-linked *OPHN1* gene.⁴⁰⁻⁴² *OPHN1* is a Rho GTPase-activating protein involved in clathrin-mediated endocytosis and dendritic spine formation; however, its role in cerebellar development is unknown. **PHACE** syndrome is characterized by Posterior fossa brain malformations, Hemangioma of the head and/or neck, Arterial lesions of the head and/or neck, Cardiac defects including aortic coarctation, and Eye abnormalities.^{43, 44} Unilateral cerebellar hypoplasia, ipsilateral to the hemangioma, and cerebrovascular lesions are the most common brain imaging findings with occasional cerebellar vermis and supratentorial malformations (corpus callosum dysgenesis, polymicrogyria, and heterotopia).^{45, 46} Given the lack of recurrences and typically unilateral involvement, **PHACE** syndrome is likely to be caused by *de novo* somatic mutations, similar to Proteus, Megalencephaly-Capillary Malformation-Polymicrogyria (MCAP) and Megalencephaly-Polydactyly-Polymicrogyria-Hydrocephalus (MPPH) syndromes.⁴⁷⁻⁵⁰

Rhombencephalosynapsis—Rhombencephalosynapsis (RES) consists of partial or complete absence of the cerebellar vermis with continuity of the hemispheres across the midline (Fig 4C), thought to be due to aberrant dorsal-ventral patterning.⁵¹⁻⁵³ The severity of RES on imaging correlates with clinical outcome.⁵⁴ When severe, the fused cerebellar nuclei arch in a horseshoe shape across the midline, with a narrow fourth ventricle; the primary and prepyramidal fissures of the vermis cannot be identified (Fig 3E). Directionally

encoded FA maps (from DTI data) showed absent transverse fibers of the vermis; instead, a bundle of fibers runs rostrocaudally in the midline of the fused cerebellar hemispheres and the superior cerebellar peduncles fail to decussate.⁵⁵ RES is often associated with midbrain abnormalities (aqueductal stenosis and midline fusion of the colliculi), and supratentorial abnormalities such as absent septum pellucidum and corpus callosum dysmorphisms.

In addition the typical clinical features of MBHB disorders, patients with RES display persistent headshaking behavior, high activity level and impulsiveness. Affected patients can be divided into at least three recognizable categories: 1) Gómez-López-Hernández syndrome (MIM 601853) combining RES with scalp alopecia and trigeminal anesthesia, 2) RES plus features of VACTERL association (Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal defects and Limb defects), and 3) RES with atypical holoprosencephaly, most severely affecting the occipital lobes.^{54, 56} Developmental outcomes vary widely; patients with isolated RES can function independently in adulthood, while patients with VACTERL features or HPE are more likely to manifest significant impairments. No genetic defects have been linked to RES and no animal models recapitulate the phenotype, so the mechanism remains unknown.

Cerebellar hyperplasia—Cerebellar hyperplasia (macrocerbellum) is a rare imaging finding that can be seen in isolation, or in a variety of disorders including chromosomal abnormalities, Alexander disease and fucosidosis, as well as Sotos, Williams, Costello, MCAP/MPPH syndromes (reviewed in Poretti et al., 2012).⁵⁷ While the developmental mechanisms underlying cerebellar hyperplasia in most of these disorders remains unknown, substantial progress has been made in the understanding of brain overgrowth in MCAP/MPPH. MCAP/MPPH are typically diagnosed due to supratentorial overgrowth and polymicrogyria.⁵⁸ Although cerebellar size is normal at birth, many patients develop macrocerbellum with normal posterior fossa size, resulting in cerebellar ectopia/Chiari I malformation and associated symptoms (posterior headache, dysphagia, stridor) and hydrocephalus. Other features include seizures, capillary malformations, macrocephaly, and polydactyly. Most patients have pathway activating *de novo* mutations in components of the PI3K-AKT-mTOR pathway that result in increased cell growth.⁴⁸⁻⁵⁰ Mutations affecting this pathway are found in a variety of cancers, opening the possibility of using drugs in development for cancer treatment to try to reduce brain overgrowth and neurological issues in patients with MCAP/MPPH.^{59, 60}

Cerebellar dysplasia—Any part of the cerebellum can be dysplastic, from small focal portions of a single hemisphere to abnormal foliation of the entire cerebellum.⁶¹ Very often, such as in JS and cobblestone malformations, hypoplastic cerebella are also dysmorphic. Outside of these well-recognized conditions, little is known about the causes of cerebellar cortical dysgenesis. One exception is Chudley-McCullough syndrome (CMS – MIM 604213), in which patients have striking disorganization of the inferior cerebellar hemisphere folia (Fig 4D). Clinically, these patients present with severe sensorineural hearing loss and mild delays, but are not usually dysmorphic and do not have other malformations.⁶² Brain imaging reveals additional abnormalities including frontal polymicrogyria with subcortical heterotopia, corpus callosum hypogenesis and arachnoid

cysts. All patients to date have biallelic truncating mutations in the *GPSM2* gene that encodes a GTPase regulator required for correct orientation of stem cell divisions in multiple tissues.⁶³ It is likely that aberrant cell division underlies the cerebellar dysplasia, but the mechanism remains unknown.

Cerebellar and Brainstem malformations

Pontocerebellar hypoplasia (PCH)—PCH occurs in a number of disorders that can be distinguished, in part, by imaging findings and associated features (Fig 3F-J). At least 6 clinical types of PCH were described before genetic causes were identified. PCH type 1 (MIM 607596 and 614678), associated with mutations in *EXOSC3*⁶⁴ and *VRKI*⁶⁵, is characterized by moderate PCH on imaging in combination with spinal muscular atrophy, resulting in substantial global weakness and decreased or absent reflexes. PCH types 2 (MIM 277470, 612389 and 612390), 4 (MIM 225753) and 5 are now known to be caused predominantly by mutations in genes that encode tRNA splicing endonucleases (*TSEN54*, *TSEN34* and *TSEN2*).⁶⁶⁻⁶⁸ Patients with PCH type 2 represent the less severe end of the spectrum with early hyperreflexia, developmental delay, and feeding problems, eventually developing spasticity and involuntary movements in childhood, while patients with PCH type 4 represent the severe end of the spectrum characterized by polyhydramnios, severe hyperreflexia, contractures and early death due to central respiratory failure. Microcephaly is present at birth in patients with PCH4, while microcephaly develops over time in PCH2. Seizures are common in both groups. A typical feature of TSEN-related PCH is more severe involvement of the cerebellar hemispheres compared to the vermis (Fig 4E).⁶⁹ Described in only one report, PCH type 3 (MIM 608027) is associated with optic atrophy and the genetic cause is unknown.⁷⁰ PCH type 6 (MIM 611523) is associated with elevated CSF lactate and caused by mutations in the *RARS2* gene.⁷¹

Other disorders can mimic the TSEN-related PCHs. Patients with *PTF1A*-related cerebellar hypoplasia present with diabetes in infancy due to agenesis of the pancreas (Fig 3G).⁷² While quite rare, this disorder highlights the essential role for PTF1A in the development of ventricular zone-derived precursors. The severe end of the spectrum of *CASK*-related disease also presents with progressive microcephaly and PCH that proportionately affects the vermis and hemispheres (Fig 3H).^{73, 74} Patients may also display dysmorphic features of the nose, eyes, and ears. The *CASK* gene is on the X chromosome, so *CASK*-related PCH is more common in females, presumably due to lethality in males. Most recently, recessive loss of function mutations in *CHMP1A* have been shown to cause severe PCH with proportionate involvement of the cerebellar vermis and hemispheres and preserved foliation pattern.⁷⁵ Described patients had moderate to severe developmental delay, acquired microcephaly, increased extremity tone and contractures. *CHMP1A* appears facilitate the repression of *CDKN2A* expression by the transcriptional repressor *BMI1*, resulting in decreased proliferation and stem cell renewal.

Pontine Tegmental Cap Dysplasia (PTCD, MIM 614688) is characterized by multiple cranial neuropathies, particularly hearing loss, trigeminal anesthesia, facial paralysis and swallowing dysfunction.^{76, 77} PTCD can be distinguished from other PCHs by the characteristic “cap” of tissue on the dorsal pons and severe hypoplasia of the inferior and

middle cerebellar peduncles (Fig 3I). Congenital heart, kidney, vertebral and rib defects are present in subsets of patients. Developmental disability is typically severe, and the degree of impairment may correlate with the severity of brainstem dysplasia, with mildly affected patients having a rounded bump (“cap”) and those more severely affected having a more angular brainstem kink (“beak”).⁷⁷⁻⁷⁹ Neither familial recurrence nor genetic causes have been reported.

Hypoplasia of the pons and cerebellum with progressive volume loss is characteristic of Congenital Disorders of Glycosylation Type 1a (CDGS, MIM 212065, Fig 3J).⁸⁰ Patients present with hypotonia and developmental delay, but can also display a striking variety of other features including abnormal fat distribution, coagulopathy, retinal degeneration, peripheral neuropathy, stroke-like episodes, and seizures. The range of developmental outcome is broad. CDG Type 1a is autosomal recessive, caused by biallelic mutations in the *PMM2* gene, required for N-glycosylation of proteins.⁸¹ The identity and role of N-glycosylated proteins during hindbrain development remain under investigation.

Many causes of PCH remain undefined, although atypical presentations of disorders such as *VLDLR*-related disequilibrium syndrome⁸² or pre- and post-natal insults (most commonly complications of extreme prematurity) may explain additional subsets of patients.⁸³

Joubert syndrome/Molar Tooth Malformation—In patients with neonatal hypotonia, abnormal eye movements and alternating apnea and tachypnea, JS should be considered. Polydactyly is present in a minority of patients and subsets of patients also develop retinal dystrophy, nephronophthisis and liver fibrosis. Brain MRI is usually diagnostic, revealing cerebellar vermis hypoplasia/dysplasia, long, thick, elevated superior cerebellar peduncles (SCPs), and a thin MBHB junction with a deep interpeduncular fossa resulting in the “molar tooth sign” on axial MRI (Fig 3K and 4G). Other brain malformations can be present, including polymicrogyria, brainstem and cortical heterotopia, agenesis of the corpus callosum and/or cephalocele.⁸⁴ DTI can be used to generate color FA maps and tractography, showing laterally displaced and dysmorphic deep cerebellar nuclei, hypoplastic medial lemnisci, and absent transverse fibers in the central vermis and deficient SCP decussation.⁸⁵

Diagnosing JS is important, since it is recessive and carries a 25% recurrence risk. In addition, close monitoring for the progressive retinal, kidney and liver disease is required to reduce complications. Mutations in 20 genes can cause JS and related disorders.⁸⁶ The gene products function in the primary cilium, the cellular antenna that mediates a variety of signaling processes, making these disorders part of an expanding group of disorders called “ciliopathies.”^{87, 88} The brain malformations may result from defects in midline fusion of the developing vermis⁸⁹ or defects in sonic hedgehog-mediated granule cell proliferation.^{90, 91}

Cobblestone malformations—Cobblestone malformations comprise a broad spectrum of clinically and genetically overlapping disorders resulting from defects in the pial limiting membrane and the attachment of radial glial fibers thereto.⁹²⁻⁹⁸ The Walker-Warburg phenotype represents the severe end of the spectrum with profoundly small and dysmorphic

cerebellar hemispheres often with cysts, absent vermis and very small brainstem, as well as other major brain malformations: cerebral cobblestone cortex, abnormal white matter, anomalous corpus callosum, enlarged dysplastic tectum, and hypoplastic/dysplastic brainstem (Fig 3L and 4H). The cerebellar cortical and subcortical cysts represent small areas of pia/subarachnoid space herniating inward through gaps in the pial limiting membrane. Patients frequently have hydrocephalus, eye abnormalities (microphthalmia, optic nerve hypoplasia, chorioretinal coloboma, cataract, glaucoma and/or high myopia), seizures, hypotonia and/or muscular dystrophy (creatine kinase levels 2-15X normal). The muscle-eye-brain phenotype represents more moderately affected patients with milder cerebellar and brainstem hypoplasia, and Fukuyama muscular dystrophy represents the mild end of the spectrum that still includes brain malformation. Recessive mutations in multiple genes (*POMT1* MIM 607423, *POMT2* MIM 607439, *POMGNT1* MIM 606822, *FKTN* MIM 607440, *FKRP* MIM 606596, *LARGE* MIM 603590, *ISPD* MIM 614631, and *GTDC2* MIM 614830) can cause overlapping phenotypes across the entire spectrum of disease, but a substantial proportion of patients remain unexplained.

Predominantly Brainstem Malformations

Congenital Cranial Dysinnervation Disorders—The term Congenital Cranial Dysinnervation Disorders was coined in 2002 to refer to abnormalities of cranial nerve development that result in abnormal movement of the face and eyes,⁹⁹ most of which do not have obvious brainstem abnormalities on clinical imaging studies. The exception is Horizontal Gaze Palsy with Progressive Scoliosis (HGPPS MIM 617313), an autosomal recessive disorder associated with a “butterfly shaped pons and medulla” (Fig 4I).¹⁰⁰ Patients typically present with progressive scoliosis during early childhood and congenital eye movement abnormalities and defects in midline axon crossing demonstrated by somatosensory and motor evoked potentials. HGPPS is due to biallelic mutations in *ROBO3* which encodes a receptor required for axon guidance.¹⁰¹

Although not apparent on clinical MRI, Athabaskan brainstem dysgenesis¹⁰² and Bosley-Salih-Alorainy syndromes (MIM 601536)¹⁰³ represent brainstem patterning disorders due to *HOXA1* loss of function in individuals of Athabaskan and Saudi descent respectively.¹⁰³ In mouse models, *HOXA1* is required for correct specification of rhombomeres 4 and 5 in the developing hindbrain,^{104, 105} as well as inner ear^{16, 17} and heart¹⁰⁶ development, so it is not surprising that patients have cranial nerve palsies, sensorineural hearing loss, abnormal intracranial blood vessels and cardiac outflow tract defects. Similarly, a number of other cranial dysinnervation disorders have facilitated the identification of genes required for cranial nerve formation/survival and axon guidance such as *CHN1*-related Duane retraction syndrome (MIM 604356)¹⁰⁷, *SALL4*-related Duane radial ray syndrome (MIM 607323),¹⁰⁸ and Congenital Fibrosis of the Extraocular Muscles Types 1-3 (MIM 135700, 602078, 600638, 609384) due to mutations in *KIF21A*, *PHOX2A*, *TUBB3* and *TUBB2B*.^{35, 109-111} Finally, the term Moebius syndrome (MIM 157900) is used to describe patients with cranial nerve dysfunction, most commonly facial palsy with impaired ocular abduction; however, the term is used quite variably, limiting its utility for guiding work-up, providing prognostic information, predicting recurrence risk or directing treatment and identifying the underlying cause(s).

Evaluation of patients with cranial nerve disorders should include 3-dimensional, heavily T2-weighted, steady state (CISS, FIESTA) MRI sequences that are able to visualize cranial nerves as they course through the cisterns at the skull base. In addition, high resolution diffusion tensor imaging of the brainstem holds some promise for further delineating axonal pathfinding disorders of the brainstem in the absence of obvious structural defects.

Predominantly Midbrain Malformations

Relatively few disorders that predominantly affect the midbrain have been described. Zaki et al. (2012) recently reported similar midbrain dysplasia in several consanguineous Egyptian families.¹¹² On imaging, the patients had rostral-caudal shortening and dorsal-ventral lengthening of the midbrain, with a deep interpeduncular cistern. In two patients, the corticospinal tracks were not detectable at the level of the pons by diffusion tensor imaging. Variable features included cortical calcifications, agenesis of the corpus callosum, ventriculomegaly, brainstem dysplasia and cerebellar vermis hypoplasia. Clinically, the patients had progressive microcephaly, spasticity, intellectual disability and seizures. Inheritance appeared to be autosomal recessive, but the genetic cause(s) remain unknown. Although the midbrain is abnormal in a number of other disorders, further delineation of midbrain malformations is required.³

Conclusions

Despite developments in genetics and neuroimaging that have facilitated the diagnosis of malformations of the MBHB in fetuses and children, these disorders remain underdiagnosed and poorly understood because of historical difficulties in assessing these areas of the brain. It is hoped that the information contained in this review in regard to the range of these disorders, the methodological clinical and radiologic approaches, the characteristic clinical and imaging findings that aid in their initial diagnoses, and the genetic studies that confirm the diagnoses will help neurologists and radiologists in this regard. Increased cognizance of these disorders among physicians, along with careful analyses of clinical and imaging studies, will raise the general awareness of them in the medical community.

Defining MBHB malformations and identifying their causes provides direct benefits to patients and their families: 1) diagnostic, carrier and prenatal testing; 2) more accurate prognostic and recurrence risk information; 3) avoidance of additional, unnecessary diagnostic testing; 4) early diagnosis of associated complications through medical monitoring; 5) reduction in stress caused by diagnostic uncertainty; 6) relief of parental guilt and anxiety for causing their child's disability. Defining the molecular pathways underlying normal and abnormal human MBHB development (Fig 1) is the first step toward developing specific therapies, although it will likely be many years before they are available to our patients. It is uncertain whether early developmental brain anomalies can be corrected, but many gene products required for brain development are later required for ongoing brain function, so intervention targeting the affected pathways may be possible. For example, loss of function in the genes associated with JS disrupts protein localization to the primary cilium¹¹³ where several neurotransmitter receptors are normally localized,^{114, 115} likely contributing to the intellectual disability, behavior problems and mental health issues

experienced by these patients. In the future, pharmacological treatments may be able to address ongoing brain dysfunction caused by ciliary receptor mislocalization.

Beyond direct benefits to patients with MBHB malformations, understanding these disorders may inform other areas of human health and disease. Developing treatments for neurological dysfunction caused by trauma, infection, and neurodegenerative conditions depends on a solid understanding of MBHB development and function in humans. Similarly, successful treatment of oculomotor, vestibular, and respiratory control dysfunction will benefit from basic knowledge about how these neurological systems develop in humans. In addition to functions typically assigned to the MBHB, mounting evidence indicates that the MBHB plays a role in autism spectrum, mental health and cognitive disorders.¹¹⁰⁻¹¹² Although recent progress in understanding normal and abnormal human MBHB development has been remarkable, further advances in brain imaging, genetics and animal modeling foretell continued progress in the future.

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Abbreviations

ACC	Agenesis of the Corpus Callosum
AD	Autosomal Dominant
AR	Autosomal Recessive
CDGS	Congenital Disorders of Glycosylation
CMS	Chudley-McCullough Syndrome
DTI	Diffusion Tensor Imaging
DWM	Dandy-Walker Malformation
EGL	External Granule cell Layer
IGL	Internal Granule cell Layer
GLH	Gómez-López-Hernández syndrome
HGPPS	Horizontal Gaze Palsy and Progressive Scoliosis
ICP	Inferior Cerebellar Peduncle
MCAP	Megalencephaly-Capillary Malformation-Polymicrogyria
MCP	Middle Cerebellar Peduncle
MPPH	Megalencephaly-Polydactyly-Polymicrogyria-Hydrocephalus
NDV	NeuroDeVeopmental
OCCS	Oculocerebrocutaneous syndrome
PC	Purkinje Cell

PCH	PontoCerebellar Hypoplasia
PHACE	Posterior fossa brain malformations, Hemangioma, Arterial lesions, Cardiac defects, and Eye abnormalities
PMG	PolyMicroGyria
PTCD	Pontine Tegmental Cap Dysplasia
RES	RhombEncephaloSynapsis
SCP	Superior Cerebellar Peduncle
VACTERL	Vertebral defects, Anal atresia, Cardiac defects, Tracheo-Esophageal fistula, Renal defects and Limb defects

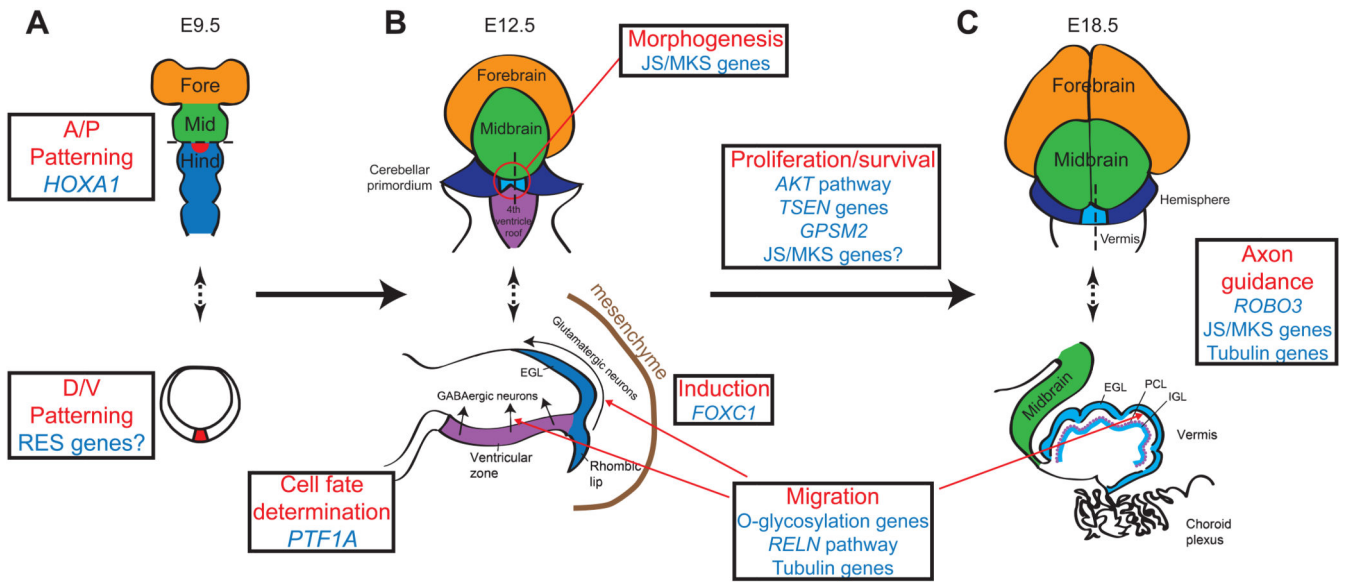


Figure 1. MBHB development and genes associated with human MBHB malformations

The diagrams depict representative stages of mouse MBHB development, the model in which MBHB development is best understood. The upper diagrams depict views from the dorsal aspect at E9.5, E12.5 and E18.5 (days after conception in the mouse embryo). Dotted lines in the upper diagrams indicate the position of the axial (A) or sagittal (B and C) cross sections depicted in the lower diagrams. (A) The lower figure represents an axial cut through most rostral level of the hindbrain. *HOXA1* is involved in Anterior/Posterior (A/P) patterning of the MBHB, while rhombencephalosynapsis may be due to defects in Dorsal/Ventral (D/V) patterning at the most dorsal and rostral aspect of the hindbrain (red area), where the cerebellar vermis is formed. (B) The upper diagram shows the location of early vermis formation at the most dorsal and anterior portion of the hindbrain (red circle). Early vermis formation may require the genes involved in Joubert/Meckel syndromes. Lower image (sagittal view) shows *PTF1A* expressed in the cerebellar ventricular zone is required for GABAergic Purkinje cell precursor fate, *FOXC1* is required for induction between mesenchyme and rhombic lip, and the *RELN* pathway, O-glycosylation genes, and tubulins are likely required for migration of precursors out of the rhombic lip and ventricular zone. (C) By E18.5, the mouse cerebellar hemispheres (blue in upper figure) and vermis (yellow in upper figure) have partially formed. The midline sagittal (lower) diagram depicts early foliation and cortical lamination. Multiple pathways are likely involved in proliferation, migration, and survival of neuronal precursors and other cell types. *ROBO3*, Joubert/Meckel and tubulin genes are required for axon pathfinding to establish connections with cerebellar and brainstem nuclei. Fore=Forebrain, Mid=Midbrain, Hind=Hindbrain

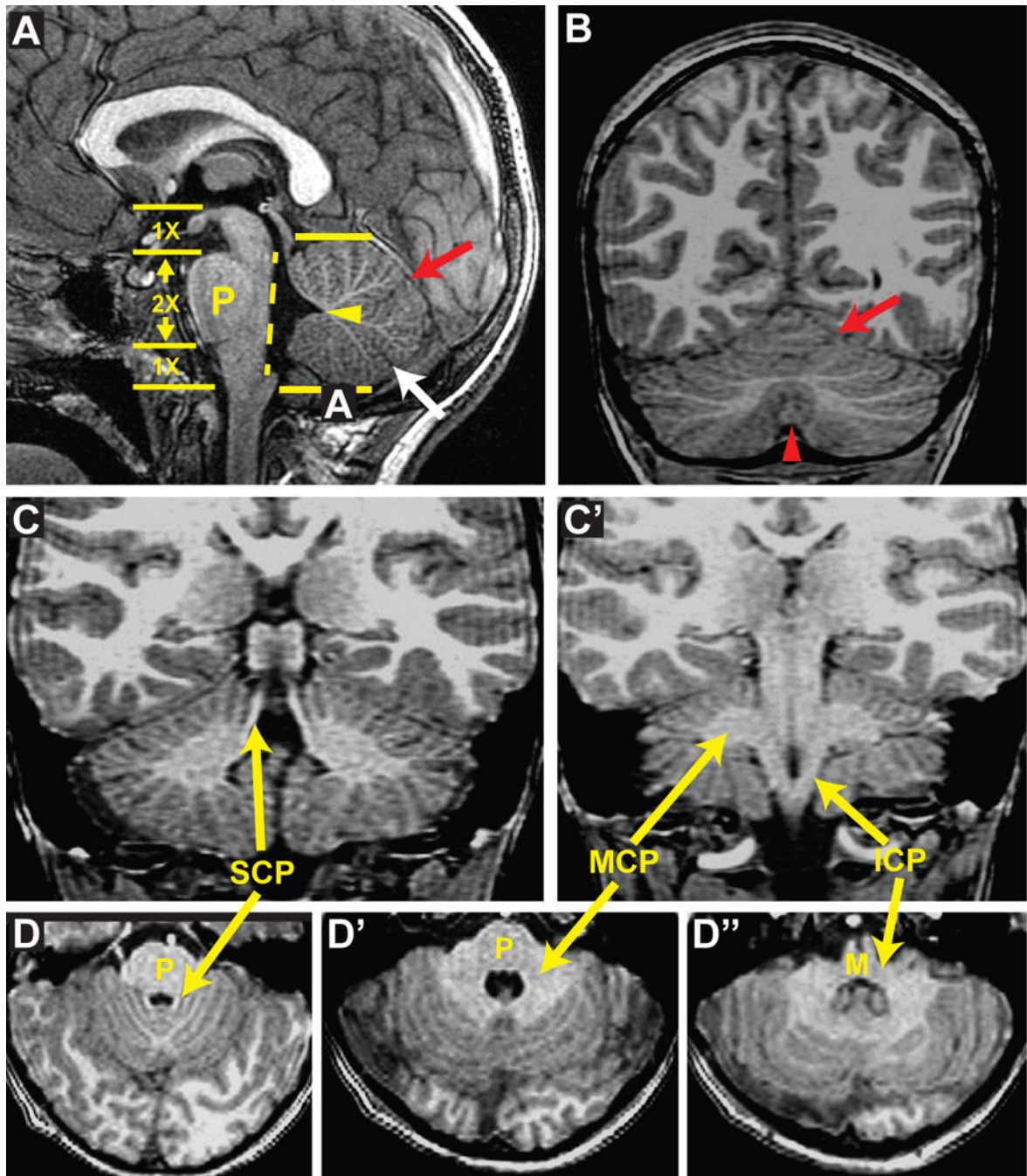


Figure 2. Normal brain MRI images

(A) Sagittal image demonstrates patent aqueduct, normal tectum, normal sized posterior fossa, vermis and pons (P), straight brainstem with flat dorsal surface (dotted line), appropriately positioned fastigium (arrowhead) just below the mid-point of the ventral pons, primary (red arrow) and pre-pyramidal (white arrow) fissures dividing vermis into 3 segments. Yellow arrows and numbers give approximate proportions of brain stem. (B) Coronal image demonstrating normal-sized cerebellar hemispheres and vermis (red arrowhead) with folia radiating toward the deep cerebellar nuclei; Note primary fissure (red

arrow). (C and C') Coronal images demonstrating superior (SCP), middle (MCP) and inferior (ICP) cerebellar peduncles. (D-D'') Axial images demonstrating SCP, MCP and ICP; note the normal-sized cerebellar hemispheres and vermis.

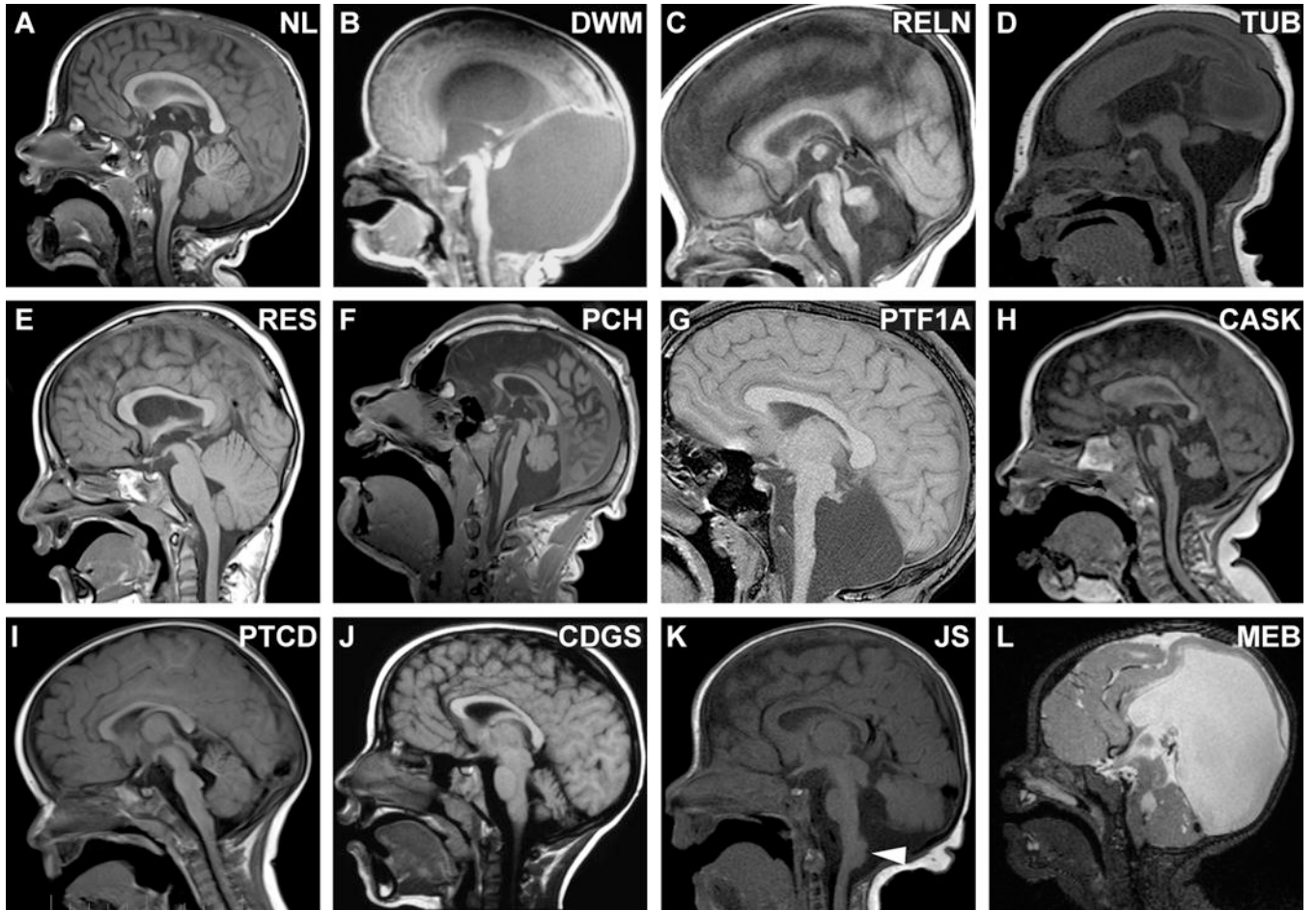


Figure 3. Sagittal views of MBHB malformations

(A) Normal sagittal image for comparison. (B) Dandy-Walker malformation (unknown cause) with hypoplastic, rotated vermis and marked enlargement of 4th ventricle and posterior fossa. (C) Cerebellar hypoplasia in a patient with biallelic *RELN* mutations, demonstrating hypoplastic brainstem and characteristic absent folia of the vermis; note the normal tectum. (D) Tubulinopathy (*TUBA1A* mutation) with brainstem hypoplasia, vermis hypoplasia, lissencephaly and microcephaly; note the large, dysplastic tectum. (E) Rhombencephalosynapsis (unknown cause) with hemisphere-like vermis morphology (the three segments described in Fig 2A are not seen); note the normal size and configuration of the pons and vermis. (F) Pontocerebellar hypoplasia (homozygous *TSEN54* mutation) with hypoplastic brainstem and vermis (which is less affected than hemispheres), note the normal tectum. (G) Pontocerebellar hypoplasia in a patient with congenital diabetes; note the extremely small vermis and flat pons with preserved tectum. (H) *CASK*-related PCH; note that the pons is not severely affected in this patient. (I) Pontine tegmental cap dysplasia (unknown cause) with ventral pons hypoplasia and an ectopic “cap” of white matter on the dorsal pons (arrowhead); the vermis is mildly hypoplastic with prominent folia. (J) Congenital disorders of glycosylation Type 1a due to biallelic *PMM2* mutations. (K) *TCTN2*-related Joubert syndrome with vermis hypoplasia (obscured by hemispheres in this image), horizontal superior cerebellar peduncles, large dysplastic tectum and heterotopia at

the dorsal cervicomedullary junction (arrowhead). With kind permission from Springer Science and Business Media: Juric-Sekhar G, Adkins J, Doherty D, Hevner RF. Joubert syndrome: brain and spinal cord malformations in genotyped cases and implications for neurodevelopmental functions of primary cilia. *Acta Neuropathol* 2012; 123: 695–709. (L) Muscle-eye-brain disease (MEB) due to *POMTGN1* mutations; note the markedly hypoplastic and dysplastic brainstem, cerebellar cysts, abnormal tectum and hydrocephalus.

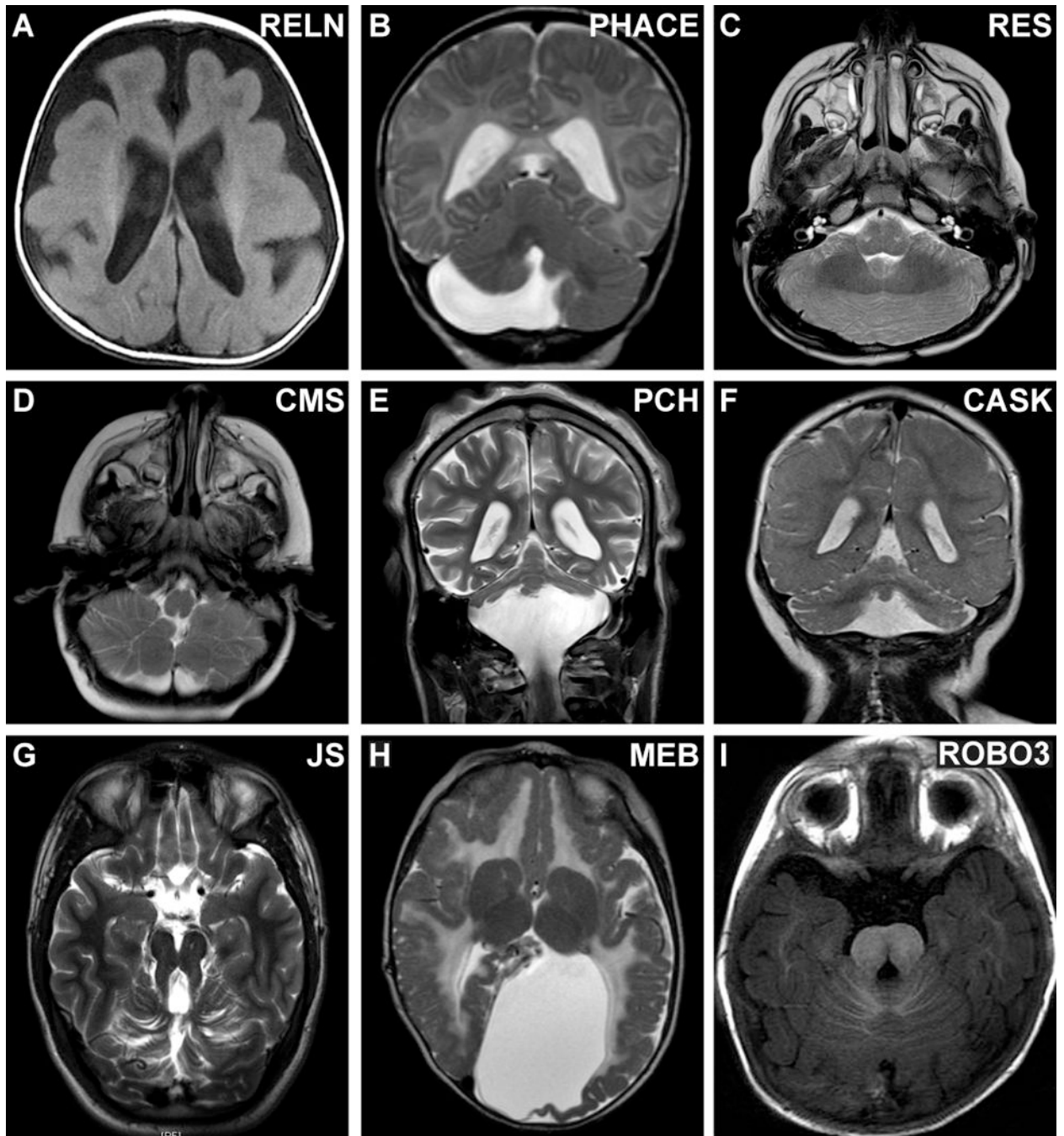


Figure 4. Other imaging features of MBHB malformations

(A) Incomplete lissencephaly (pachygyria) in a patient with biallelic *RELN* mutations. (B) Unilateral cerebellar hemisphere hypoplasia with milder vermian hypoplasia in a patient with PHACE syndrome (unknown cause). (C) Deficient vermian and fused cerebellar white matter tracts in a patient with rhombencephalosynapsis (unknown cause). (D) Inferior cerebellar hemisphere dysplasia in a patient with Chudley-McCullough syndrome (CMS) due to a homozygous *GPSM2* mutation. (E) Cerebellar hypoplasia with relatively preserved vermian in a patient with PCH due to biallelic *TSEN54* mutations. (F) Cerebellar hypoplasia with

proportionally affected hemispheres and vermis in a patient with PCH due to a *CASK* mutation. (G) Molar tooth sign in a patient with Joubert syndrome due to a homozygous *TMEM216* mutation. (H) Cobblestone cortical malformation and abnormal white matter signal in a patient with Muscle-eye-brain disease due to *POMTGN1* mutations. (I) Dysplastic pons in a patient with HGPPS due to biallelic *ROBO3* mutations; compare to Figure 2D.

Table 1
Common clinical features in patients with MBHB malformations

Hypotonia
Ataxia
Abnormal eye movements (nystagmus, oculomotor apraxia, abnormal smooth pursuit, saccades, optokinetic nystagmus and/or vestibulo-ocular reflex)
Motor delay
Vestibular issues (e.g. poor balance, head shaking, disequilibrium)
Dysarthria
Cranial nerve deficits
Dysphagia
Trigeminal anesthesia
Hearing loss
Dysarthria
Cognitive-affective signs and symptoms
Cognitive impairment
Hyperactivity/Impulsivity
Emotional lability
Autistic behaviors

Table 2
Typical clinical, imaging and genetic characteristics of specific MBHB malformations involving the cerebellum*

Disorder	Clinical features	Imaging features	Causes/testing	Inheritance
Dandy Walker malformation	Macrocephaly common Variable cognitive, NDV impairment Axenfield-Rieger syndrome (<i>FOXC1</i>)	Hypoplastic vermis, variable hemisphere hypoplasia, large posterior fossa, upwardly rotated vermis	<i>FOXC1</i> (rare), <i>ZIC1/ZIC4</i> deletions (rare), most unknown	Sporadic (recurrence risk <5%)
Lissencephaly-related MBHB malformations	Spasticity, seizures Severe NDV impairment in patients with <i>RELN</i> mutations Broad range of NDV outcome in patients with tubulinopathies and <i>ARX</i> mutations	Heterogeneous <i>RELN</i> : pachygyria with mildly thickened cortex <i>ARX</i> : variable spectrum, lissencephaly with moderately thick cortex (more severe posteriorly), small to absent basal ganglia, ACC, small pons with normal cerebellum Tubulinopathies: highly variable spectrum of PMG to lissencephaly, enlarged tectum, dysmorphic basal ganglia, thin/absent CC	<i>RELN</i> , <i>ARX</i> , <i>TUBA1A</i>	AR (<i>RELN</i>), X-linked (<i>ARX</i>), <i>de novo</i> AD (<i>TUBA1A</i>)
<i>VLDLR</i> -related cerebellar hypoplasia	Dysequilibrium, quadripedal locomotion reported in some, substantial ataxia Moderate to severe NDV impairment	Cerebellar hypoplasia with decreased foliation (vermis worse than hemispheres), simplified cortical gyral pattern	<i>VLDLR</i>	AR
X-linked intellectual disability with cerebellar hypoplasia	Moderate NDV impairment	Mild vermis hypoplasia, mild cerebellar hemisphere hypoplasia, variable ventriculomegaly	<i>OPHN1</i>	X-linked
PHACE syndrome	Segmental hemangioma (usually head and neck), intracranial and great vessel abnormalities Variable NDV impairment in <50% (usually mild)	Unilateral cerebellar hypoplasia with or without vermis involvement, DWM Dysmorphic or absent major vessels Occasional heterotopia, PMG	Unknown	Sporadic
Oculocerebrocutaneous syndrome	Orbital cysts, micro/anophthalmia, focal skin defects and appendages	Severely hypoplastic vermis, normal or hypoplastic cerebellar hemispheres,	Unknown	Sporadic

Disorder	Clinical features	Imaging features	Causes/testing	Inheritance
		enlarged dysplastic tectum, thick, vertical SCPs, ACC, frontal PMG		
RES all types	Alopecia, trigeminal anesthesia (GLH syndrome), head shaking (usually "figure of eight" pattern), hyperactivity/impulsivity, VACTERL features (<50%), variable ataxia Full range of NDV outcome	Absent septum pellucidum, aqueductal stenosis, fused colliculi, posterior holoprosencephaly (rare), absent olfactory bulbs (<50%)	Unknown	Sporadic (one recurrence reported)
Cerebellar hyperplasia	Highly variable features of Alexander disease, fucosidosis, Sotos, Williams, Costello, MCAP/MPPH syndromes	Large cerebellum, cerebellar ectopia, cerebellum wrapped around brainstem	Chromosomal anomalies, genes for associated disorders	Various depending on specific disorder
CMS	Hearing loss, mild or no ataxia Mild NDV impairment	Cerebellar hemisphere dysplasia, inferior cerebellar vermis hypoplasia, partial agenesis of the corpus callosum, frontal subcortical heterotopia, frontal PMG, arachnoid cysts	<i>GPSM2</i>	AR
PCH Type 1	Spinal muscular atrophy	Hypoplastic pons (often mild), proportional vermis and hemispheres hypoplasia	<i>EXOSC3, VRK1</i>	AR
<i>TSEN</i> -related PCH	Neonatal encephalopathy, severe progressive microcephaly, increased tone, dyskinesia, seizures, cortical visual impairment NDV impairment usually profound	Postmigrational microcephaly, small pons and cerebellum, atrophic appearing cortex, thin corpus callosum, vermis less hypoplastic than hemispheres	<i>TSEN54, TSEN2, TSEN34</i>	AR
PCH Type 6	Elevated cerebrospinal fluid lactate	Small pons and cerebellum, vermis more severely hypoplastic than hemispheres	<i>RARS2</i>	AR
<i>PTF1A</i> -related PCH	Congenital diabetes, intrauterine growth retardation, microcephaly Severe NDV impairment	Small to absent cerebellum, small pons	<i>PTF1A</i>	AR
<i>CASK</i> -related PCH	Typically females (rare males), progressive microcephaly, variable hearing loss Severe NDV impairment	Small pons and cerebellum (can be mild), proportionate cerebellar vermis and hemisphere hypoplasia	<i>CASK</i>	X-linked
<i>CHMP1A</i> -related PCH	Acquired microcephaly, increased extremity tone and contractures	Small pons and cerebellum, proportionate	<i>CHMP1A</i>	AR

Disorder	Clinical features	Imaging features	Causes/testing	Inheritance
	Moderate to severe NDV impairment	vermis and hemisphere hypoplasia		
PTCD	Hearing loss, trigeminal anesthesia/corneal scarring, dysphagia, variable cardiac and vertebral/rib defects, substantial ataxia Moderate to severe NDV impairment	Hypoplastic pons, mildly hypoplastic cerebellum, "cap" of white matter on dorsum of pons, markedly hypoplastic middle and inferior cerebellar peduncles	No specific testing	Sporadic
CDGS Type 1a	Abnormal fat distribution, retinitis pigmentosa, other diverse features: failure to thrive, elevated transaminases, coagulopathy, hypothyroidism, hypogonadism, seizures, stroke-like episodes, substantial ataxia Mild to severe NDV impairment	Pontocerebellar hypoplasia with progressive atrophy, cortical atrophy in some patients	<i>PMM2</i> , transferrin glycosylation analysis	AR
Joubert syndrome	Hypotonia, alternating apnea and tachypnea (improves with age), other diverse features: Retinal dystrophy, coloboma, liver fibrosis, nephronophthisis, polydactyly, substantial ataxia Moderate-severe NDV impairment	Vermis hypoplasia, long/thick, horizontal SCPs, encephalocele (rare), foramen magnum cephalocele (occasional), anterior midbrain and dorsal medulla heterotopia (occasional), PMG and ACC (rare)	<i>AHI1, ARL13B, C5ORF42, CC2D2A, CEP41, CEP290, INPP5E, KIF7, MKS1, NPHP1, OFD1, RPGRIP1L, TCTN1, TCTN2, TCTN3, TMEM67, TMEM138, TMEM216, TMEM237</i>	AR, X-linked (<i>OFD1</i> only)
Dystroglycanopathies (Walker-Warburg syndrome, Muscle-eye-brain disease, Fukuyama muscular dystrophy)	Eye involvement (cataracts, coloboma, high myopia), muscle involvement (variably increased CK) Severe NDV impairment	Kinked brainstem, large tectum, cerebellar hypoplasia, subcortical cerebellar cysts, cobblestone cortex, abnormal myelination	<i>POMT, POMGNT1, FKRP, POMT1, POMT2, FKTN, LARGE, GPR56, ISPD, GTDC2</i>	AR

* Note that information published for many of the disorders is quite limited, so the full spectrum of characteristics is likely broader than depicted in this table.

Table 3
Typical clinical, imaging and genetic characteristics of specific MBHB malformations primarily involving the brainstem*

Disorder	Clinical features	Imaging features	Causes/testing	Inheritance
HGPPS	Scoliosis, horizontal gaze palsy Normal NDV outcome	Brain: Dorsal midline cleft leads to “butterfly” appearance of pons, medulla Spine: early and progressive scoliosis	<i>ROBO3</i>	AR
Duane retraction syndrome, Duane radial ray syndrome	<i>CHN1</i> mutations Limited eye adduction with globe retraction and palpebral fissure narrowing <i>SALL4</i> mutations Radial ray abnormalities (thenar hypoplasia, thumb hypoplasia/aplasia, triphalangeal thumb, shortened forearm, preaxial polydactyly), kidney malformations, coloboma, cardiac malformations (rare), hearing loss Normal NDV outcome	Hypoplastic/absent abducens nerve, likely other oculomotor nerve defects	<i>CHN1</i> , <i>SALL4</i>	AD (<i>SALL4</i> , ~50% <i>de novo</i>)
Athabaskan brainstem dysgenesis and Bosley-Salih-Alorainy syndromes	Cranial nerve palsies, sensorineural hearing loss, abnormal intracranial blood vessels and cardiac outflow tract defects	No published brain imaging abnormalities	<i>HOXA1A</i>	AR
Moebius syndrome	Facial palsy with impaired ocular abduction (variable involvement of other cranial nerves) Variable somatic malformations Variable NDV outcome	Heterogeneous: hypoplastic brainstem with calcifications, hypoplastic or absent cranial nerves	Misoprostol exposure <i>in utero</i> , <i>TUBB3</i> , <i>HOXA1A</i> and <i>HOXB1</i> mutations in patients with Moebius features	Sporadic (rarely AD and AR)
Diencephalic–mesencephalic junction dysplasia	Progressive microcephaly, spasticity, intellectual disability, seizures	rostral-caudal shortening and dorsal-ventral lengthening of the midbrain, deep interpeduncular cistern Variable features: cortical calcifications, agenesis of the corpus callosum, ventriculomegaly, brainstem dysplasia and cerebellar vermis hypoplasia	Unknown	AR

* Note that information published for many of the disorders is quite limited, so the full spectrum of characteristics is likely broader than depicted in this table.