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REVIEW

New concepts on posterior fossa malformations

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Introduction

Understanding posterior malformations requires knowledge of the embryology of this region of the brain and its associations with the rest of the neuraxis. The cerebellum is the primary centre of motor coordination; however, there is increasing recognition of the cerebellum's role in neurocognition, learning, planning, judging time and sensory discrimination [1, 2].

A full description of the embryology of the posterior fossa (PF) is beyond the scope of this review; several recent publications are recommended [3, 4]. Specific aspects of the processes involved are, however, reviewed as a background to malformations that involve defects or errors occurring at critical stages during the embryogenesis of the PF structures.

Posterior fossa embryology and related defects

The earliest phases of development, which extend from week 3 to week 8, involve the formation of the neural plate and then neural tube. The rostral end of the neural tube becomes expanded, undergoes constrictions and folding (flexures), with formation of three primary brain vesicles, the prosencephalon (forebrain), mesencephalon (midbrain) and rhombencephalon (hind brain). The rhombencephalon is separated from the mesencephalon by the cephalic flexure and from the spinal cord by the cervical flexure. The prosencephalon will go on to form the future cerebral hemispheres, caudate nuclei and putamina (telencephalon) and thalamus, hypothalamus and globus palladi (diencephalon), whilst the mesencephalon gives rise to the midbrain, cerebral peduncles and contributes to the vermis. The pontine (or rhombic) flexure, which underpins cerebellar development, appears at about the fifth gestational week, dividing the rhombencephalon into the metencephalon (pons and cerebellum) and myelencephalon (medulla). The cerebellum differentiates at the dorsal part of the metencephalon whilst the pons differentiates at the ventral part.

Neural tube closure, which occurs at approximately 3 weeks' gestational age, is a process governed by specific embryonically expressed genes. Fusion commences at the site of the future craniocervical junction (somite 4), and proceeds in a zipper-like fashion both rostral and caudal to this site. Recent research, however, indicates that there may be more than one site of primary closure of the neural tube, with anything up to five sites, which may account for the multiple locations of neural tube defects commonly encountered [5].

Partitioning of the neural tube occurs in dorsoventral and anteroposterior axes. Dorsoventral partitioning occurs as a result of patterning events governed by the notochord under the influence of sonic hedgehog homolog, a protein key to organizing brain organogenesis located on chromosome 7q36 [6]. An embryonic organizing signalling centre, the isthmic organizer (IO), forms at rhombomere 1 in the roof of the rhombencephalon (pontine flexure). This controls growth and patterning of the neural tube along the anteroposterior (AP) axis, establishing the early cerebellar territory (mesencephalon–pons and cerebellum, and metancephalon–medulla). Signalling molecules secreted by the IO become integrated with dorsally and ventrally

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derived signals that govern normal midbrain and cerebellar development [6, 7]. At various stages of development, the IO controls cell survival, identity, neural precursor proliferation and neuronal differentiation. Targeted damage to genes in this location will lead to abnormalities of cerebellar and collicular development.

The rhombencephalic roof divides into anterior and posterior membranous areas (AMA and PMA). The rostral AMA forms paired lateral thickenings, the rhombic lips (the primordia of the cerebellar hemispheres), which expand and roll over to fuse in the midline to form the vermis [8]. Germinal matrix formed from the rhombic lips and AMA generates precursor cells that go on to form the cerebellar hemispheres and deep cerebellar nuclei. The cerebellar vermis forms upon fusion of the cerebellar hemispheres at about the 9th gestational week, a process that commences rostrally and proceeds caudally. The vermis cannot be formed without appropriate cerebellar development. The AMA involutes, becoming incorporated into the developing choroid plexus. The PMA forms a caudally orientated diverticulum (Blake's pouch), which cavitates in the midline to form the foramen of Magendie.

The flocculonodular lobe forms at approximately the 10th week of gestation, followed by the anterior and posterior lobes of the cerebellum. The primary fissure separates the cerebellum, where it is deepest, into the anterior and posterior lobes, by the 11th to 12th weeks. Cerebellar formation is essentially complete by the 16th week.

Effects of injury to the developing posterior fossa structures

The cerebellum is one of the earliest CNS structures to form, but undergoes a prolonged process of development and maturation, characterized by cellular proliferation and migration that extends into the first few postnatal months. This protracted developmental period makes the cerebellum particularly vulnerable to noxious events occurring over a wide time period.

Posterior fossa malformations may occur as a consequence of chromosomal abnormalities, single gene mutations, extrinsic teratogens or, most commonly, unknown factors. The type of insult is, however, probably less important than the timing and duration of exposure to the noxious agent.

At the earliest phases errors in the development of the neural tube or primordial midbrain/hindbrain organization may express themselves as neural tube defects (encephalocoeles and Chiari 2 malformation). Errors in formation of the AMA include the Dandy-Walker malformation and Dandy-Walker variant; PMA anomalies include mega cisterna magna and a persistent Blake's pouch.

Impaired development of midline mesencephalic structures and the vermis may also cause a variety of dysplastic and malformative conditions, which primarily effect midline structures (such as molar tooth syndrome, rhombencephalosynapsis). An interesting manifestation of the influence of timing of the insult in generation of defects is the so-called kinked brainstem [9]. An insult occurring at approximately 5–7 weeks' gestation may lead to arrested development during the period when the rostral neural tube flexes, resulting in a characteristic kinked appearance simulating the primitive hindbrain flexures. Reflecting the impact of an insult occurring at this stage, cerebellar hypoplasia is uniformly present (Fig. 1). The importance of recognizing this entity on fetal US or MRI is that it portends a dire outcome, providing guidance for in utero and subsequent genetic counselling. Other defects may span a wider range during the early period of PF development, as characterized by the entity of tectocerebellar dysraphism (Fig. 2). This condition is characterized by vermian hypoplasia, occipital encephalocoele, deformation of the tectal plate and brainstem, with fused colliculi extending as a beak posteriorly to the site of the encephalocoele [10]. The patterning of insult thus indicates defects spanning both neural tube closure and programmed development of the AMA.

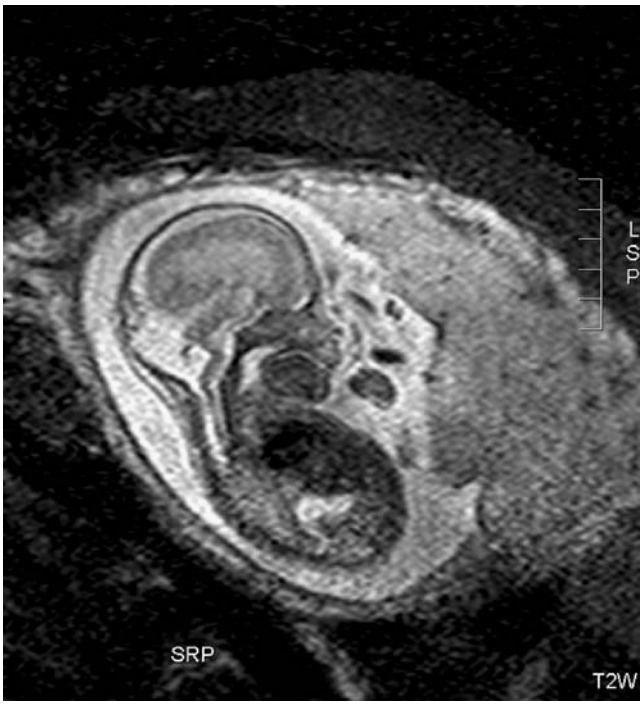

Fig. 1 Kinked brainstem syndrome. Fetal MRI (HASTE) at 20 weeks' gestation. Note the characteristic pontine kinking, severe vermian and cerebellar dysgenesis and thickening and irregularity of the cerebral cortex

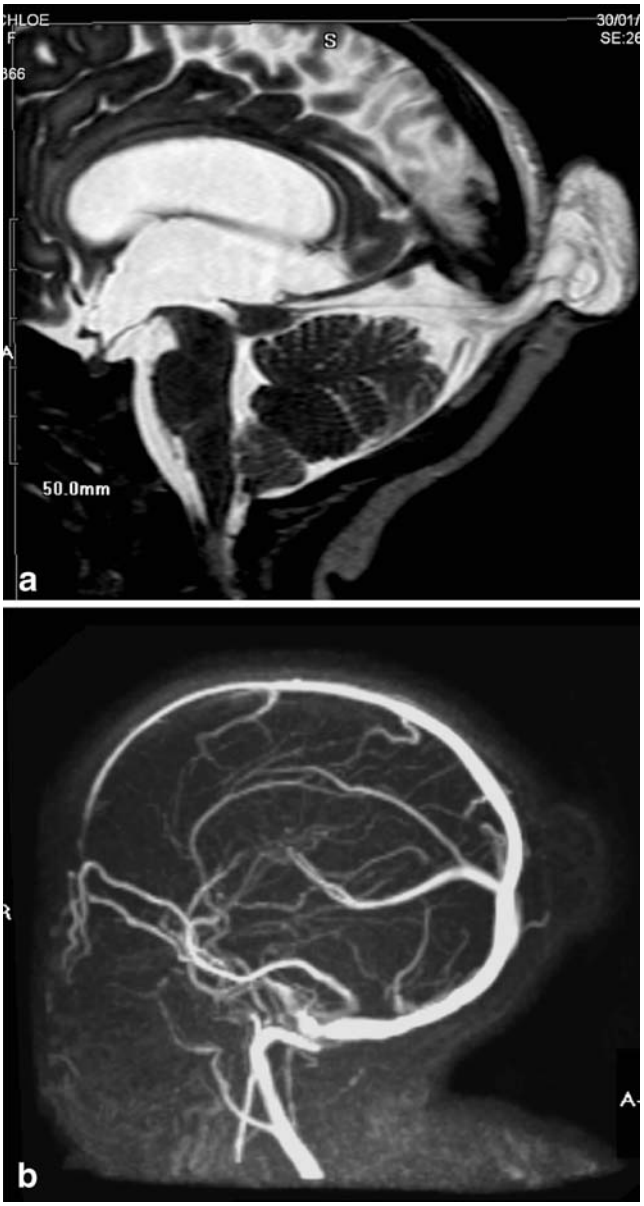

Fig. 2 Tectocerebellar dysraphism. **a** Sagittal T2-W 3-D volume acquisition. Note the posterior neural tube defect (occipital encephalocoele), vermian dysgenesis and tectal tail extending to the cephalocoele. **b** MR venography confirms lack of involvement of the torcula, but accompanying dysmorphic deep venous development

Radiological analysis of posterior fossa malformations

As the embryology of the PF is complex and incompletely understood, and as the cause of the abnormality is unknown in the majority of cases, a pragmatic approach involves morphological evaluation of the pathology employing imaging-based techniques and, where possible, postmortem material. The increased pressures brought to bear by the organ retention crisis in the UK have led to a dramatic decrease in the number of postmortem examinations undertaken in early life. MRI has consequently taken on a more significant role in understanding, diagnosing and prognosticating PF pathology during life (including in utero) as well as serving as a surrogate for postmortem examinations ex vivo [11].

Radiological evaluation of such pathology is enhanced by the use of high-quality MR-based imaging techniques, including 3-D T1-W and T2-W volume acquisitions and hybrid echoplanar techniques in fetal MRI. More advanced MR-based techniques, such as diffusion-tension imaging (DTI) and tractography, as well as BOLD functional MRI, have not yet been fully evaluated, but offer considerable future potential for defining aberrations of neural pathways and functional reorganization associated with PF malformations.

Patel and Barkovich [12] provided a comprehensive classification of cerebellar malformations based upon a review of in vivo MR imaging in 70 cases [12]. Anomalies were assessed according to the presence or absence of hypoplasia and dysplasia and whether they are focal or diffuse, brainstem malformations and associated cerebral involvement. Problems of classification arise, however, in areas of overlap such as hypoplasia, atrophy and malformation. Analysis of the morphological abnormalities involved assessment of the extent of cerebellar and vermian development, folial pattern of cerebellar hemispheres and vermis, characteristics of the cerebellar hemispheres and vermis (hypoplastic, dysplastic, absent), relative size of the fissures and folia, presence of a PF CSF collection, size of the posterior fossa, evidence of mass effect (position of torcula, bone remodelling) and brainstem development. Generalized anomalies of development involve both cerebellar hemispheres and vermis, whereas focal anomalies are localized to a single cerebellar hemisphere or vermis.

Cerebellar hypoplasia is considered to be a small cerebellum with fissures of normal size compared with the cerebellar folia, which occurs as a disorder of cerebellar formation. Focal lesions may affect the vermis or a cerebellar hemisphere in isolation. Generalized hypoplasias may involve an abnormally expanded fourth ventricle (Dandy-Walker malformation and Dandy-Walker continuum) or normal fourth ventricle with a small or normal pons (pontocerebellar and cerebellar hypoplasia).

Cerebellar dysplasia represents disorganized development of the cerebellum, e.g. abnormal folial pattern with heterotopic gray matter nodules. Focal dysplasias may be isolated to the vermis (molar tooth malformation, rhombencephalosynapsis) or cerebellar hemisphere (focal cortical dysplasia/heterotopia, L'hermitte-Duclos-Cowden syndrome). Generalized dysplasias include congenital muscular dystrophies, lissencephaly (with RELN mutation or agenesis of the corpus callosum), diffusely abnormal foliation and may be associated with CMV infection and diffuse cerebral polymicrogyria.

Cerebellar atrophy is characterised by a small but formed cerebellum with shrunken folia and large cerebellar fissures. Vermian abnormalities are considered as hypogenesis (formed superior vermis but absent or hypogenetic inferior vermis) and dysplasia (missing middle vermian lobules).

Chiari II malformations reflect a lack of expansion of the embryonic fourth ventricle with consequent hypoplasia of the post fossa or anomalies of the craniocervical junction. Leakage of CSF into the amniotic fluid through the defect of the almost universally accompanying myelomeningocele, occurring at the interface of two neural tube closure sites, leads to hypotension within the developing neural tube. Insufficient expansion of the fourth ventricle coupled with impaired or absent induction of the mesenchyme forming the PF leads to the cerebellum and brainstem developing within an abnormally small PF, forcing these structures down through the foramen magnum [13]. The spectrum and severity of the hind brain malformation is, however, broad ranging from an ostensibly normal size and appearing PF to the extremes of PF descent and accompanying tectal and cerebellar dysmorphology. High-resolution, 3-D T2-W imaging is particularly useful for defining the more complex anatomical dysmorphology associated with such entities (Fig. 3).

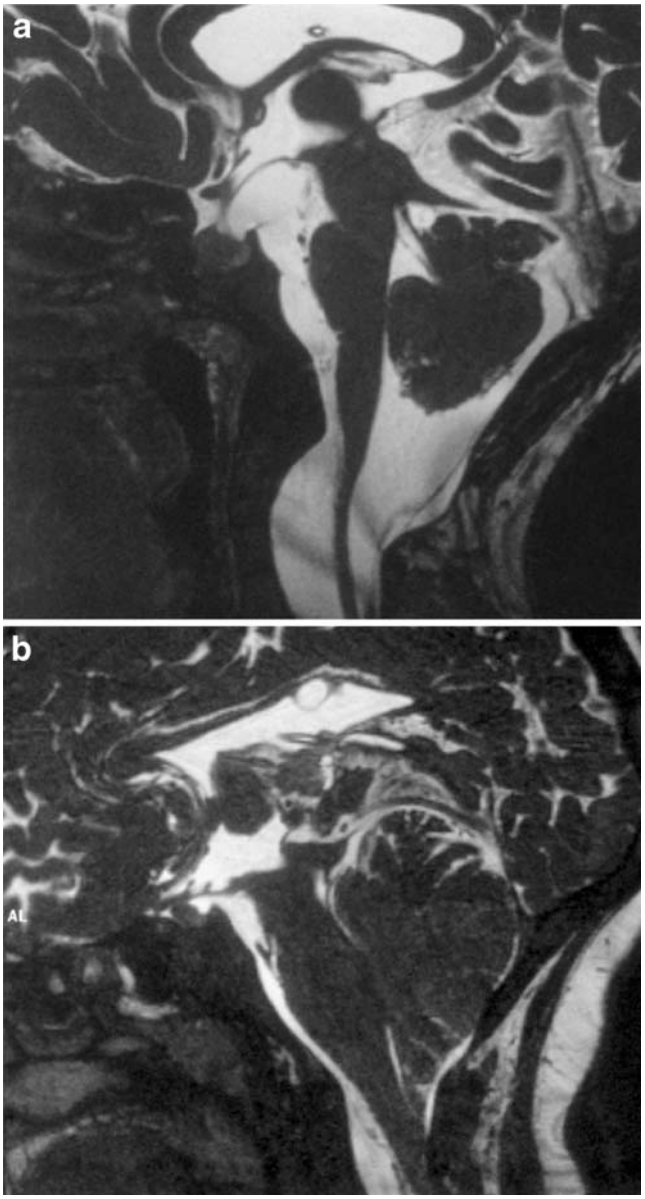

Fig. 3 Chiari II malformation. Spectrum of features defined by high-resolution sagittal T2-W (CISS) imaging. (**a**) The posterior fossa is small; however, the cerebellum and brainstem retain an orthodox position. Note the dysgenetic vermis, clival concavity, inferior tectal beaking and anterior third-ventricular extra-commissural band. (**b**) In this patient, a small posterior fossa is associated with descent of the medulla and cerebellar vermis through the foramen magnum. Tectal beaking with a small tectal tail and typical third ventricular dysmorphology is present (floor beaking and anterior extra-commissural band)

Fetal imaging and a fetal approach to classification

The increasing profile of fetal MRI and the importance of this modality in the assessment, prognosis and management of CNS abnormalities has led to the development of new approaches to the classification of PF abnormalities. One such approach is based on whether malformations are cystic or non-cystic and are associated with a small, normal or enlarged PF. Using fetal US and MRI, Guibaud proposed a pragmatic approach to PF abnormalities, emphasising the advantages of combining US with MR assessment of these complex lesions [14]. Abnormalities were evaluated according to the status of the PF fluid-filled spaces, cerebellar biometry and focal nature of lesions:

Increased PF fluid-filled space

1. Enlarged PF with ascent of the torcula and tentorium: Dandy-Walker malformation
2. Normal PF size with abnormal cerebellar anatomy/biometry and cisterna magna >10 mm: cerebellar agenesis; pontocerebellar hypoplasia; atrophy/destruction
3. Normal PF size and normal cerebellar anatomy/biometry: isolated mega cisterna; retro/infero-cerebellar cyst with or without hydrocephalus.

Decreased prenatal cerebellar biometry

1. Normal cerebellar anatomy with globally decreased cerebellar biometry: cerebellar hypoplasia- isolated, syndromic, infectious; pontocerebellar hypoplasia; atrophy

2. Normal cerebellar anatomy with focally decreased biometry: ischaemic and haemorrhagic mechanisms; focal dysplasia
3. Abnormal cerebellar anatomy with decreased cerebellar biometry: Chiari II malformation; vermian agenesis-isolated (e.g. genetic conditions such as Joubert syndrome) or syndromic (e.g. Walker-Warburg malformation with cerebral/extracerebral malformations); rhombencephalosynapsis.

Focal echogenic lesion of the cerebellum

Most are haemorrhagic in nature, with mixed MR signal patterns helping to confirm the nature of the abnormality.

Adamsbaum et al. [15] provide a further paradigm for evaluating the fetal posterior fossa by MRI, forming a basis for prognostic triage. Key elements evaluated were: position of the tentorium cerebelli, volume of the posterior fossa, size of the posterior fossa CSF spaces, shape of the fourth ventricle, presence or absence of the primary fissure of the cerebellum and posterior/anterior lobe ratio, appearance of the cerebellum (normal/abnormal, symmetrical/asymmetrical), status of the normal pontine bulge and associated supratentorial abnormalities (cortical abnormalities, corpus callosum, ventricular dilatation). The significance of posterior fossa abnormalities was then divided into those with a poor neurological prognosis, those with an uncertain prognosis and those with a good neurological outcome.

Poor prognosis

1. Neural tube defects, including the Chiari 2 malformation as a surrogate marker of a spinal myelomeningocele.
2. Supratentorial abnormalities (e.g. major migrational abnormalities) associated with a posterior fossa lesion such as Walker-Warburg syndrome, features of CMV infection.
3. Absent pontine curvature due to pontocerebellar atrophy/hypoplasia (PCAH): Absence of the normal pontine curvature connotes a poor neurological outcome. Although reflecting different stages of damage (e.g. atrophy affecting the later stages of pregnancy or early infancy), the outcome for both atrophy and hypoplasia is equally poor. Affected individuals may be characterized by muscle weakness, swallowing difficulties and respiratory distress (PCAH type 1) or microcephaly, abnormal movements and absent motor and mental development with seizures and premature death (PCAH type 2) [16].
4. Cerebellar hypoplasia: global cerebellar hypoplasia without pontine involvement probably arises as a result of environmental and genetic factors, with numerous chromosomal abnormalities detected by amniocentesis.
5. Rhombencephalosynapsis: lack of vermis with midline fusion of usually hypoplastic cerebellar hemispheres with a characteristic small round 4th ventricle and transverse cerebellar folding seen on postnatal MRI.
6. Vermian agenesis, which may be isolated or associated with different syndromes such as the molar tooth syndrome (notably Joubert syndrome) associated with lack of decussation of superior cerebellar peduncles, pontine and corticospinal tracts. Prenatal identification can be challenging due to partial voluming from the cerebellar hemispheres. Identification of an absent primary fissure or posterior lobe of the vermis is better made on postnatal MRI.

Diagnoses associated with uncertain prognosis

1. Dandy-Walker continuum (DWC): a heterogeneous group of malformations ranging from classic Dandy-Walker malformation (DWM), characterised by vermian agenesis, cystic dilation of the posterior fossa communicating with the fourth ventricle and a high tentorium and enlarged PF, to Blake's pouch.
2. Isolated cerebellar hypoplasia: There is considerable potential for overlap between the Dandy-Walker continuum and isolated cerebellar hypoplasia.
3. Cerebellar hemispheric abnormality

Diagnosis associated with a good neurological prognosis

Mega cisterna magna and closed arachnoid cyst.

Nelson et al. [17] consider cystic lesions as a separate entity, based upon the pathology of the cyst wall and embryological development of the hindbrain, choroid plexus and meninges. The authors note the potential for overlap between arachnoid cysts, Blake's pouch and cysts associated with the DWC. The authors suggest that because the histology of the cyst wall is usually unknown, a more pragmatic and useful approach is to describe the cyst location (retrocerebellar, supracerebellar, cerebello-pontine angle) and its effect on local structures. The position of the choroid plexus in the fourth ventricle may help to differentiate between the major types of cystic malformation, which is normal with arachnoid cysts, absent in DWM and displaced into the superior cyst wall in Blake's pouch.

Effects of prematurity on the developing cerebellum

Preterm extra-uterine life appears to have an adverse effect on cerebellar development, inhibiting normal growth of the formed cerebellum even in the absence of an obvious primary injury. Preterm infants suffering cerebellar injury show a strong prevalence for neurocognitive and behavioural dysfunction when assessed by long-term follow-up. The sym-

metrical cerebellar volume reduction that may occur as a consequence of extreme prematurity probably reflects selective vulnerability of the developing cerebellum between 24 and 30 weeks' gestation, working in synergy with additional adverse factors such as haemosiderin deposition, resulting in destruction of immature structures and development arrest [18].

Such consequences of prematurity thus come into the differential diagnosis of cerebellar malformations, particularly the DWC, pontocerebellar hypoplasia and pontoneocerebllar hypoplasia. Vanishing cerebellar volumes in cases of extreme prematurity, assessed by serial US and MRI, suggest that if interruption of normal developmental steps occurs between 24 and 30 weeks, due to genetically determined factors or noxious agents, the outcome may be similar to congenital cerebellar malformations. The pathology seen in extreme prematurity probably reflects interrupted or disrupted cerebellar developmental due to developmental failure or acquired damage. Increasing realisation of the effects of prematurity on the development of the cerebellum will be the focus of greater attention in the future as more infants survive birth at gestational ages of 23–28 weeks.

Conclusion

MR imaging has enabled a greater level of understanding of posterior malformations, which provides exquisite characterization of the anatomy of the developing and formed structures both in utero and postnatally. Knowledge of the embryology assists in predicting the injury patterns associated with noxious insults occurring at various stages of development. There is considerable overlap of the pathological damage and appearances; as such a descriptive approach to the abnormalities is called for, enabling a more effective assessment on the impact on functional outcome. Rapidly evolving MR technology should assist in further defining the interrelationships between the cerebellum and cerebral hemispheres and the role of the cerebellum in higher level functioning, including leaning, memory and speech.

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