Clinical Anatomy 31:488–500 (2018)

ORIGINAL COMMUNICATION

Embryology of the Craniocervical Junction and Posterior Cranial Fossa, Part II: Embryogenesis of the Hindbrain

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Although pathology of the hindbrain and its derivatives can have life altering effects on a patient, a comprehensive review on its embryology is difficult to find in the peer-reviewed medical literature. Therefore, this review article, using standard search engines, seemed timely. The embryology of the hindbrain is complex and relies on a unique timing of various neurovascular and bony elements. Derailment of these developmental processes can lead to a wide range of malformations such as the Chiari malformations. Therefore, a good working knowledge of this embryology as outlined in this review of the hindbrain is important for those treating patients with involvement of this region of the central nervous system. Clin. Anat. 31:488–500, 2018.

Key words: genetics; anatomy; malformation; Chiari; brain, nervous system; cerebellum; brain stem

INTRODUCTION

The Developmental Anatomy of the Cerebellum

Current understanding of the embryogenesis of the cerebellum is indebted to observations made during the late 19th to early 20th centuries. The following discussion is based on the studies of Bailey and Miller (1921), Dow (1942), Frazer (1931), Hamilton et al. (1952), Heisler (1907), Hochstetter (1919), Keibel and Mall (1912), Keith (1948), Minot (1892), Patten (1968), Piersol (1918) and Stroud (1897). More recent observations have been obtained from in vitro and in vivo fetal sonography and magnetic resonance imaging (Babcook et al. 1996; Chong et al. 1997; Malinger et al. 2001; Limperopoulos et al. 2005; Liu et al. 2011).

The primary neural tube, which gives rise to the hindbrain, expands cranially to form three vesicles separated by two constrictions, one between the forebrain and midbrain vesicles and the other between the midbrain and hindbrain vesicle. The constriction between the midbrain and hindbrain is called the *isthmus* and appears even before the cranial closure of the neural tube (Heisler, 1907). An additional two constrictions appear in the region of the forebrain and hindbrain yielding a five-vesicle neural tube composed of the telencephalon, diencephalon, mesencephalon, metencephalon and myelencephalon (Fig. 1). Transfer from a three-vesicle to a five-vesicle neural tube is associated with bending of the neural tube at three levels (midbrain, midportion of hindbrain, and cervicomedullary junction) and there is a spatial change from a craniocaudal to ventrodorsal orientation of the vesicles (Heisler, 1907).

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Received 1 January 2018; Accepted 15 January 2018

Published online 9 March 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/ca.23048

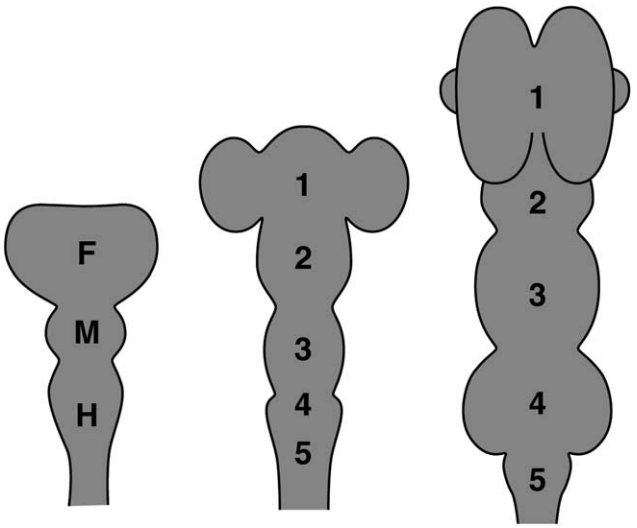

Fig. 1. Schema of the cranial neurocele at three-vesicle and five-vesicle stages (reproduced from Heisler (1907) with slight modifications). Expansion of the cranial neurocele initially yields the forebrain (F), midbrain or mesencephalon (M), and hindbrain (H). With further subdivision, the telencephalon (1), diencephalon (2), mesencephalon (3), metencephalon (4), and myelencephalon (5) are formed.

The rhombencephalon (hindbrain) extends from the isthmus to the cervical flexure (Minot, 1892). In the mid-portion of the rhombencephalon, the basal and alar plates lie in the same plane. Moving upward and downward, the alar plates on both sides approximate each other in the dorsal midline (Fig. 2) and tend to attain a dorsal position in much the same way as in the spinal cord (Frazer, 1931). Thus, the roof plate is wider in the mid-portion and narrower in the cranial and caudal portions of the rhombencephalon. Just beneath the isthmus and as a result of the rapid initial growth of the midbrain, the rostral ends of the right and left metencephalic alar plates, which are in close proximity in the dorsal midline, are pushed downward. This creates an internal bend in the metencephalic alar plate (Fig. 2). A medial portion located rostrally lies transversely beneath the isthmus. The lateral arms located caudal to this bend are initially longitudinally oriented (Frazer, 1931).

At the fourth week of fetal life, the roof of the rhombencephalon is bounded laterally by the rhombic lip, inferiorly by the obex and superiorly by the metencephalic alar plates (Keith, 1948). Dorsal extension of the metencephalic alar plate over the roof plate forms a thickened *metencephalic rhombic lip* at the junction between the roof plate and the alar plates (Hamilton et al. 1952). The metencephalic alar plates then thicken and bulge internally toward the fourth ventricle and externally toward the cisterna magna to form the intraventricular and extraventricular parts of the cerebellar plates, respectively (Hamilton et al. 1952). At this stage, the cerebellar plates have three layers: ependymal, mantle, and marginal, from inside to out (Hamilton et al. 1952). Between the sixth and eighth weeks, the pontine flexure is maximized. The metencephalic rhombic lip and cerebellar plates including the previously longitudinal arm caudal to its internal bend are now in a transverse plane. At the second month, the growth of the intraventricular part dominates owing to the proliferation of precursor neural cells (neuroblasts) in the subependymal region forming a mantle layer.

The growth of the cerebellar plates (and later, the primordium) is considerably heterogeneous in space and time, causing the appearance of several topographically distinguishable regions during the course of their development (Fig. 2). Initially, the cerebellar plates grow in a transverse direction, expanding them laterally (Bailey and Miller, 1921). The transverse growth coincides with the growth of the intraventricular part during early embryonic stages. The lateral parts of the cerebellar plates corresponding to the cerebellar peduncles grow more slowly than the medial parts (Keibel and Mall, 1912). During the third month, the two transversely-lying cerebellar plates fuse in the dorsal midline to form a single cerebellar primordium (Keibel and Mall, 1912). The two cerebellar plates fuse externally, leaving the two intraventricular parts separate at the midline (Bailey and Miller, 1921). The cerebellar primordium is connected to the roof of the midbrain anteriorly and the choroid plexus of the fourth ventricle posteriorly by two thin membranes, the anterior and posterior medullary vela. Subsequently, the cerebellar primordium grows mostly through longitudinal expansion of its extraventricular part (Bailey and Miller, 1921). The neuroblasts migrate from the metencephalic rhombic lip and mantle layer of the intraventricular part, and contribute to the formation of cerebellar gray matter within the extraventricular part (Hamilton et al. 1952).

The development of cerebellar gray matter follows several stages: (1) first, neuroblast migration yields the superficial cerebellar cortex; (2) a group of neuroblasts migrates toward the surface deep to the superficial cerebellar cortex to form Purkinje cells; (3) neuroblasts of the superficial cerebellar cortex migrate deeply beneath the Purkinje cell layer; and (4) the remaining mantle zone neuroblasts form the deep cerebellar nuclei (Hamilton et al. 1952). Ultimately, subependymal neuroblast proliferation ceases. The migration of precursor neuronal cells and cessation of subependymal neuroblast proliferation are associated with the gradual disappearance of the intraventricular part of the cerebellar primordium, a process referred to as "*eversion of the cerebellum*" (Hamilton et al. 1952) (Fig. 3). The eversion is thus mainly due to a shift in the pattern of cerebellar growth from intraventricular to predominantly extraventricular. The cerebellar primordium is mainly extraventricular in an 80 mm crown-rump length (CRL) embryo, corresponding to about the fourteenth week of fetal life (Hamilton et al. 1952). Despite the cessation of subependymal neuroblast proliferation, the metencephalic rhombic lip continues to generate new neuroblasts destined for the extraventricular part of the cerebellum (Keibel and Mall, 1912). The longitudinally growing extraventricular part then overlaps the superior and inferior medullary vela (Bailey and Miller, 1921).

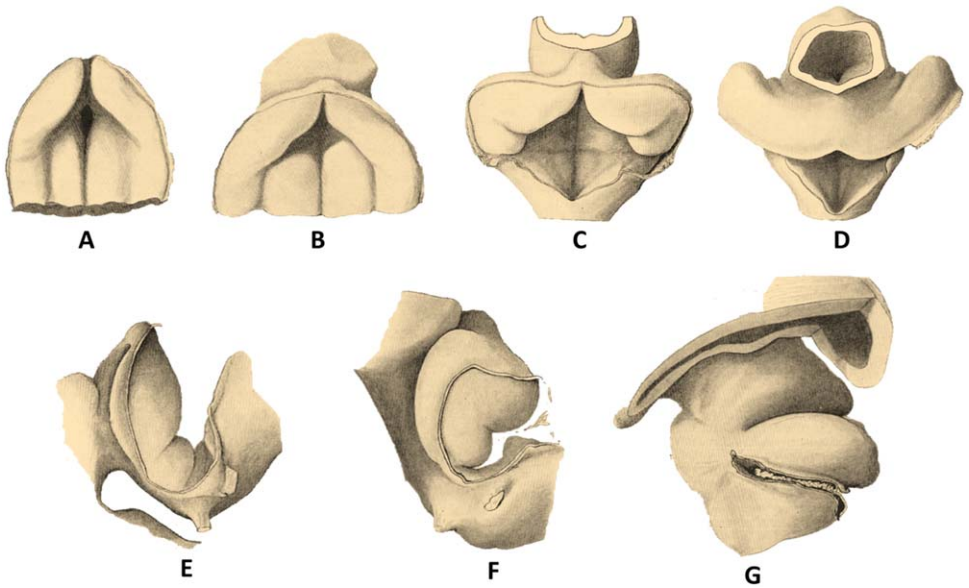

Fig. 2. Schema of the posterior (**A**-**D**) and lateral (**E**-**G**) views of the developing cerebellum (after Frazer (1931) with slight modifications). **A**: the right and left metencephalic alar plates approximate each other rostrally and are in an inverted V-shape position. **B**: the enlarging mesencephalon pushes the metencephalic alar plates downward. This creates an internal bend in each alar plate, clearest in C and F. **C**: The cerebellar plates are composed of longitudinal and transverse parts marked by the internal bend. The transverse parts begin to fuse rostrally and externally beneath the mesencephalic isthmus. **D**: The dorsomedian fusion of the cerebellar plates progresses caudally. **E**: The lateral view corresponding to **B** shows the intraventricular growth of the cerebellar plates at this stage. **F**: The lateral view corresponding to **C** shows the transverse and longitudinal parts of the cerebellar plates. The internal bend is maximized. The extraventricular part of the cerebellum is enlarging. **G**: The lateral view corresponding to **D** shows that the extraventricular part of the cerebellum has grown considerably. The longitudinal part of the cerebellum grows more slowly than the transverse part, and the intraventricular part of the cerebellum is now substantially regressed. [Color figure can be viewed at wileyonlinelibrary.com]

In brief, the transverse growth of the cerebellar plates precedes the longitudinal growth of the primordium, and the growth of the intraventricular part precedes that of the extraventricular part. The fusion of cerebellar plates into a single cerebellar primordium marks a shift in the pattern of early cerebellar development and growth. The longitudinal growth of the cerebellar primordium during the second trimester results in the appearance of several cortical sulci and fissures. After the initial rapid transverse growth of the cerebellar plates (before fusion and during the second month of fetal life), the transverse growth of the cerebellar primordium continues more slowly during the third to fifth months. Following the fifth month of fetal life and mainly during the third trimester, the cerebellum experiences its most rapid transverse growth compared to all other parts of the brain. What follows below is a discussion of the development of the vermis and cerebellar hemispheres.

Dorsomedian fusion of the cerebellar plates begins rostrally at the ninth week of fetal life (Lemire et al. 1975). The region of median fusion gives rise to the vermis. The embryogenesis of the vermis has two stages. Following rostral fusion of the extraventricular part of the cerebellar plates through their thickened rhombic lips, the anterior vermis is first to form. Until the eighteenth week of gestation the vermis covers only the rostral half of the fourth ventricle (Babcook et al. 1996). The anterior vermis is anatomically continuous with the germinating rhombic lip laterally and the rhombic roof inferiorly. It grows progressively in a caudal direction, closing the posteroinferior interhemispheric cleft and entirely covering the fourth ventricle between 18 and 21 weeks of fetal life (Babcook et al. 1996). The vermis undergoes progressive caudal growth by specialization of the adjacent part of the rhombic roof, and mainly by the growth of the rhombic lips toward the midline and their fusion favored by the mechanical effects of the transversely-expanding lateral hemispheres. Once the vermis is completely closed, it continues to grow linearly in both longitudinal and anteroposterior directions after the fifth month of fetal life. This growth is closely proportionate to the transverse growth of the cerebellum (Malinger et al. 2001). While the vermis grows in a craniocaudal direction during the first half of fetal life, its further growth during the second half occurs circumferentially, ultimately leaving two notches between the cerebellar hemispheres, one anteriorly and one posteroinferiorly.

At the end of third month, the cerebellum is dumbbell-shaped with two lateral masses and a relatively thin median vermis (Keith, 1948). As mentioned earlier, the cerebellar primordium comprises metencephalic alar plates, which partially extend into the roof

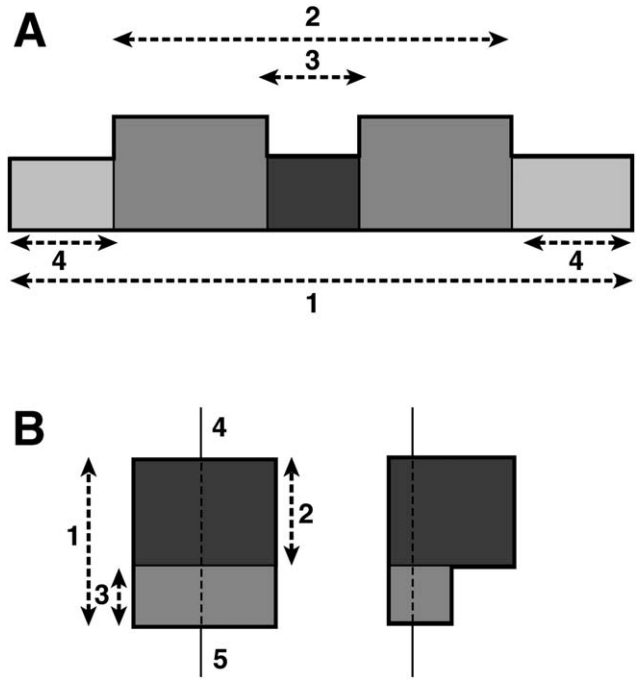

Fig. 3. Schematic representation of the heterogeneous growth of the cerebellar primordium. The transverse section (**A**) through the cerebellar primordium (1) shows a medial region (2) and two lateral arms (4). The medial region comprises a median vermis (3) and lateral (hemispheric) masses between the vermis and lateral arms. The lateral arms form the cerebellar peduncles (Keibel and Mall, 1912). The sagittal section (**B**) through the cerebellar primordium (1) shows the cranial and caudal parts derived from the metencephalic alar plates (2) and thickened rhombic lip (3), respectively. The superior and inferior medullary vela are attached to the cerebellar primordium and arbitrarily divide it into intra- and extraventricular parts marked by the dashed lines. As depicted here, the median vermis, lateral arms and caudal region of the cerebellar primordium grow more slowly.

plate forming a thickened metencephalic rhombic lip. The metencephalic rhombic lip continues to yield neuroblasts, which migrate superficially to the cerebellar cortex (Keibel and Mall, 1912). As a result of the differential growth of the metencephalic alar plate and rhombic lip, three sulci successively appear between them; one in the median area (sulcus postnodularis) and then two in the lateral areas (sulcus floccularis). These sulci (postnodularis and floccularis) later become continuous to form the posterolateral fissure, the first fissure to appear in the developing cerebellum (Hamilton et al. 1952); it separates the flocculonodular lobe from the rest of the cerebellum (corpus cerebelli) (Piersol, 1918). In this way, the thickened rhombic lip gives rise to the nodulus and flocculus (Keibel and Mall, 1912).

During the fourth and fifth months, the cerebellar cortex grows rapidly in the longitudinal axis resulting in the appearance of several other transverse sulci or fissures and intervening lobules (Patten, 1968; Keibel and Mall, 1912). The longitudinal growth of the cerebellum occurs superficially, first in the median region corresponding to the vermis, and later, to a greater extent, in the lateral regions corresponding to the cerebellar hemispheres. The first fissure to appear in the median (vermian) region of the corpus cerebelli is the fissura prima of Elliot-Smith or sulcus primarius of Bolk, which separates the anterior and posterior cerebellar lobes during the fourth month of fetal life (Piersol, 1918; Patten, 1968; Liu et al. 2011). Initially, the growth rates of the anterior and posterior cerebellar lobes are proportionate, and the volumes of the two lobes are rather similar. However, beginning in Week 16, the posterior lobe grows faster (Liu et al. 2011). The minor cerebellar fissures appear until the seventh month of fetal growth (Keith, 1948).

The fourth month of fetal life is marked by cortical growth of the median vermis (Keibel and Mall, 1912). At this time, the lateral masses of the corpus cerebelli are smooth (Keibel and Mall, 1912). The hemispheric masses subdivide during the fifth month of fetal life once the basic subdivision of the vermis has taken place (Piersol, 1918). With the rapid longitudinal growth of the cerebellum within the posterior fossa during the second trimester, the cerebellar primordium gradually becomes wedge-shaped, with the apex backwards because of mechanical factors (Keith, 1948). Concurrently, the transverse growth is relatively slow and the expanding lateral hemispheres roll in toward the midline overlapping the vermis (Keibel and Mall, 1912). This results in the formation of a median longitudinal fissure between the two hemispheres. The transverse length of the cerebellum is three times the longitudinal length of the vermis during the early part of the second trimester (Liu et al. 2011). However, by the end of the second trimester, the transverse length is about twice the longitudinal length of the vermis (Liu et al. 2011). This could have implications. First, the longitudinal growth of the vermis overrides the transverse growth of the cerebellar hemispheres during the second trimester. Second, cerebellar growth is faster than the expansion of the confined posterior cranial fossa, which brings about a state of relative posterior fossa overcrowding. This overcrowding results in the compression and spreading out of the vermis sandwiched between the two cerebellar hemispheres. The mechanism is depicted in Figure 5.

The fetal cerebellum goes through a phase of rapid growth after 28 weeks of fetal life (Limperopoulos et al. 2005) and the third trimester is marked by transverse growth of the cerebellar hemispheres, further contributing to the overcrowding of the posterior fossa (Malinger et al. 2001). Wedging of the cerebellum becomes more evident toward the end of pregnancy, probably because the posterior fossa is more yielding anteroposteriorly than transversely late in the fetal period. During this phase of growth, which is mainly due to the massive proliferation and migration of the cortical granule cells, the cerebellar volume increases ~2.8-fold (Limperopoulos et al. 2005). The intracranial and cerebral volumes increase ~2-fold during the same period (Limperopoulos et al. 2005).

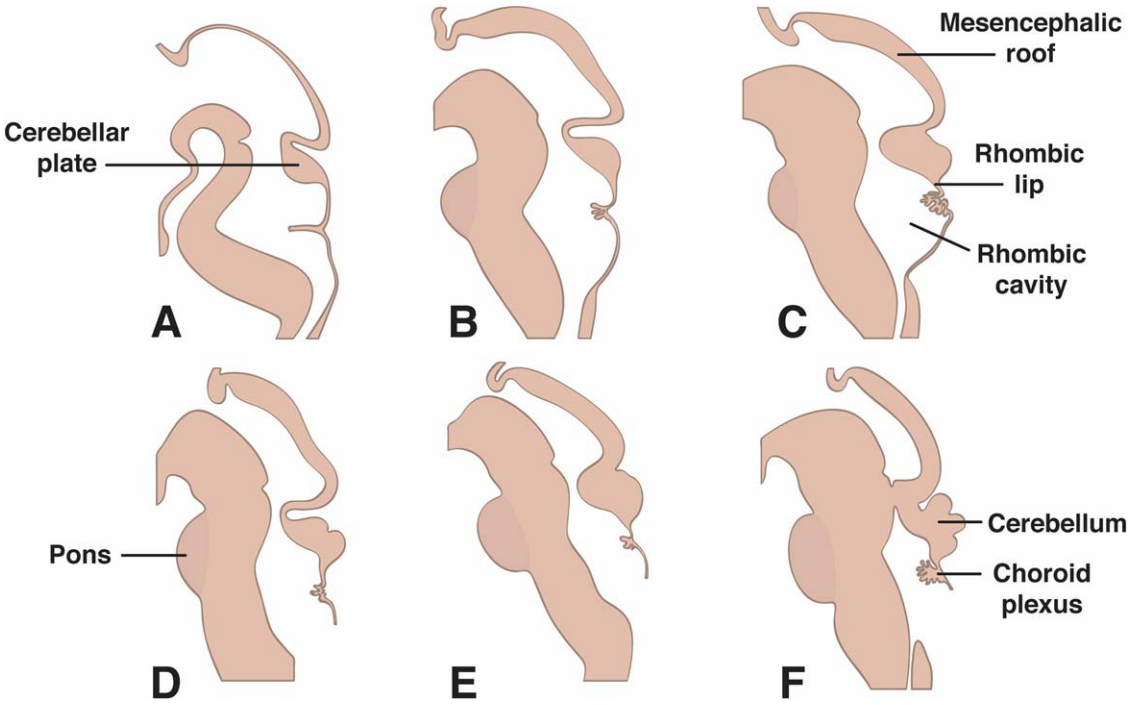

Fig. 4. Parasagittal sections through the midbrain/hindbrain showing the successive stages of cerebellar development and the process of cerebellar eversion (reproduced with modifications from Hochstetter, 1919). The cerebellar primordium is mainly intraventricular in **A** and is extraventricular in **B** to **F**. The fusion of the cerebellar plates (not shown here) marks the transition from intraventricular to extraventricular development of the cerebellum. Note that the ventral pons, which contains corticopontocerebellar fibers, grows and the pontine flexure straightens concomitantly with development of the extraventricular cerebellum. [Color figure can be viewed at wileyonlinelibrary.com]

The embryogenesis of the cerebellar lobules is beyond the scope of the current review. The reader is referred to the review by Dow (1942) for details of the ontogeny and phylogeny of cerebellar lobulation. Several different systems of nomenclature and subdivision have been proposed. Ingvar (cited by Dow, 1942) noted that the region in front of the primary fissure and the one behind the prepyramidal fissure are morphologically the most constant regions in the mammalian cerebellum. However, the region between the primary and prepyramidal fissures is phylogenetically variable. This phylogenetically variable region of the cerebellum (the middle lobe of Ingvar) receives the cortico-ponto-cerebellar afferents, and according to Dow should be designated the neocerebellum. Phylogenetically, the flocculonodular lobe and the lingula (the so-called archicerebellum) are the oldest parts of the cerebellum. This is followed by the appearance of the paleocerebellum, composed of the anterior lobe (except lingula), pyramis, uvula, and paraflocculus, and subsequently the appearance of the neocerebellum (the rest of cerebellum).

According to Ingvar, while the archicerebellum essentially receives vestibular inputs, the paleocerebellum and neocerebellum receive spinal and cortical inputs, respectively. In lower primates, the paraflocculus is larger than the flocculus, projects between the latter and the lateral part of the corpus cerebelli, and is connected by a stalk to the uvula and pyramis (Stroud, 1897; Dow, 1942). The paraflocculus is retained as a small and vestigial structure in humans (Stroud, 1897) and is often referred to as an accessory paraflocculus (Anthony, 1994). It lies close to the flocculus and varies markedly in shape from a flat lamella to a rosette-like cluster of folia akin to the flocculus (Tagliavini and Pietrini, 1984). There are controversies about the origin of the tonsils (the lowest part of the corpus cerebelli) in humans. While some advocate that they are a part of the middle lobe in front of the prepyramidal fissure that grows downwards and secondarily becomes contiguous with the uvula, others believe that they represent the growth of the stalk of the paraflocculus intervening between the uvula/pyramis and the vestigial paraflocculus in humans (Dow, 1942).

Development of the Rhombic Roof

A discussion of the embryogenesis of the roof of the fourth ventricle is not complete without referring to the outstanding work of Weed (1917). In human embryos and other mammals, Weed identified an oval thinned-out area of epithelial differentiation (the so-called *area membranacea superior*) in the superior portion of the ependymal roof of the fourth ventricle (Fig. 6). The superior and inferior border of this area

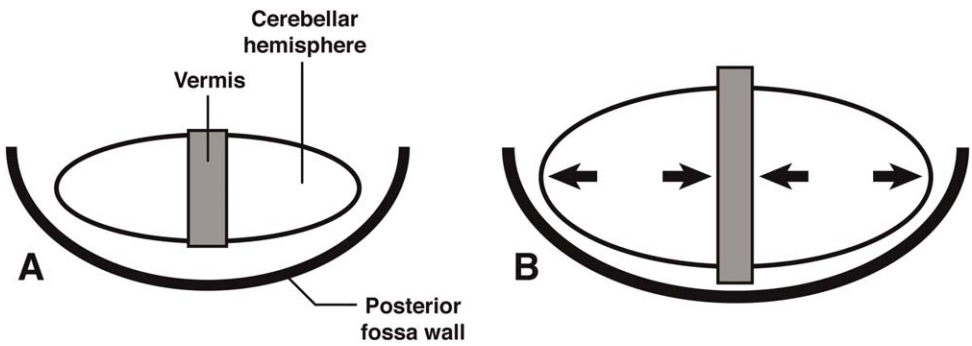

Fig. 5. Schema depicting the relative overcrowding of the posterior cranial fossa from the early (**A**) to the late (**B**) second trimester. Arrows indicate the conflict between the growing cerebellar hemispheres and the midline vermis and the wall of the posterior fossa. Slight degrees of overcrowding are favored because the transverse growth rate of the cerebellar hemispheres is greater than that of the posterior cranial fossa. Relative overcrowding is a normal event, beginning during the second trimester and continuing into the third trimester and early postnatal life. Exaggerated overcrowding as a result of a small posterior fossa can result in upward and downward herniation of the vermis.

was continuous with the ependymal layer, and its lateral borders were flanked by a hypercellular region of ependyma on either side. With further development of the rhombencephalon and formation of the pontine flexure, the rhombic roof is invaginated at the midpoint of its caudo-cephalic axis to be developed into the choroid plexus. At this stage, the area membranacea superior is separated from the inferior portion of the rhombencephalic roof by the primordium of the choroid plexus. Shortly thereafter, the area membranacea superior in the human embryo is replaced by the growth of ependymal cells originating from its proliferative lateral borders. At the same time, the ependymal lining below the invaginated roof also thins out and undergoes epithelial differentiation to form the *area membranacea inferior* (Fig. 6). The latter extends from the choroid plexus primordium superiorly to the obex inferiorly. The mesenchyme posterior to the area membranacea inferior is broken down, retaining only a pial layer and arachnoid strands extending from the condensed mesenchymal layer of dura mater to the area membranacea inferior. The space between the dura and area membranacea inferior develops into the cisterna magna. The inferior membrane, which separates the fourth ventricle from the developing cisterna magna, bulges backward and is covered internally by a thin ependymal layer.

The embryonic fate of the saccular invagination (outpouching or diverticulum) at the caudal portion of the rhombic roof was once a controversial topic (Wilson, 1937). Wilson cited Blake (1900) as stating that the saccular invagination gradually becomes larger and ultimately disappears in humans but not in lower mammals. With the degeneration of a considerable part of the caudal sac, its neck is retained at the margin of the foramen Magendie (Wilson, 1937). Thus, in adults, the rhombic roof is made up of the inferior medullary velum, tela choroidea, and the area membranacea inferior of Weed, the foramen Magendie being found in the middle portion of the latter. The

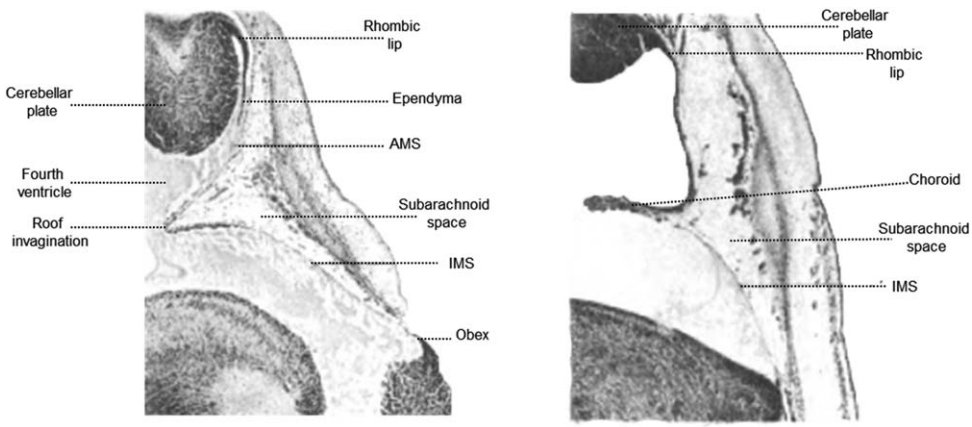

Fig. 6. Embryogenesis of the rhombic roof (reproduced from Weed (1917) with slight modifications). AMS, area membranacea superior; AMI, area membranacea inferior. Note the developing cerebellum is mainly intraventricular at these stages.

inferior medullary velum flanks the nodulus of the cerebellum (Wilson, 1937) and is in fact derived from the most caudal part of the metencephalic rhombic lip, the rostral part of which contributes to the flocculus.

Abnormal Cerebellar Development and Morphology Associated with Neural Tube Defects and the Chiari II Malformation

Prenatal period. In twin embryos of around 25 mm CRL (7–8 weeks), Padget (1972) made an interesting observation: one of the embryos had a lumbosacral spina bifida aperta and the other was normal. The posterior fossa and fourth ventricle (rhombic cavity) were smaller in the embryo with the neural tube defect. The cerebellar plates, which were intraventricular at this stage, were of similar size in the two embryos. The intraventricular cerebellar plates approximated each other in the dysraphic embryo with a small rhombic cavity and tended to fuse prematurely. Thus, the transverse diameter of the intraventricular cerebellum in the dysraphic embryo was diminished during the late embryonic period because of a small and unyielding posterior fossa. It can be assumed that if the later longitudinal growth of the extraventricular cerebellum occurs about a restricted transverse axis, the disproportionate longitudinal expansion (especially of the midline vermis) would result in its upward or downward herniation. A later stage of cerebellar development has been studied by van Hoytema and van den Berg in a fetus of 140 mm CRL with spina bifida aperta. In normal fetuses at this stage, the rhombic roof is being perforated and the cerebellum simultaneously undergoes an inward rotation such that its caudal part (i.e., caudal vermis) turns inside and into the fourth ventricle. In a fetus with spina bifida, however, the rhombic roof is thick and infiltrated by the choroid plexus and is only partially perforated; no inward rotation of the caudal cerebellum occurs, and the lower part of the vermis is pulled down by its arachnoidal attachments to the overcrowded choroid plexus and thick rhombic roof (van Hoytema and van den Berg, 1966). A substantially reduced transverse cerebellar diameter and obliterated cisterna magna have also been detected by ultrasound examination of fetuses older than 15 weeks with spina bifida (Pilu et al. 1988). Taken together, the subnormal cerebellar development in fetuses with spina bifida is characterized by a tendency toward early fusion of the cerebellar plates, restricted transverse growth, and failure of inward rotation of the caudal cerebellum.

Post-natal period. The total and lateral (hemispheric) cerebellar volumes are reduced in pediatric patients with Chiari II malformation (Salman et al. 2009). The vermian volume is near normal, but the midsagittal vermis area and longitudinal and anteroposterior diameters of the vermis are increased (Salman et al. 2009). This implies that (1) the cerebellum in patients with Chiari II malformation is smaller (secondary to hypoplasia or atrophy), (2) the hypoplasia or atrophy predominantly affects the lateral cerebellar hemispheres, and (3) elongation and expansion of the cerebellar vermis probably result from side-to-side compression by the two cerebellar hemispheres in an unyielding posterior cranial fossa. Moreover, while the absolute and relative (i.e., fraction of total) volumes of the posterior cerebellar lobe are reduced in Chiari II malformation, the absolute and relative volumes of the anterior cerebellar lobe are increased (Juranek et al. 2010). This also implies that the overall reduction in size of the cerebellar hemispheres in Chiari II malformation is related to subnormal growth of the posterior cerebellar lobe. The enlarged anterior cerebellar lobe could be a secondary compensation for the compromised posterior lobe (Juranek et al. 2010).

Rhombencephalosynapsis

Complete and partial rhombencephalosynapsis occurs rarely in association with the Chiari II malformation (Utsunomiya et al. 1998; Sener and Dzelzite, 2003). Rhombencephalosynapsis is an uncommon anomaly in which the two cerebellar hemispheres are fused. In its most complete form, the vermis is totally absent and the two cerebellar hemispheres and the dentate nuclei are fused or are in opposition with each other (Sener and Dzelzite, 2003). In partial rhombencephalosynapsis, the anterior vermis is usually absent and the posterior vermis is hypoplastic (Utsunomiya et al. 1998). The developmental origin of this malformation is controversial. It has been mentioned that the cerebellar primordium demonstrates a heterogeneous pattern of growth following midline fusion of the cerebellar plates. Generally, the growth of the vermis is slower than that of the lateral hemispheres. This differential growth pattern makes the median fused region (vermis) topographically distinct from the cerebellar hemispheres. Rhombencephalosynapsis is expected to occur if the growth of the vermis is either retarded following the early fusion or paradoxically enhanced to a level comparable to that of the cerebellar hemispheres. However, there is no direct evidence by which to assess this statement.

Agenesis or Occlusion of the Foramen of Magendie in Chiari I Malformation

In 1950, Gardner and Goodall reported 17 patients with Chiari I malformations with or without associated hydromyelia or basilar impression. All the patients had an occluded foramen of Magendie due either to atresia or to arachnoid adhesions between the impacted cerebellum and the medulla oblongata (Gardner and Goodall, 1950). Symptoms were relieved following release of this obstruction. Gardner et al. (1957) posited that the atresia or agenesis of the foramen of Magendie resulted from persisting remnants of the embryonic rhombic roof, which not only covers the foramen of Magendie but also occludes the foramina of Luschka laterally. Depending on the elasticity and permeability of this occluding membrane, a unified embryological theory was proposed accounting for Chiari malformation, Dandy-Walker syndrome, arachnoid cysts of the cerebellum and hydromyelia/syringomyelia. According to this account, if the occluding membrane is not

permeable the anomaly is severe. If the membrane is elastic, the fourth ventricle bulges into the cisterna magna and Dandy-Walker syndrome results. If it is not elastic, the Chiari malformation occurs. If the membrane is split, an arachnoid cyst appears between the two layers of the rhombic roof. Gardner et al. (1957) proposed that occlusion of the foramen of Magendie is physiologically more significant than that of the foramina of Luschka as the former is located in the midline and acts to dissipate the ventricular pulse wave substantially into the subarachnoid space. These findings faced skepticism when subsequent studies showed occlusion of the foramen of Magendie in only a small proportion of Chiari I patients (Tubbs et al. 2004a).

Development of the Tentorium Cerebelli

At the eighth week of fetal life, mesenchymal condensation of the cerebrocerebellar fissure intervening between the cerebellum and the occipital lobe of the cerebrum forms a small transverse fold on either side of the midbrain (Klintworth, 1967; Padget, 1972; Friede, 1981). These tentorial folds attach to the otic capsules laterally (Friede, 1981) and are symmetrical, initially separate, transparent, and histologically composed of a central core of loosely-packed mesodermal cells sandwiched between two layers of flattened mesodermal cells (Klintworth, 1967). The median fusion of the bilateral tentorial folds begins dorsally during the third month of the fetal period to form a single tentorium cerebelli. Once the dorsal tentorial fusion attains a considerable length (10 mm) at about the fifth week of gestation, the fusion is completed leaving a notch (i.e., tentorial incisura) between the ventral non-united portion of the tentorium through which the midbrain traverses (Klintworth, 1967). Henceforward, the growth of different parts of the tentorium continues more or less proportionally and the loosely-packed mesenchymal core is gradually replaced by dense collagenous tissue (Klintworth, 1967). The tentorium is subject to continuous traction because of differential encephalization (disproportionate growth of the cerebrum and cerebellum) (Friede, 1981; Jeffery, 2002b). This stretches the tentorial insertion over the otic capsules and results in enhanced bone deposition along its basicranial attachments corresponding to the crest of the petrous temporal bone, which marks the boundary of the posterior cranial fossa with the middle fossa (Friede, 1981).

From an evolutionary point of view, the tentorial folds fused relatively late in the evolution of mammals, and the ratio of the length of the fused tentorium to that of the incisura (known as the tentorial index) is greater among higher mammals (Klintworth, 1968). The tentorium cerebelli in humans has two other characteristics: it has the largest surface area relative to body size amongst primates and mammals and, comparatively, it is the most posteroinferiorly positioned (Jeffery, 2002b; Klintworth, 1967; Klintworth, 1968). Notably, in patients with Chiari II malformation, the tentorium is often dysplastic, its calvarial attachment is displaced inferiorly toward the foramen magnum, and the tentorial index is low (Peach, 1965; Gardner, 1973).

Posterior Cranial Fossa Volume and Its Determinants

Assuming that the posterior cranial fossa is a triaxial ellipsoid, its volume can be estimated by the following formula:

$$V = \frac{1}{6}\pi xyz$$

Where π is a constant approximately equal to 3.14, and x, y and z are respectively the width (maximum transverse diameter), length (distance from the dorsum sella to the internal occipital protuberance), and height (distance from the basion to the peak of the tentorium cerebelli corresponding to its ventral edge on the midsagittal plane) of the posterior cranial fossa (Greenlee et al. 1999). Any factor affecting the width, length and height of the posterior cranial fossa affects its volume proportionately. The bulk of evidence indicates that patients with Chiari I malformation have a small or overcrowded posterior fossa, albeit to a varying extent and pattern. It seems that a reduced height of the posterior fossa is the main culprit in most patients with Chiari I malformation (Schady et al. 1987; Stovner et al. 1993; Greenlee et al. 1999; Karagöz et al. 2002). The shallowness of the bony posterior fossa is a consequence of supraoccipital and basioccipital hypoplasia, platybasia, and basilar invagination. The length of the fossa can be low or normal in pediatric patients (Greenlee et al. 1999; Furtado et al. 2009), and is occasionally greater than normal in adult patients (Karagöz et al. 2002). Some have advocated that the increase in the length of the posterior fossa in adult patients with Chiari I malformation is a compensation for its reduced height (Nyland and Krogness, 1978; Karagöz et al. 2002). Only a few studies have measured the width of the fossa, and both reduced and normal widths have been reported among pediatric patients (Greenlee et al. 1999; Furtado et al. 2009). As mentioned earlier, the foramen magnum tends to be slightly bigger in Chiari I malformation. On the other hand, the small posterior fossa in Chiari II malformation is associated with a prominently enlarged foramen magnum (Burgener et al. 2002).

The boundary of the posterior cranial fossa is established by the end of the embryonic period. Initially, the posterior fossa is larger and partially opened posteriorly. During the third month, its posterior boundary is completed. Ventricular distension and cerebellar growth are among the main factors expanding the posterior fossa during the embryonic period and even later. Subsequently, the volume of the fossa is reduced by two main mechanisms: rotation of the tentorium, and petrous bone during the second and third trimesters. Cerebellar growth is well accommodated and the reduction in volume is compensated for by the growth of the basicranial synchondroses and upward reflection of the extensible tentorium.

Hormonal factors are also crucial in the growth of the posterior fossa. Any discordance between the mechanisms tending to reduce the volume and those tending to expand the posterior cranial fossa can potentially lead to a small fossa or more than normal crowding (i.e., overcrowding), hindbrain herniation being a consequence.

We conclude with a discussion of some of the factors affecting the size of the posterior fossa during the embryonic, fetal, and early postnatal periods.

1. Ventricular Distension

   The role of ventricular distention in expanding the posterior cranial fossa was studied by McLone and Knepper (1989) in a mouse embryo model with a caudal neural tube defect. With cerebrospinal fluid drainage through a defect in the neural tube, the cranial neurocele including the hindbrain vesicle partially collapses. The incomplete distension of the hindbrain vesicle leads to the formation of a small posterior fossa owing to the lack of adequate forces and mechanical induction necessary to expand the surrounding mesenchymal or chondrified primordium. McLone and Knepper (1989) proposed that a decrease in ventricular distension explains the occurrence of a small posterior fossa in Chiari II malformation. It should be noted that ventricular distension is only one factor influencing the size of the posterior fossa and affecting its dimensions during the embryonic and early fetal periods. Therefore, antenatal repair of the neural tube defect between 19 and 25 weeks of gestation does not affect the overall posterior fossa size during the late fetal period (Grant et al. 2011).

2. Rotation of the Intracranial Attachment of the Tentorium Cerebelli

   During the fetal period, the tentorium rotates backwards and downwards toward the foramen magnum (Jeffery, 2002b). The tentorial rotation ranges from 90° to 180° and mainly occurs in a fetus <160 mm CRL (before 22 weeks of fetal life), a period when the otic capsule is still precartilaginous or cartilaginous (Hochstetter, 1939; Moss et al. 1956; Butler, 1957; Spoor and Zonneveld, 1998; Lemire, 2000). Differential encephalization (i.e., greater expansion of the cerebrum in relation to the cerebellar expansion) is the main factor influencing this rotation and determining the final intracranial-tentorial attachment (Jeffery, 2002b; Spoor and Zonneveld, 1998). With the expansion of the supratentorial space and posteroinferior rotation of the tentorium, the infratentorial angle (the angle formed between the lines extending from the calvarial attachment of the tentorium to the center of the pituitary fossa and from the latter to the basion) decreases by ~40% between 10 and 22 weeks and by ~10% between 22 and 29 weeks of the fetal period (Jeffery, 2002b). The gradual cessation of tentorial rotation after 22 weeks of the fetal period corresponds temporally to the stage in which ossification of the otic capsule has just begun and is progressing. The posteroinferior tentorial rotation diminishes the volume of the posterior cranial fossa by reducing its height.

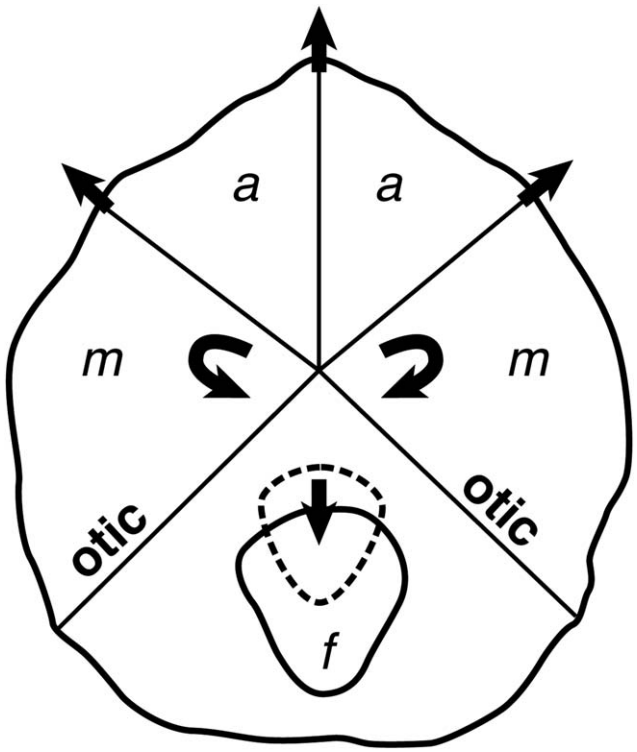

Fig. 7. The pattern of basicranial growth and rotation of the otic capsule (petrous temporal) during the second and third trimesters (from Lee et al. (1996) with slight modifications; reproduced with permission from John Wiley and Sons). Note that the anterior cranial fossa (*a*) extends forward, the middle cranial fossa (*m*) expands with backward rotation of the petrous, and the foramen magnum (*f*) enlarges and is displaced posteriorly with fetal growth.

3. Rotation of the Otic Cartilage and Petrous Temporal Bone and Shift in the Pattern of Posterior Cranial Fossa Growth

   By the end of third month of fetal life, the width and length of the posterior cranial fossa are similar, and the fossa is rather circular or funnel-shaped in outline. During the second trimester, the posterior fossa grows more in width than in length so it gradually becomes broader (Jeffery, 2002a). The preferentially transverse growth of the posterior fossa during the second trimester is concomitant with, and probably favored by, the predominantly transverse growth of the cerebellum. The late phase of fetal posterior fossa growth is characterized by more longitudinal growth concomitant with expansion of the middle cranial fossa. During the second half of fetal life, the otic cartilage and petrous temporal bone rotate backwards (Lee et al. 1996) (Fig. 7). This rotation is

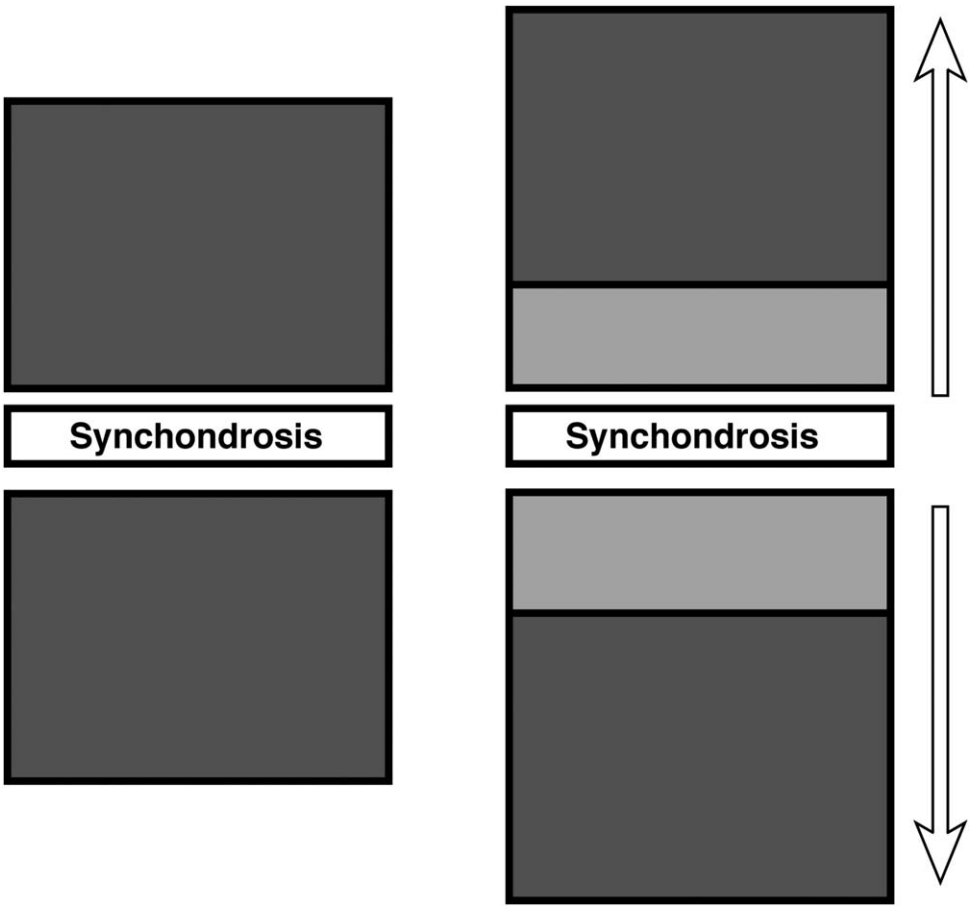

Fig. 8. Schema showing the growth of a synchondrosis with introduction of new bone into the flanking osseous segments and centrifugal displacement of those segments (Friede, 1981).

temporally and mechanistically distinct from the tentorial rotation. While the latter ceases around 20–22 weeks of fetal life, the former becomes more prominent following this period. Posteroinferior tentorial rotation occurs on a vertical plane and about a horizontal axis. In contrast, the backward rotation of the petrous bone is essentially on a horizontal plane and around a vertical axis. It results from expansion of the floor of the middle cranial fossa, which lodges the temporal lobe of the cerebrum (Lee et al. 1996). The squeezing of the posterior fossa tends to diminish its width along with the posterior rotation of the petrous bones. However, rapid anteroposterior elongation of the posterior fossa accommodates the growing cerebellum during the late fetal period (Lee et al. 1996).

4. Growth of the Basicranial Synchondroses

At the fifth month of fetal life, the wall of the posterior cranial fossa is composed of several osseous segments (basiocciput anteriorly, supraocciput posteriorly, and exocciputs and portions of the petromastoid temporal bone laterally) joined by the intervening synchondritic cartilages (Fig. 8) (Friede, 1981). Synchondrosis is a cartilaginous growth plate made up of a middle resting zone of quiescent chondrocytes sandwiched between pairs of proliferating and hypertrophic zones (McBratney-Owen et al. 2008). The growth of synchondrosis results in the deposition of new bone at the flanking osseous segments and growth of the basicranium (Fig. 7). The petrooccipital and occipitomastoid synchondroses contribute to the transverse growth of the posterior fossa, and the sphenooccipital, anterior and posterior intraoccipital and occipitomastoid synchondroses contribute to elongation (Friede, 1981). This growth, beginning as early as the fourth to fifth month of fetal life (Lee et al. 1996), continues into postnatal life until the synchondroses become non-functional and are replaced by sutures, which are then ossified and fully obliterated with the concomitant fusion of the adjacent bones (Madeline and Elster, 1995). The synchondroses show different rates of growth and

timing for closure between genders (Madeline and Elster, 1995). Generally, the posterior intraoccipital synchondrosis is the first to close, followed by the anterior intraoccipital synchondrosis and then the petrooccipital, occipitomastoid and sphenooccipital synchondroses (Madeline and Elster, 1995). Closure of the anterior and posterior intraoccipital and sphenooccipital synchondroses is usually later in males than females (Madeline and Elster, 1995).

Histologically, the middle resting zone contains the precursor cells of proliferating chondrocytes and is maintained by bone morphogenetic protein 3 (BMP3) (Kettunen et al. 2006). The maintenance of synchondrosis depends on the proliferation of chondrocytes (Matsushita et al. 2008) and the balance between the zones of proliferating and hypertrophied chondrocytes (Shum et al. 2003). The phenotypic transition from proliferating to hypertrophic chondrocytes and later to osteoblasts occurs toward the chondro-osseous junction of the synchondrosis and results in the introduction of new bone around the synchondrosis (Matsushita et al. 2008). Several mediators and signaling pathways control this transition. Fibroblast growth factor receptor isoform 3 (FGFR3) is expressed in the proliferating chondrocytes of the basicranial synchondroses (Rice et al. 2003). In a mouse model, overactivation of FGFR3 signaling resulted in a rapid phenotypic transition and accelerated closure of the synchondroses (Matsushita et al. 2008). BMP4 also exerts a biphasic effect on the basicranial synchondroses characterized by an early phase of enhanced proliferation of chondrocytes followed by an accelerated phase of transition into the hypertrophic phenotype (Shum et al. 2003). In humans, the sphenooccipital synchondrosis demonstrates a characteristically delayed postnatal closure. Its closure starts at eight years of age and is almost complete in 50% and 95% of individuals by the ages of 14 and 16–18 years, respectively (Madeline and Elster, 1995). Premature closure of the sphenooccipital synchondrosis is a suggested cause of clival hypoplasia (shortened clivus) in patients with Chiari I malformation (Noudel et al. 2009).

5. Upward Reflection of the Tentorium Cerebellum

Although generally considered a stiff membrane, the dura mater has considerable viscoelastic properties (Galford and McElhaney, 1970; Twomey and Tsui, 2007), enabling it to react to the tensions and forces applied to it with a rapid phase of expansion mediated by the elastic component and a slow phase mediated by the viscous component. In a cadaveric study, the dura mater had an extensibility of 10–30% (Kargapol'tseva, 1975). Connective tissues containing collagen fibers and elastin are also capable of remodelling by changing the intermolecular crosslinks to adapt maximally to mechanical stresses (Alter, 2004; Lundon, 2007). These properties of the tentorium enable it to reflect upwards and expand to compensate for the increased volume of the infratentorial contents. Although the short-term tentorial expansion is restricted by its viscoelasticity, remodelling of its fibers as a result of prolonged stress could lead to greater tentorial expansion in the long term.

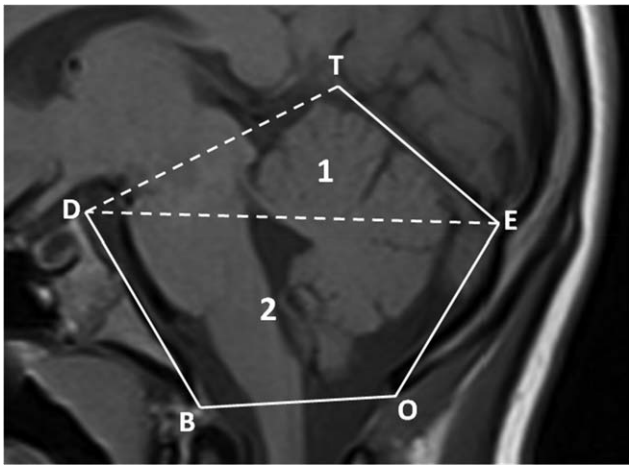

Fig. 9. A midsagittal plane of the posterior cranial fossa shows its divison into tentorial (1) and bony (2) regions. B, basion; D, dorsum sellae; E, endinion; O, opisthion; T, apex or peak of the tentorium. The T-E-O angle is the tentorial angle; T-E-D, the angle of the tentorium to Twining's line; D-E-O, the supraoccipital angle; E-D-B, the clival angle; and D-B-O, Boogard's angle.

Tentorial extensibility has important anatomical relevance. As mentioned earlier, a slight degree of overcrowding in the posterior cranial fossa is normal during fetal development. This ovcrowding pushes the expanding tentorium upwards. As the tentorium is peripherally attached to the inner surface of the occipital bone and the superior crest of the petrous bone and its attachments are fixed after the second trimester, tentorial expansion makes it concave downward. In the midsagittal plane, the ventral edge (apex) of the tentorium is the peak of this structure and is located above the upper level of the bony posterior fossa. Thus, the posterior fossa can be divided into two regions as shown in Figure 9. Unlike the lower bony region, the upper tentorial region ought to be expansile owing to the extensibility of the tentorium. In adult patients with Chiari I malformation, the tentorial region expands to compensate for overcrowding of the posterior fossa (Nishikawa et al. 1997).

6. Hormonal Influences

The basicranial synchondroses are homologous to the epiphyseal growth plates of the long bones. In experimental and human studies, endochondral and periosteal bone growth as well as bone turnover and remodelling are influenced by such hormones as tyroxine, cortisol,

estrogen, testosterone, parathyroid hormone, growth hormone, and activated vitamin D (cholecalciferol) (Raisz and Kream 1983a, 1983b, Raisz, 1988; Lombardi et al., 2011; Ohlsson et al. 1998; Wit and Camacho-Hübner, 2011; Ahmed et al. 2007). To what extent the growth of the posterior fossa is affected by these hormones and their disturbances is not yet clear. In vitro, hydrocortisone and parathyroid hormone dose-dependently enhance glycosaminoglycan synthesis by the chondrocytes derived from the sphenooccipital synchondrosis of the rabbit (Takano et al. 1987; Takigawa et al. 1988), and hydrocortisone and cholecalciferol increase the proliferation of these chodrocytes (Takigawa et al. 1988; Takano-Yamamoto et al. 1992). The sphenooccipital synchondrosis can remain open until the fourth decade of life in patients with hypothyroidism (Tubbs et al. 2003). The basiocciput is shorter in patients with growth hormone deficiency (Tubbs et al. 2003). The posterior fossa was significantly smaller in a series of patients with rickets than in healthy controls, and ~30% of those patients had Chiari I malformation (Tubbs et al. 2004b). These data indirectly indicate that various hormones regulate posterior fossa growth. Further studies are required to elucidate this aspect of development and especially the role of sex hormones.

CONCLUSIONS

Derailment of the developmental processes of the hindbrain can lead to a wide range of malformations such as the Chiari malformations. Therefore, a good working knowledge of this embryology as outlined in this review is important for those treating patients with involvement of this region of the central nervous system.

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