Developmental Anatomy

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4.1 Early Development of the Nervous System

Formation of the central nervous system (CNS) during embryonic life takes place in distinct stages. The three most important are gastrulation, primary neurulation and secondary neurulation. Gastrulation includes the ability of the ectodermal layer to develop the neuroectoderm, by a process known as neural induction. Primary neurulation forms the whole of the CNS, down to and including the conus, by closure of the developing neural tube. Secondary neurulation is the stage during which the cauda equina and the sacral elements are formed by a process of cavitation of a caudal cell mass. Secondary neurulation is not important for the development of Chiari or syringomyelia, which are both effects of primary neurulation.

4.1.1 Gastrulation

Early in the 2nd week of development, prior to implantation of the blastocyst, its inner cell mass (the embryoblast) develops into a two-layered structure, made up of a primitive ectoderm (the epiblast) and a primitive endoderm (the hypoblast). By the beginning of the third week, a 'primitive streak' has appeared on the dorsal surface of the ectodermal layer. This structure develops at what will become the caudal end of the embryo, but at the cranial end of the streak itself, a distinct elevation forms, as a result of proliferation of cells. This structure is known as

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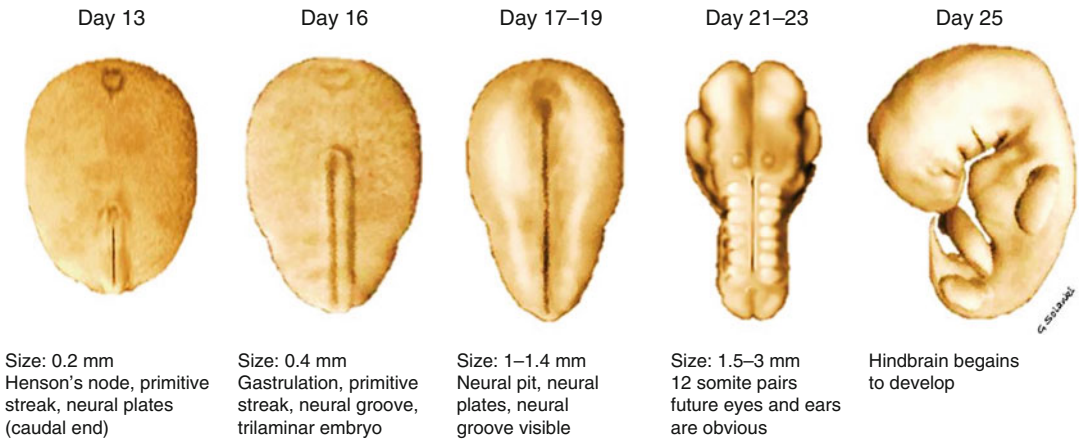

Fig. 4.1 Gastrulation and primary neurulation Embryo stages from development of Hensen's node on day 13 to closure of anterior neuropore on day 25

Hensen's node, and cells arising here begin to migrate into the interface between the ectoderm and endoderm, to form the mesodermal layer. This stage is known as gastrulation as it results in the formation of the primitive gut cavity, but it also defines the period in which the three basic germ cell layers form. Those mesodermal cells that migrate along the midline give rise to the notochord. The immediately overlying ectodermal cells then begin to develop into the neural plate, by a process referred to as neural induction. This neural plate becomes the source of the majority of neurons and glial cells in the mature mammal (Fig. 4.1).

4.1.2 Primary Neurulation

Further development of the neural plate begins the process of primary neurulation. This sees the plate begins to invaginate, between neural folds on each side of the midline. Cells at the top of the neural folds are referred to as neural crest cells. The neural folds then begin to fuse at several points, concomitant with the appearance of the budding somites.[1]

The main driving force for the shaping of the neural plate seems to be a medially directed movement of cells, with intercalation in the midline, leading to a narrowing and lengthening of the plate, a process known as convergent extension[2] (Keller et al. 2000; Copp et al. 2003), illustrated in Fig. 4.2. The result of this process is the formation of a tubular structure, below the surface of the ectoderm, by week 4 of development (Table 4.1). The cranial end of this neural tube (the anterior neuropore) seals by the 25th day, and its location, in the mature central nervous system, is represented by the lamina terminalis. The caudal end of the neural tube (the posterior neuropore) closes between 26 and 28 days (Norman et al. 1995) (Fig. 4.3).

This infolding of the neural plate is usually described as starting at the craniocervical junction and proceeding both rostrally and caudally, in a 'zipper'-like fashion. Recent evidence suggests, however, that the closure actually occurs simul-

[1] A somite, or primitive segment, is a division of the body of an animal. Somites form the vertebral column, dermis and skeletal muscle. They are derived from the paraxial mesoderm.

[2] Convergent extension is a mechanism of cellular morphogenesis, whereby cells within a structure converge and extend possibly by the action of actin-myosin contractions at cellular boundaries. The process is under the control of myosin regulatory chains found at these boundaries, which direct contraction of cell boundaries perpendicular to the axis of elongation and elongation along this axis. Structures that undergo convergent extension become elongated and thinned out without any net increase in cell volume or number. It is an important mechanism in the formation, extension and shaping of the neural tube.

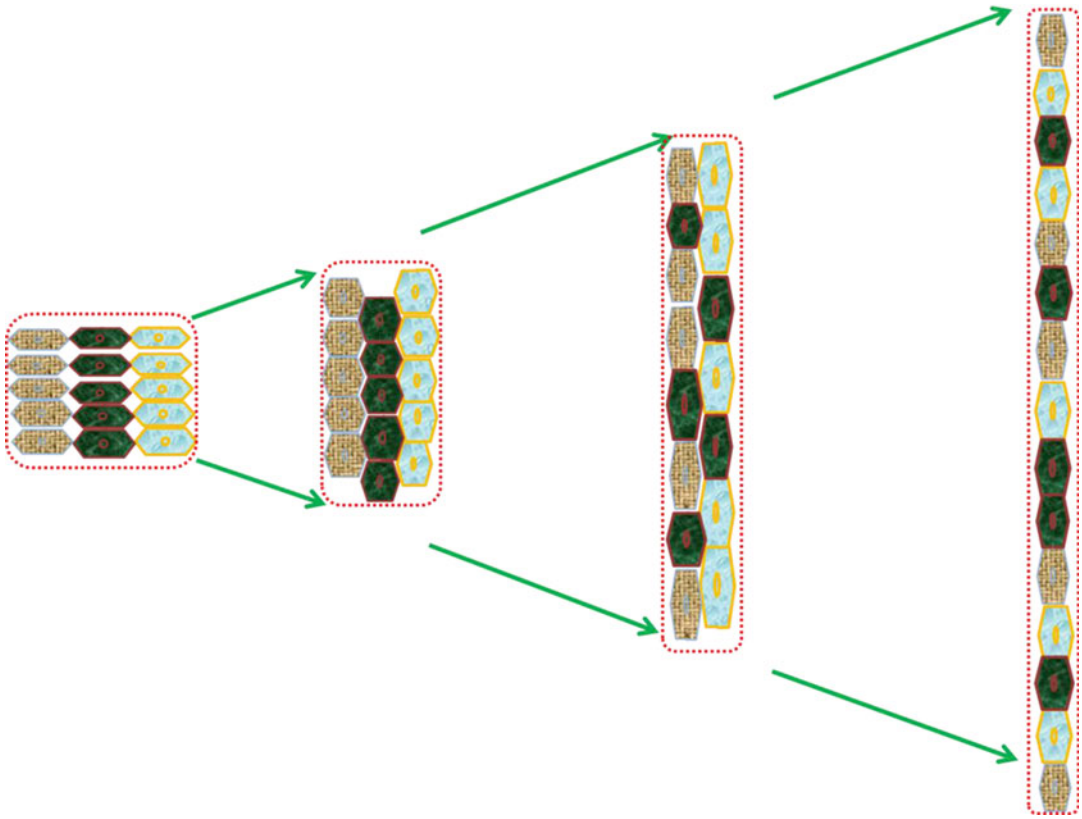

Fig. 4.2 Illustration depicting the mechanism of convergent extension. This results in gene-regulated convergence (narrowing) along one axis and extension (lengthening or elongation) in a perpendicular axis. The three cell layers first converge and intercalate causing constriction. Further morphogenesis occurs with contraction of exact cell boundaries perpendicular to growth direction and redistribution of cells into two layers along the growth axis with elongation in a sequential fashion. Finally reducing the cellular layer numbers on one axis (convergence) and adding these cells along the perpendicular elongation axis causes extension. Both gastrulation and primary neurulation cellular morphogenesis depend on effective convergent extension

Table 4.1 Stages in cranial neural tube closure

Shape of neural tube	Stage	Process
Biconvex	Inner biconvex morphology of neural folds	Expansion of the cranial mesoderm
Transitional	Dorsolateral neural plate bending	Under sonic hedgehog homologue signalling the apices of the neural folds begin to come into apposition in the dorsal midline
Biconcave	Midline approximation of neural folds	Contraction of subapical actin microfilaments is thought to be the process that pulls the folds together towards the midline
	Dorsal neural crest cell migration	Emigration of the neural crest occurs as the midline approximates and thins down. Timing differs between cranial and spinal ends
	Ventral plate neuroepithelial cell deposition	Maintenance of a proliferative neuroepithelium
Tubular	Midline neural plate	Believed to be an apoptotic process
	Neural tube separation from dorsal epithelium	Apical apoptotic cell death is involved in epithelial remodelling following closure

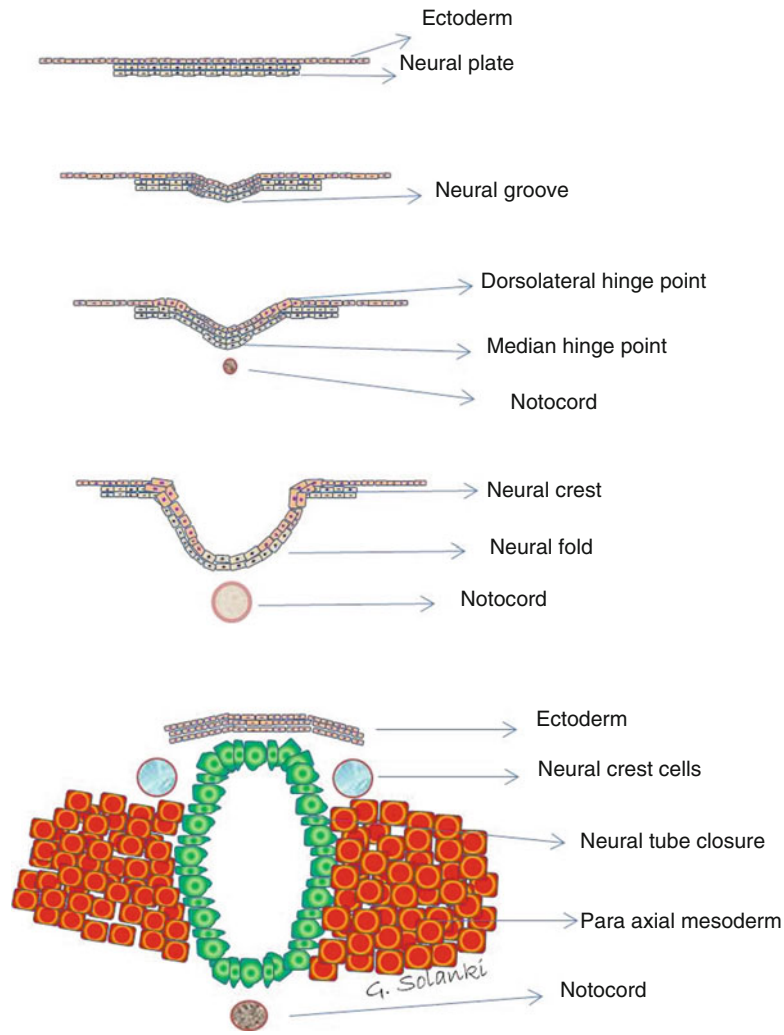

Fig. 4.3 Primary neurulation. The ectoderm germ layer by a process of columnarisation forms a thickening, the flat neural plate. The neural plate then grooves and develops a medial hinge point, folds in upon itself, developing bilateral dorsolateral hinge points and neural crests. As the neural folds are pushed upwards and towards the midline by the expanding paraxial mesoderm, the neural crest cells separate from the neuroectoderm which begins to separate from the ectoderm by a process of apoptosis. This process is achieved by neural plate switching from expressing E-cadherin to N-cadherin and N-CAM expression. This allows the approximating neural tube in the midline to recognise as the same tissue and close the neural tube

taneously at multiple sites. In the mouse embryo, for example, neural tube closure initiates at three distinct locations, with an intermittent pattern of subsequent closure (Golden and Chernoff 1993). A study of neural tube defects in human embryos indicated that five closure sites exist (Van Allen et al. 1993), and other investigators have confirmed these views (Ahmad and Mahapatra 2009; Nakatsu et al. 2000), suggesting that the mode of closure in humans is different from that in other animal species. Sites identified as points of initiation include the future cervical region, the mesencephalic-rhombencephalic boundary, the anterior neuropore and the posterior neuropore. The existence of multiple simultaneous closure points help to explain why neural tube defects occur preferentially at certain sites. Examples include the lumbosacral myelomeningocoele and frontal and occipital meningo-encephalocoeles.

It is also becoming clear that neural tube closure is dependent on an apoptotic process, rather than just a proliferative growth of cells that meet in the midline. In an experimental study in chicken embryos, the apoptosis inhibitor Zvad-fmk[3] was shown to prevent cell death in the neural plate and to inhibit neural tube closure.

[3] Zvad-fmk (carbobenzoxy-valyl-alanyl-aspartyl-[*O*-methyl]-fluoromethylketone) is a cell-permeant pan caspase inhibitor that irreversibly binds to the catalytic site of caspase proteases. In this way it inhibits the induction of apoptosis.

Furthermore, the way in which brain and spinal cord components of the neural tube close differs. In the spinal region, the neural tube closes first, and outward migration of neural crest cells only begins several hours after this process is complete (Franz 1992). This contrasts with the cranial closure, where outward migration of the neural crest cells occurs before closure. Indeed, it is likely that neural crest migration is required to trigger the neural tube closure at this level.

Primary neurulation subserves the future development of the whole of the central nervous system. As a result, the vast majority of CNS anomalies, ranging from fatal deformities such as anencephaly to open neural tube defects, occur during this stage. The causes of most of these brain anomalies are still unknown (Norman et al. 1995), although advances in genetics and developmental embryology, as well as various clinical studies, looking at congenital conditions and their causes, genetic or otherwise, have found new mutations. Their effects on children and adults with brain anomalies or malfunctions are identifying an increasing number of responsible chromosomal aberrations, single gene mutations and extrinsic teratogens.

The period of time for which a deformed embryo survives is determined by the type and location of the neural tube defects. Almost all embryos with total dysraphism die by 5 weeks of gestation, and those with an opening over the rhombencephalon die by 6.5 weeks. In contrast, those with a defect at the frontal and parietal regions may survive beyond 7 weeks (Nakatsu et al. 2000). For example, even when there is severe failure of neural tube closure anteriorly, such as leading to anencephaly, the foetus may survive even to birth, although the condition is always fatal thereafter. This suggests that, in terms of survival of an embryo, normal development of the hindbrain is more important than development of the forebrain or the distal spine.

Spina bifida occurs from failure of posterior tube closure. Two varieties may arise, referred to as spina bifida aperta and spina bifida occulta. In the former, the neural elements are openly exposed with sometimes leaking CSF through thin dysplastic skin. Its most severe form leads to an open neural tube placode with cauda equina nerves lying outside of the spinal canal in a myelomeningocoele pouch. Less severe forms include dermal sinuses and meningocoele sacs. In spinal bifida occulta the anomaly includes open laminae and perhaps a neural tube lesion but covered by intact muscle and skin.

4.1.3 Molecular Control of Primary Neurulation

Differentiation of ectodermal cells into skin cells is regulated by the action of a protein, known as bone morphogenetic protein (BMP). Normally BMP4 causes ectodermal cells to differentiate into epidermis. During neural induction, however, two proteins, known as Noggin and Chordin, are produced by the notochord and its enveloping mesoderm. They diffuse locally into the overlying ectoderm and inhibit the activity of BMP4, allowing these cells to differentiate into neural cells. Thereafter closure of the dorsal neural tube is patterned in two stages, midline neural plate closure and neural tube separation from the dorsal epithelium. It is believed that these processes are brought about by a combination of programmed cell death, on the one hand, and epithelial remodelling, on the other hand, probably modulated once again by BMP4.

Development of the dorsal neural plate (the alar plate) is controlled by its flanking ectodermal plate. Initial growth of the ventral part (the basal plate) is organised by the notochord, which regulates much of the development of the nervous system (Jessell et al. 2000). The ventral neural tube is subsequently patterned by the protein sonic hedgehog homologue (SHH).[4] Sonic hedgehog plays a key role in regulating vertebrate organ formation, including organisation of the brain and growth of digits on limbs. It also controls cell division of adult stem cells and has been implicated in the development of some cancers, such as medulloblastomas, which mostly

[4] Sonic hedgehog homologue (SHH) is one of three proteins in the mammalian signalling pathway family called hedgehog; desert hedgehog (DHH) and Indian hedgehog (IHH) are the other two. Sonic hedgehog was named after Sega's video game character Sonic the Hedgehog.

occur in the region of the hindbrain. Sonic hedgehog can function in different ways, according to the cellular substrate upon which it acts. It also has different effects on the cells of the developing embryo, depending on its concentration. Basal (floor) plate-derived SHH subsequently signals to other cells in the neural tube and is essential for proper specification of ventral neuron progenitor domains.

SHH binds to a protein, named protein-patched homologue 1 (PTCH1). This then results in uncoupling of PTCH from a receptor named smoothened. This in turn results in activation of the Gli family of transcription factors (Gli1, Gli2 and Gli3), which are the ultimate effectors of this SHH signalling. In this context SHH acts as a morphogen, inducing cell differentiation dependent on its concentration. At low concentrations it promotes formation of ventral interneurons; at higher concentrations it induces motor neuron development, and at highest concentrations it induces floor plate differentiation. Failure of SHH-modulated differentiation results in holoprosencephaly, a condition where there is failure of midline clefting of the forebrain, with cortex crossing the midline, often associated with agenesis of the corpus callosum and a single midline thalamic mass.

4.2 Development of the Spinal Cord

As the spinal part of the neural tube develops, neuroblasts proliferate in two zones, creating the characteristic butterfly-shaped mantle of grey matter seen in cross section. The lateral walls of the tube thicken but leave a shallow, internal, longitudinal groove called the sulcus limitans, which separates the developing grey matter into a dorsal (alar) plate and a ventral (basal) plate. The sulcus limitans extends the length of the spinal cord and beyond to the mesencephalon. Cell bodies in the alar plate form the nuclei, which make up the uninterrupted dorsal column of grey matter (Fig. 4.4). These nuclei receive and relay input from somatic and visceral afferent neurons, whose fibres run in the dorsal roots of spinal nerves. In the basal plate, cells likewise form an uninterrupted column of ventral grey matter that extends the length of the cord. Axons of these efferent neurons project motor fibres to skeletal muscle and make up the ventral roots of the spinal nerves. Further proliferation and bulging of alar and basal plates results in the formation of the external longitudinally running dorsal median septum and ventral median sulcus.

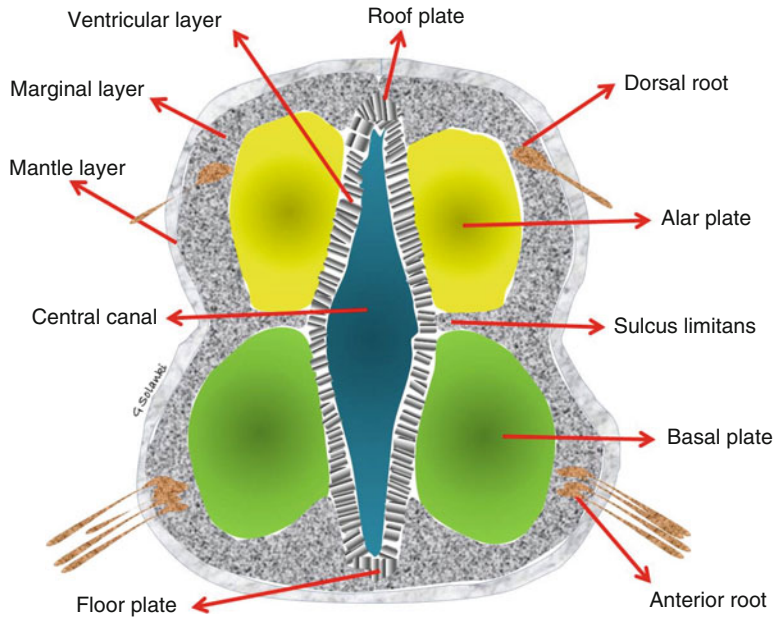

Fig. 4.4 The spinal cord
Three layers (ventricular, mantle and marginal) develop from the neural tube.
The ventricular layer contains undifferentiated neurons.
The grey matter of the spinal cord will develop from differentiating neurons in the mantle layer and the white matter from the nerve fibres in the marginal layer

Concurrently the lumen of the neural tube becomes reduced to a small central canal. Addition of longitudinally running intersegmental axons, long ascending and descending axons and incoming dorsal root sensory fibres, on the outside of this grey matter, creates a marginal layer. Beginning in the 4th month, these fibres acquire myelin sheaths and form the white matter of the cord.

4.3 Formation of the Brain

Progressive dilatation and folding into flexures of the cranial end of the neural tube creates three distinct, primitive brain vesicles, the prosencephalon, the mesencephalon and the rhombencephalon. The mesencephalon remains undivided, to form the future cerebral peduncles and quadrigeminal plate. The alar and basal plates of the prosencephalon, on the other hand, will divide to form the telencephalon and diencephalon, respectively. The optic vesicles, which will develop into the optic nerves, retinas and irises, expand out from lateral extensions of the diencephalon. The cerebral hemispheres develop from the dorsal alar plate of the telencephalon. The basal and alar rhombencephalic plates will form the metencephalon (future pons and cerebellum) and myelencephalon (future medulla oblongata). Different parts of the future basal ganglia (nuclei basales) arise separately, the caudate nucleus and the putamen from the alar plate telencephalon and the globus pallidus, from basal plate diencephalon. The thalamus and hypothalamus also arise from basal plate diencephalon.

4.3.1 The Brainstem

Neuroblasts of the brainstem develop in a manner similar to those in the spinal cord. Alar and basal plates form sensory and motor columns of cells that supply cranial nerves, but the topographical layout of these nuclei differs in the brainstem, as compared with the cord. The mesencephalon remains undivided and consists of the basal midbrain and alar quadrigeminal plate. The pons consists of two parts, the basis pontis and the pontine tegmentum. The former is ventrally located and is phylogenetically newer. The latter is the older portion, is dorsal in position and is continuous with the medulla. The pontine tegmentum and the medulla together form the floor of the fourth ventricle. Here, the alar and basal plates are separated by a sulcus limitans, but unlike in the spinal cord, they are disposed laterally and medially, instead of dorsal and ventral. With continued development, alar and basal plates shift laterally but retain their respective functions, with the alar plates containing afferent nuclei and the basal plates forming efferent nuclei. Portions of the alar plate migrate ventrally and form the inferior olivary nucleus. Nuclei of the basis pontis migrate there from the alar plate. They receive synapses of cortically originating fibres. Medullary pyramids consist of fibres from the cerebral cortex and develop on the ventral surface near the midline

4.3.2 The Cerebellum

Caudal to the mesencephalon lies the metencephalon, which is the rostral portion of the hindbrain. It differentiates into two major structures, the cerebellum and the pons. At the rostral edge of the roof of the fourth ventricle lie the rhombic lips, which arise from the dorsolateral alar plates of the rhombencephalon. At about the fifth or sixth week, these lips start forming the cerebellar primordia. Their growth and infolding into each other causes them to fuse in the midline, creating the cerebellar plate, which covers the fourth ventricle caudal to the mesencephalon. Although the cerebellum accounts for approximately 10 % of the human brain's volume, it contains over 50 % of the total number of neurons in the brain. The cerebellum, like the frontal lobe, is the last of the structures to develop. Chiari tonsillar descent, for example, has not been identified earlier than 10 weeks on antenatal ultrasound scans (Blaas et al. 2000). Another example of the effect of disordered

Table 4.2 Components of the basal and alar plates

Basal plate components	Alar plate components
Nucleus of cranial nerve VI	Vestibulocochlear components of cranial nerve VIII
Motor components to muscle of branchiomeric origin of cranial nerves V and VII	Trigeminal sensory for pain and temperature, cranial nerve V
Superior salivary nucleus of cranial nerve VII	Solitary nucleus for taste and visceral sensation of cranial nerves VII, IX and X
	Pontine nuclei in the basis pontis upon which corticofugal fibres terminate

development and growth on this late maturation is seen in severe prematurity,[5] where cerebellar function and volume may be affected. Recent evidence shows that individuals born very preterm have significantly smaller cerebella than their term-born peers, and that this difference remains statistically significant after controlling for whole brain volume and other potentially confounding variables (Allin et al. 2001).

4.3.3 The Cranial Nerves

By the 5th week of gestation, all cranial nerves are recognisable except for the olfactory and optic nerves. The pure motor cranial nerves (III, IV, VI and XII) have no external ganglia and arise from the basal (motor) plate. Sensory nerves have conspicuous ganglia near the brain and most have motor components, except for the eighth. Apart from the third and fourth cranial nerves, which arise from the midbrain, the 5th to the 12th cranial nerves arise from the rhombencephalon (Table 4.2). *Hox* genes play an important role in temporospatial development of motor neurons of the trigeminal and facial nerves, as we will see later.

[5] Severe prematurity or extremely premature or extremely low GA (gestational age) refers to the youngest of premature newborns, usually born at 27 weeks' gestational age or younger. These infants also have an extremely low birth weight defined as a birth weight of less than 1,000 g (2 lb, 3 oz).

4.3.4 The Ventricular System

The cranial part of the neural canal (lumen of neural tube) forms the ventricular system of the brain. The shape of the ventricles is determined by the brain folding around the two primary flexures (cephalic and cervical), forming three primitive vesicles, during week 4 of gestation. These bends arise as a result of tremendous cell proliferation, occurring within the confined space of the cranial vault, causing the neural tube to buckle as the brain develops. Towards the end of week 4 and early into week 5, the primitive 3-vesicle brain divides further to become a 5-vesicle structure. Each vesicle contains its own ventricle (Table 4.3). The prosencephalon gives rise to paired lateral telencephalic vesicles, which become the cerebral hemispheres. It also forms the diencephalon, from which the optic vesicles also extend. During week 6, in the 5-vesicle stage, the pontine flexure develops. This divides the rhombencephalon into a rostral metencephalon, which will form the pons and cerebellum, and a caudal myelencephalon, which becomes the medulla. Later, the disproportionate expansion of the cerebral hemispheres alters the configuration of the lateral ventricles, which become 'C'-shaped. These flexures also create specific narrowings within the ventricles. The foramina of Monro are located at the level of the telencephalon/diencephalon division. The cerebral aqueduct remains as a relatively simple tubular channel within the unflexed mesencephalon. During the fifth and sixth weeks, the roof of the fourth ventricle thins out in the midline to form the foramen of Magendie and, laterally, the foramen of Luschka (Melsen 1974; Koseki et al. 1993). By approximately the 7th week, a connection between the fourth ventricle and the subarachnoid space is established. The foramina of Luschka and Magendie lie at the division of the rostral metencephalon and caudal myelencephalon. More caudally, below the cervical flexure, the central canal lies within and along the spinal cord.

The development of the three primary vesicles (5th week) and subsequently, at 7 weeks, the five secondary vesicles (telencephalon, diencephalon,

Table 4.3 Development of the flexures, ventricular system and foramina

Timing	Event	Flexures	Primitive vesicles	Secondary vesicles	Future ventricles
Early 4th week Day 22	Neural tube closure and primary neurulation start	Cephalic and Cervical	Prosencephalon Mesencephalon Rhombencephalon		
5th week	Primary vesicles subdivide. Future foramina of Monro will form between forebrain and midbrain	Cephalic	Prosencephalon	Telencephalic Diencephalic	Paired lateral ventricles Third ventricle
	Does not divide		Mesencephalon	Mesencephalic	Cerebral aqueduct
	Pontine flexure develops. Separates pons and cerebellum from medulla at level of future foramina of Luschka and Magendie	Pontine	Rhombencephalon	Metencephalic Myelencephalic	Fourth ventricle
	Cervical or cervicomedullary flexure separates medulla from the spinal cord (future foramen magnum)	Cervical			Vestigial central canal of the spinal cord

mesencephalon, metencephalon and myelencephalon) is accomplished by the development of flexures. These flexures may also help maintain the CSF between them in a state of tension, so as to expand the ventricular system in an asymmetric way. Our ventricular system was moulded by flexural kinks into different shapes and sizes, aided by the moulding weight of the developing brain around it (Fig. 4.5). The hydrostatic tension within the ventricles acts as a vital scaffold upon which the parenchyma develops and grows. Premature unfolding of a particular flexure will impact on the CSF tension within the corresponding vesicle and almost certainly cause a degree of collapse of the dorsal structures upon it. Hypothetically, if the distal pontine flexure – which develops around the seventh week, between the pons, cerebellum and medulla oblongata – and/or the cervical flexure were to 'unkink', then this could result in lesser tension in the metencephalic vesicle and a smaller posterior fossa, as seen in occipital somite (skull base) development anomalies. On the other hand, if there was a continuous caudal CSF leak, as we see with leaking myelomeningocoeles, then the normal tension within the ventricular system would be reduced. The effect would be a sequential collapse of dorsal structures upon the floppy metencephalic and myelencephalic vesicle centres, causing a small posterior fossa and its caudal dislocation. An inward suction/decompression effect on the most rostral part of the ventricle could also occur, leading to flattening of the forehead. This may hypothetically explain why foetuses develop the typical lemon appearance of the forehead and the banana sign[6] on ultrasounds of myelomeningocoele and Chiari II malformation. It may also help explain the tectal

[6] An early cranial ultrasound may give indirect signs of myelomeningocoele-derived loss of CSF and hindbrain hernia, even before the actual spinal lesion can be observed. At the level of the cerebellum and cistern magna, unwinding of the nearest (pontine) flexure, due to CSF leakage in the lumbosacral spine, likely releases the hydrostatic CSF pressure maintaining the posterior fossa 'scaffold' and causes descent and herniation of the cerebellar vermis through the foramen magnum, giving the cerebellum the appearance of a banana. Frontally, on both sides of the metopic suture (in between the two frontal bones), a depression or buckling occurs, giving the anterior calvarium the pointed shape of a lemon (the 'lemon sign'). Both signs are associated with and the consequence of spina bifida aperta and associated with Chiari II malformation. Once the CSF tension drops through the pontine flexure, the whole ventricular axis may be affected. It is interesting to note that, if the spinal leak is sealed antenatally by the second trimester, the Chiari II malformation is less severe or does not occur.

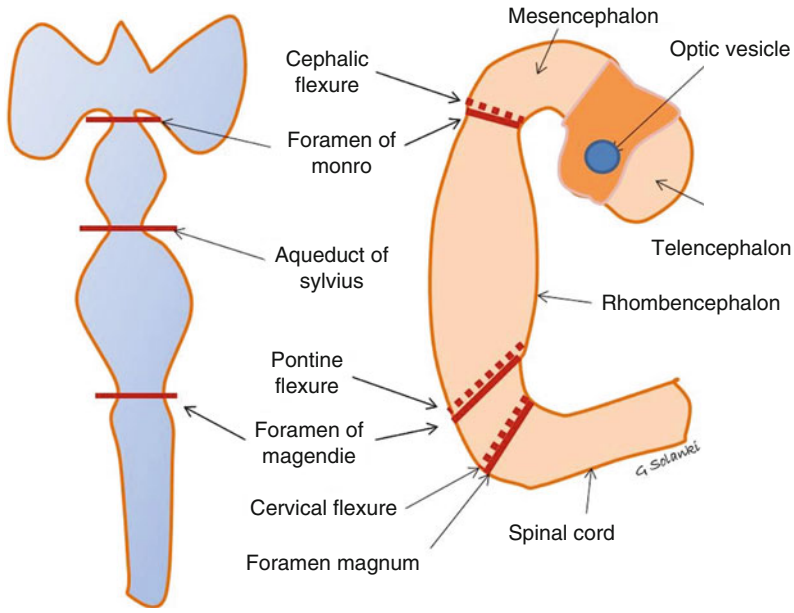

Fig. 4.5 Development of the ventricular system Neural canal develops two flexures and three vesicles. Remodelling and mantle laying of grey matter deforms the canal further into three flexures and five vesicles. The two original flexures are at the level of the foramen of Monro and foramen magnum. Above the future foramina of Monro, the prosencephalon divides into two vesicles, the mesencephalon and diencephalon. A further flexure, known as the pontine flexure, develops in the rhombencephalon, splitting it into a rostral metencephalon (the future pons and cerebellum) and a caudal myelencephalon (the future medulla oblongata). This occurs at the level of the future lateral foramina of Luschka and medial foramen of Magendie. Flexures help maintain tension within the ventricles, which may act as an internal scaffold for the mantle layer cellular proliferation

beaking and neuronal migration disorders seen in association with Chiari II malformations and myelomeningocoele.

4.4 Development of Mesodermal Elements

The neural tube and its future coverings develop hand in hand. As the folding of the neural tube progresses, it becomes surrounded ventrally by the mesoderm-derived notochord, dorsolaterally by the paraxial mesoderm and neural crest cells and in the midline dorsally, by the ectoderm.

4.4.1 Somite Development

Somites are masses of mesoderm, distributed along the two sides of the neural tube, that will eventually become dermis (dermatome), skeletal muscle (myotome) and vertebrae (sclerotome). During the 4th week of gestation, 42 somites are formed. These are made up of 4 occipital somites, 8 cervical, 12 thoracic and 5 lumbar; the remainder are sacrococcygeal (Muller and O'Rahilly 1980; Gasser 1976; Arcy 1965) . Each somite then differentiates into an outer dermatome, an inner myotome and a medial sclerotome (Fig. 4.6). Because the sclerotome differentiates before the other two components, the term 'dermomyotome' is sometimes used to describe the combined dermatome and myotome. Each sclerotome has three parts, a hypocentrum, a centrum and a neural arch. The first four sclerotomes go on to form the skull base and the foramen magnum. The hypocentrum forms different structures at each level (see Table 4.4). The sclerotomes are ventromedial to the neural tube and will surround the notochord and go on to form the vertebral bodies. This topography means that the skull base develops ventral to the rostral notochord (Melsen 1974).

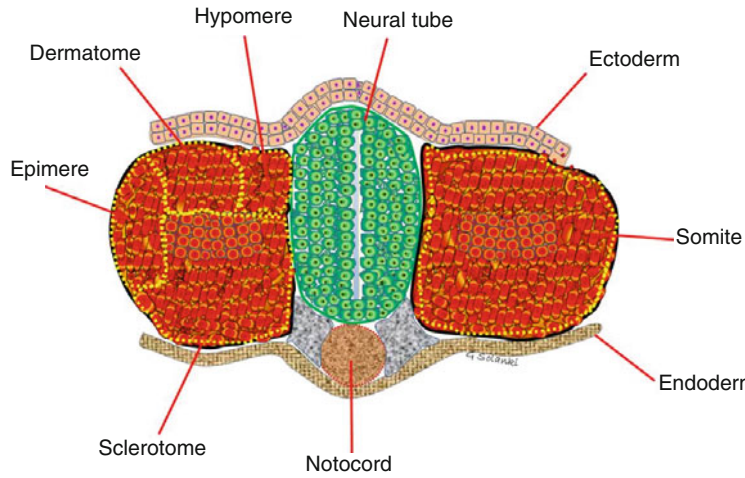

Fig. 4.6 Budding somite derived from paraxial mesoderm The sclerotome lies ventromedially, adjacent to the neural tube. After its detachment the remaining somite is known as dermomyotome. The dermomyotome splits to form the dermatome and the myotome and then the myotome splits into epimeres, which form the deep muscles of the back, and hypomeres, which form the musculature of the lateral and anterior body wall

Table 4.4 Structures developed from occipital and first two spinal sclerotomes

Origin	Process/division	Anatomical part
Neural crest cell derived	Membranous ossification	Skull vortex and calvarium
All four occipital sclerotomes, derived from the paraxial mesoderm	Enchondrosis	Skull base
1st and 2nd occipital sclerotomes		Clivus – basiocciput
3rd occipital sclerotome	Exoccipital bone	Jugular tubercles
4th occipital sclerotome (proatlas)	Hypocentrum	Anterior tubercle of clivus
	Centrum	Dens apex
		Apical ligament
	Ventral neural arch	Basion - anterior margin of foramen magnum
		Occipital condyles
		Midline third occipital condyle
	Lateral neural arch	Cruciate ligament
		Alar ligaments
	Caudal neural arch	C2 lateral mass
		Superior portion of posterior arch of C1
	Dorsal fusion of first 4 sclerotomes	Posterior margin of FM
		Occipital bone
1st spinal sclerotome	Hypocentrum	Anterior arch of C1
	Centrum	Dens
	Neural arch	Inferior portion of posterior arch of C1
	Hypocentrum	Disappears
2nd spinal sclerotome	Centrum	Body of axis
	Neural arch	Facets
		Posterior arch of atlas

The clivus and the occipital bone and, hence, the foramen magnum are derived from the four occipital somites. The first two occipital sclerotomes give rise to the basiocciput (Fig. 4.7). The tip of clivus, the anterior tubercle of the C1, the dens apex and the apical ligament are derived from the fourth occipital sclerotome, otherwise referred to as the proatlas (Menezes 1996; Gladstone and Wakeley 1925; Gasser 1976). The anterior margin of the foramen magnum, as well as the occipital condyles and the midline third occipital condyle (Fig. 4.8), arises from the ventral portion of the proatlas (Prescher et al. 1996). The cruciate ligament

and the alar ligaments arise from the lateral part of proatlas. The C2 lateral mass and the superior portion of the posterior arch of the atlas develop from the caudal proatlas. The posterior rim of the foramen magnum and the occiput develop from the dorsal fusion of the first four (occipital) sclerotomes. The odontoid process and the atlas vertebra are formed from the first spinal sclerotome. The atlas shows several ossification centres in development (Keynes and Stern 1988). While the lateral masses of C2 are present at birth, complete ossification may not occur until about 3 years of age when a complete ring may then be seen. The dens is the central portion of the first sclerotome, which fuses with the axis body. The neural arch of this first spinal sclerotome proceeds to form the posterior and inferior portion of the C1 arch (Menezes 1995; Koseki et al. 1993). With further development, the hypocentrum of the second spinal sclerotome disappears, but the centrum goes on to form the body of the axis body. Division of the neural arch forms the facets and the posterior arch of the axis vertebra (Keynes and Stern 1988). In summary, most of the dens develops from the first spinal sclerotome, but the terminal portion of the odontoid process arises from the proatlas, and the most inferior portion of the axis body is formed by the second spinal sclerotome (Table 4.4).

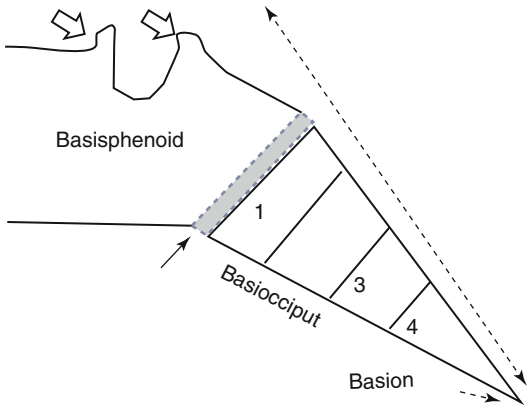

Fig. 4.7 The clivus The clivus is made up from the basisphenoid, the basiocciput and the sphenooccipital synchondrosis (*closed arrow*), as well as the anterior and posterior clinoids – otherwise referred to as the basiendosphenoid (*open arrows*). It also includes the basion, which forms the anterior lip of foramen magnum. The basiocciput is formed by the occipital sclerotomes. The basion is formed by the 4th occipital sclerotome, or proatlas. Anomalies of the 4th occipital sclerotome are associated with Chiari malformations

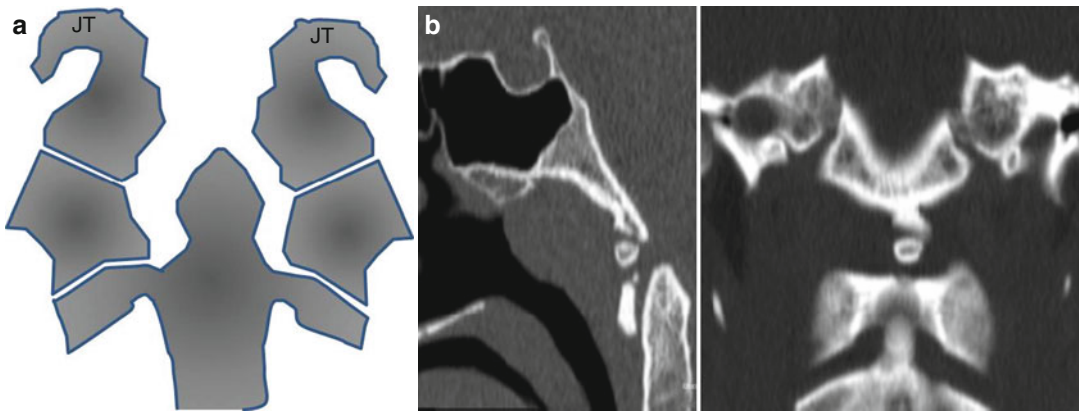

Fig. 4.8 (**a**) Bony structures related to the lateral boundaries of the foramen magnum**.** In higher vertebrates, the foramen magnum is surrounded by a ring of four bones. They arise from the third occipital sclerotome. The basioccipital bone lies in front of the opening, the two exoccipitals lie to either side, and the larger supraoccipital lies posteriorly. The jugular tubercles (*JT*) arise from the two exoccipital bones, which lie lateral to the foramen magnum. (**b**) Third occipital condyle. (*a*) CT sagittal. (*b*) Coronal multiplanar reconstruction. The third occipital condyle (condylus tertius or median occipital condyle) was first described by J.F. Meckel in 1815. It is a bony process in the anterior midline of the foramen magnum, forming a rudimentary articulation above the C1 arch. It sometimes persists into adult life

4.4.2 Development of the Skull

The skull develops by two different processes. The calvarium and facial bones develop by membranous ossification (Kessel and Gruss 1991; Christ and Wilting 1992; Dietrich and Kessel 1997) as does the occipital skull above the nuchal line, although this component is thought to arise, originally, from neural crest cells, rather than from the paraxial mesoderm. The skull base and the remainder of the occipital bone develop from a cartilaginous framework, in which deposition of bone occurs. This process is driven mainly by distorting forces generated by the developing brain. Just as remodelling of the anterior cranial fossa occurs as the prosencephalon folds down, posterior fossa expansion occurs following the growth of its neural contents. In response to the pontine and medullary enlargement, the clivus elongates at the basiocciput and lowers the front margin of the foramen magnum. Downward cerebellar displacement pushes the opisthion downward and backward. These processes result from a combination of endochondral resorption and sutural growth.

Some parts of the skull base also continue to develop later in life, in response to the growth of surrounding structures. For example, growth of the sphenooccipital and sphenopetrosal synchondrosis, along with adjacent endochondral and intramembranous ossification, results in an elongation of the clivus and the posterior skull base (Menezes 1998). This process can continue until late adolescence and will ultimately model the final shape and size of the posterior fossa.

4.4.3 Genetic Control of Mesodermal Growth

The process of segmentation at the craniocervical junction and along the spine is tightly regulated by control genes. Proteins promoted by these genes modulate the transcription of specific downstream genes, thereby controlling morphogenesis and providing specific identify for each vertebra (Lufkin et al. 1992). The main genetic groups involved in mesodermal and neuroectodermal development of the craniocervical junction are the *SHH* genes, for basal development, the *Hox* genes[7] for dorsal neural folding and tube closure and the *PAX* genes[8] for segmentation. Subsequent re-segmentation of the sclerotomes then occurs, to establish vertebral boundaries. This process seems to be independently controlled by two regulatory genes of the *PAX* family (Koseki et al. 1993).

Following segmentation, the *Hox* genes play a critical role. They are part of the developmental-genetic toolkit[9] and contain the phylogenetically highly conserved homeobox[10] domain. *Hox* genes regulate the establishment of the body plan in a temporospatial manner. They achieve this by the phenomenon of colinearity.[11] *Hox* genes are ordered in a linear fashion, precisely correlated with the order of both the segments and regions they affect and with the timing in which they are affected. Any mutation leading to a loss or gain in the gene cluster causes precise and specific similar changes in the affected segments and regions. The precise identity of each

[7] *HOX* genes organise dorsal neural folding and tube closure. This happens in the craniocaudal plane. At the same time sonic hedgehog and *PAX* genes are working on the basal plane and segmentation at each somite, respectively.

[8] *PAX* genes encode for a family of closely related transcription factors (TGF). In their absence segmental development fails. For example, PAX1/PAX9 double-mutant mice completely lack the medial derivatives of the sclerotomes, the vertebral bodies, intervertebral discs and the proximal parts of the ribs.

[9] The developmental-genetic toolkit consists of a small fraction of the genes in an organism's genome whose products control its overall development.

[10] A homeobox is a 180-base pairs long DNA sequence found within genes that are involved in the regulation of patterns of anatomical development (morphogenesis). These homeobox genes switch on cascades of other genes by using transcription factors. The homeobox encodes a protein domain (the homeodomain) which when expressed binds to DNA in a sequence-specific manner.

[11] Colinear property of Hox genes – the sequence of *Hox* genes matches the sequence in which they act along the body axes. *Hox* colinearity is pivotal in embryogenesis and is described in three ways: functional colinearity describes the order in which *Hox* genes act along a body axis, spatial colinearity refers to the spatial order in which the *Hox* genes are expressed and temporal colinearity is the time sequence in which they are expressed.

Table 4.5 Human CNS malformations

Days of gestation	Event	Resultant malformation
0–18	Formation of 3 germ layers and neural plate	Death or unclear effect
18	Formation of neural plate and groove	Anterior midline defects
22–23	Appearance of optic vessels	Hydrocephalus (18–60 days)
24–26	Closure of anterior neuropore	Anencephaly
26–28	Closure of posterior neuropore	Cranium bifidum, spina bifida cystica, spina bifida occulta
32	Vascular circulation	Microcephaly (30–130 days) Migration anomalies
33–35	Splitting of prosencephalon to make paired telencephalon	Holoprosencephaly
70–100	Formation of corpus callosum	Agenesis of the corpus callosum

hindbrain and prevertebral segment (and for every segment along the embryo) is controlled by *Hox* genes.

It is likely that a number of malformations have a basis in anomalies of regulatory gene function or of their signalling molecules, starting early in the gastrulation phase and continuing into primary neurulation (Table 4.5). The dorsally placed hindbrain and the craniocervical junction are particularly sensitive to *Hox* gene anomalies and/or disruption. In the hindbrain, cells in each rhombomere[12] do not cross established boundaries and are programmed to form only one precise part of the hindbrain (Fraser et al. 1990; Lumsden 1990). In this way, rhombomeres 2 and 3 induce formation of the motor neurons of the trigeminal nerve, rhombomeres 4 and 5 are responsible for the motor nerves of the facial nerve and rhombomeres 6 and 7 for the glossopharyngeal and vagus nerves. Retinoic acid treatment has been shown to alter the expression boundaries of homeobox genes and to cause homeotic transformations in the hindbrain (Marshall et al. 1992; Kessel 1993; Alexander et al. 2009) and within the vertebrae (Kessel and Gruss 1991). Marshall and colleagues reported in 1992 that retinoic acid alters hindbrain *HOX* code[13] and induces transformation of rhombomeres r2/r3 into an r4/r5 identity.[14] A main feature of this rhombomeric phenotype is that the trigeminal motor nerve is transformed to a facial identity. Neural crest cells derived from rhombomeres r2/r3 also express posterior *HOX* markers, suggesting that the retinoic acid-induced transformation extends to multiple components of the first branchial arch (Marshall et al. 1992). Such anomalies also extend to the craniovertebral junction, where a

[12] Rhombomeres (r) are eight distinct segments of the neural tube located distal to the cephalic flexure. They determine the pattern of maturation of the rhombencephalon (developing hindbrain) into its final parts – pons, cerebellum and medulla. Each rhombomere develops its own set of ganglia and nerves. Transcription factors (T-box) have been linked to the proper development of migrating cells in the region extending from one rhombomere to another.

[13] The *HOX* code is an ordered molecular system of positional values provided by the *HOX* genes. The *HOX* code is responsible for the patterning of hindbrain, craniofacial structures, vertebrae and limbs.

[14] While rhombomeres were discovered and histologically characterised in the early nineteenth century, only recently has their role in development become known. In all vertebrates, rhombomeres and branchial nerves (cranial nerves V, VII, IX for branchial arches I, II and III) are organised in a pair-wise fashion, such that the motor neurons of trigeminal nerve arise from r2 and r3, the facial and auditory neurons arise from r4 and r5 and the glossopharyngeal and vagus neurons extend caudal to r6. This specificity is controlled by the *HOX* genes. The segmental specification for each rhombomere within the hindbrain neuroectoderm remains, despite surgical transplantation into the next even-/odd-numbered rhombomere. In contrast, spinal nerve segmentation depends entirely on the pattern of somites. This implies that cranial nerve patterning is brought about by factors intrinsic to rhombomeres and to the attached neural crest cell populations. The patterns of the neuroectoderm and of the peripheral nervous system (PNS) are specified early in hindbrain development and cannot be influenced by tissue transplantation. In rhombomeres without neural crest cells (odd-numbered r3 and r5), transplantation leads to neurons migrating back to their appropriate (original) rhombomere nerve root exit site rather than the closest exit site in the transplanted rhombomeres for that root.

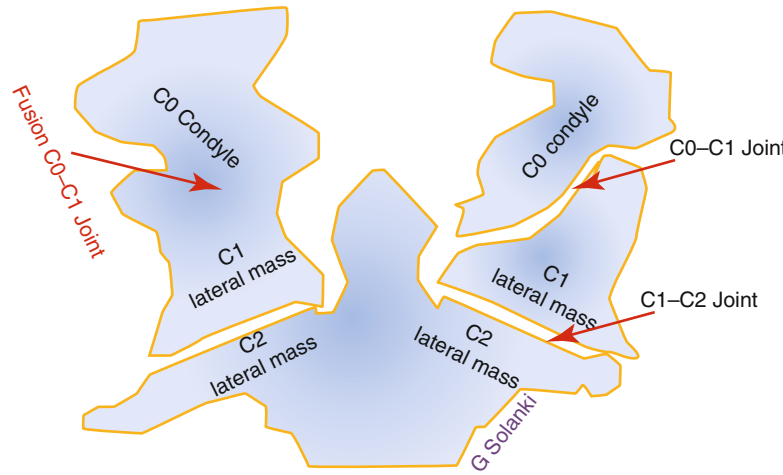

Fig. 4.9 Anterior homeotic transformation. Mutation of the *Hox* gene (loss of function) results in C1 arch fusion to the occiput. This artist's rendering of a cervical spine, in a coronal view, shows fusion of the occipital condyle to the C1 lateral mass on the right side

variety of homeotic transformations[15] can occur. When there is loss of a *Hox* gene, the corresponding region fails to segment from its cranial neighbour. This anomaly produces an anterior homeotic transformation, where the C1 arch will remain fused to the occiput and clivus. When there is a gain of function in the Hox gene, a posterior homeotic transformation occurs, where the distal clivus is assimilated into C1 or C1 into the tip of the dens (Fig. 4.9). Teratogen-induced disturbance of Hox gene expression, or mutation in the Hox genes themselves, can cause alterations in the morphology or number of cervical vertebra that are formed. Inactivation of the HOX-d3 gene in mice, for example, produces mutations with assimilation of the atlas into the basiocciput and failure of occipital somite development, resulting in a small or contracted occiput and leading to a small posterior fossa (Condie and Capecchi 1993).

4.5 Developmental Anomalies of the Craniocervical Junction

The endochondral skull base of foetuses with Chiari malformations is shorter than normal and elevated in relation to the spinal axis (Marin-Padilla and Marin-Padilla 1981). This underdevelopment of the occipital bone results in a short and small posterior fossa of inadequate volume for the normal hindbrain. A secondary effect is elongation of the odontoid process, the so-called dolicho-odontoid process, or dolichoid dens. This is often associated with a short basiocciput, and these two features result in basilar invagination, an appearance seen not uncommonly with Chiari malformations.

Anomalies of development of the proatlas and the spinal sclerotomes may lead to segmentation failures of the proatlas and development of occipital vertebrae (Tominaga et al. 2002; Rao 2002; Koseki et al. 1993; Gasser 1976). Hindbrain herniation is seen in 33 % of affected children. Another anomaly is the Klippel-Feil deformity, where there is failure of segmentation between the fourth occipital and the first spinal sclerotome (VonTorklus and Gehle 1972; Menezes 1995; Gehweiler et al. 1983). Basilar invagination is a secondary phenomenon, with associated hindbrain herniation, in about 40 % of cases.

A number of anomalies of the craniofacial skeleton are associated with the Chiari malformations and syringomyelia (Thompson and Rudd 1976). Craniofacial syndromes, which include lambdoid synostosis, severe brachyturricephaly[16] or pansynostosis, are quite likely to have an associated Chiari I malformation (Koseki et al. 1993).

[15] Homeotic transformation means that a normal body part is replaced by a body part which is regularly found in other regions. This can be anterior or posterior.

[16] Brachyturricephaly is an abnormal head shape where there are sagittal narrowing, coronal widening and increase in skull height, generally seen in syndromic craniosynostosis and bicoronal synostosis.

This may not be regarded as an essential component of the syndromic phenotypes but can be seen as a secondary effect of the craniocephalic mismatch, be this supratentorial or infratentorial. Indeed, calvarial augmentation surgery often resolves the hindbrain hernia in such cases, without the need for foramen magnum decompression (Iskandar et al. 2004; Frias et al. 1988; Nakai et al. 1995; Solanki et al. 2009).

4.5.1 Embryology of Chiari Malformations

Several different theories have been considered in explaining the embryogenesis or origins of Chiari malformations (Thompson and Rudd 1976), but a unifying theory has yet to emerge. Based on our current understanding of gastrulation and neurulation, the onset for the Chiari malformations lies in the embryonic period, somewhere between the 3rd and the 5th week and is likely to happen prior to, during and following closure of the neural tube. The association of Chiari I malformation with other spine, skull, somatic and craniofacial abnormalities, which are the result of mesodermal maldevelopment, would suggest a paraxial mesoderm origin of Chiari malformations and point towards a common pathway for these insults (Lee et al. 2003; Tubbs et al. 2003; Tubbs and Oakes 2005) (Table 4.6). The association of craniosynostosis and Chiari I malformation is well documented and is strongest in cases of syndromic, multi-suture and lambdoid synostosis. Nearly a 100 % association is noted with Kleeblatschadel.[17] The incidence of Chiari I malformation in Crouzon syndrome is about 70 % but is much lower in syndromes such as Apert (2 %) (Cinalli et al. 2005). It is most likely that the Chiari malformations arise from anomalies of the mesoderm, resulting in axial skeletal defects but with a range of associated neurological anomalies, proportionate

[17] The Kleeblattschadel deformity is a form of craniosynostosis where there are prominent temporal bones, leading to a clover leaf-type appearance of the skull.

Table 4.6 Associations reported with Chiari malformations

Group	Syndrome or anomaly
Craniosynostosis	Antley-Bixler syndrome
	Apert syndrome
	Crouzon syndrome
	Jackson-Weiss syndrome
	Kleeblattschädel syndrome
	Lambdoid synostosis
	Loeys-Dietz syndrome type I
	Metopic synostosis
	Pansynostosis
	Pfeiffer syndrome
	Seckel syndrome
	Shprintzen-Goldberg syndrome
Hydrocephalus	Obstructive hydrocephalus
Endocrine	Very rare in achondroplasia
	Acromegaly
	Growth hormone deficiency
	Hyperostosis
	Craniometaphyseal dysplasia
	Erythroid hyperplasia
	Osteopetrosis
	Paget disease
	Bone mineral deficiency
	Familial vitamin D-resistant rickets
	Familial hypophosphataemic rickets
Haematology	Sickle-cell disease with hypertrophy of diploic layer
Cutaneous/ neurocutaneous disorders	Acanthosis nigricans
	Blue rubber bleb nevus syndrome
	Giant congenital melanocytic nevi
	LEOPARD syndrome
	Macrocephaly-cutis marmorata telangiectatica
	Neurofibromatosis type I
	Phacomatosis pigmentovascularis type II
	Waardenburg syndrome
Spinal neurulation defects	
Primary neurulation	Lipomeningomyelocoele
Secondary neurulation	Caudal regression syndrome
Spinal somitic defects	Atlantoaxial assimilation
	Basilar impression
	Odontoid retroflexion
	Klippel-Feil syndrome
	Spondyloepiphyseal dysplasia

Table 4.6 (continued)

Group	Syndrome or anomaly
Space-occupying lesions	Posterior fossa
	Supratentorial
	Spinal cord
	Congenital space-occupying lesions
Other	Beckwith-Wiedemann syndrome
	CHERI syndrome *Ch*iari 1 malformation with or without cleft palate, deviant EEG or *e*pilepsy and *r*etarded *i*ntelligence with delayed language development (Haapanen 2007)
	Cloacal exstrophy
	Costello syndrome
	Cystic fibrosis
	Ehlers-Danlos syndrome
	Fabry disease
	Kabuki syndrome
	Situs inversus
	Williams-Beuren syndrome
	Pierre-Robin syndrome

Modified from Loukas et al. (2011)

Table 4.7 Theories of pathogenesis of Chiari malformations

Caudal traction
Hindbrain dysgenesis and developmental arrest
Lack of embryological ventricular distension
Hydrocephalus and hydrodynamic theory of Gardner
Small posterior fossa/hindbrain overgrowth theory

to the extent of the mesodermal disturbance. Many features of Chiari malformations, including neuronal migration anomalies,[18] are now believed to be secondary, rather than primary (Gardner et al. 1975) (Table 4.7). What was previously considered as a primary neuronal migration anomaly, as part of the Chiari II presentation, may in fact occur secondary to physical changes resulting from an open spina bifida. The loss of tension within the ventricular system distorts the brain parenchyma with a dorso-caudal movement. This elongation of parenchyma may lead to loss of cortical rugosity, sulcation anomalies, beaking of the tectum and so on.

Both genetic and environmental factors, including teratogens, might also play a role in the development of Chiari malformations. For example, administration of a single dose of vitamin A to pregnant hamsters, early during the morning of their 8th day of gestation, induces the formation of type 1 and type 2 Chiari malformations (Marin-Padilla and Marin-Padilla 1981). The critical defect arises from inhibition of a diffusible retinoid inducing factor, during gastrulation, causing a primary paraxial mesodermal insufficiency. The consequent underdevelopment of occipital somite, leading to a short clivus and a small occipital bone, results in a shallow posterior fossa (Tominaga et al. 2002). This, coupled with the later, rapid development, leads to a range of hindbrain abnormalities consistent with Chiari I and II malformations, as well as other mesenchymal anomalies. Interference with induction by the prechordal plate[19] at or before stage 8 (18 days) would also be expected to affect future development, particularly of the mediobasal part of the neural plate. Such anomalies occur by the 4th week post-ovulation (Muller and O'Rahilly 1980). Failure of the pontine flexure to form normally during primary neurulation from the 28th to 29th day of gestation may lead to formation of elongated brainstem and Chiari I and II malformations. Signs of Chiari malformations have certainly been noted on antenatal ultrasound as early as 10 weeks (Blaas et al. 2000), and there is evidence for accelerated growth of the cerebellum in the 20th week; this,

[18] Neuronal migration anomalies are a wide spectrum of developmental malformations of the cortex caused by disruption to its normal process of formation, which includes proliferation, migration and organisation (lamination, gyration and sulcation). The most well known are, for example, megalencephaly (proliferation), lissencephaly (migration) and heterotopias (organisation).

[19] 'Prechordal plate' and 'prochordal plate' are essentially synonymous terms referring to the horseshoe-shaped band of thickened endoderm rostral to the notochord. The prechordal plate starts as a thickening of the endoderm at the cranial end of the primitive streak. It is located at the anterior end of the notochord, which appears in early embryos as an integral part of the roof of the foregut. It contributes mesodermal type cells to the surrounding tissue. Cells derived from the prechordal plate become incorporated into the cephalic mesenchyme, which is thought to contribute, later, to the meninges. Failure of induction leads to cyclopia, holoprosencephaly and other mediobasal defects.

in the presence of arrested occipital somite development, may cause the typical hindbrain herniation seen in the commoner Chiari types I and II.

4.5.2 Chiari II Malformation

Chiari II malformation is virtually always present in neonates with open spinal dysraphism. The anatomical severity and resultant physiological effects of the malformation vary from one child to another. We encounter a range, from a near-normal-sized posterior fossa with no real descent of the vermis or brainstem to other children that may be affected by permanent nocturnal central hypoventilation, requiring noninvasive ventilation (Bhangoo et al. 2006).

The open neural tube defect arises during primary neurulation. Failure of developmental closure of the caudal neural tube results in an unfolded neural tube, known as neural placode, exposed to the dorsal surface in the midline. CSF leaks through the defect into the amniotic sac, resulting in chronic CSF hypovolemia and hypotension within the developing neural tube. This creates a small ventricular system and inadequate dilatation of the future fourth ventricle. It also fails to induce the posterior cranial fossa perineural mesenchyme (McLone and Knepper 1989). The dominant features of Chiari II malformation, up to 20 weeks of gestation, are the result of these developmental failures. After 20 weeks the accelerated and disproportionate growth of the cerebellum dominates (Beuls et al. 2003; Paek et al. 2000; Bouchard et al. 2003; Sutton et al. 1999). Both cerebellum and brainstem are eventually forced to develop within a smaller than normal posterior fossa and consequently herniate through both the tentorial hiatus and the foramen magnum.

In lambs, adding a myelotomy to experimentally induced dysraphic lesions leads to formation of a hindbrain hernia that is similar to that observed in the human Chiari II malformation. Further, repair of myelomeningocoele in a human foetus reverses the hindbrain herniation and restores gross anatomy of the vermis (Bouchard et al. 2003; Sutton et al. 1999). The posterior fossa will expand in time to allow further normal growth of both the cerebellum and brainstem.

CSF hypotension in the supratentorial brain may also impair neuronal migration, producing various associated malformations of the nervous tissue. Although histologically normal, the cerebral cortex in patients with Chiari II malformation is abnormal in gross appearance. The gyri are abnormally numerous and small, although the term polymicrogyria is best avoided because of its association with an abnormal four-layered cortex that is not present in Chiari II malformation; the term polygyria is to be preferred (McLendon et al. 1985). Partial-to-total agenesis of the corpus callosum is seen in a third of patients with Chiari II malformation; nearly two thirds of those have below average intelligence (Venes et al. 1986).

Multiple ventricular anomalies are found commonly in the patient with Chiari II malformation. The fourth ventricle, which is typically small and poorly visualised, is frequently displaced into the cervical canal, along with its choroid plexus. The aqueduct is similarly small and rarely seen on routine imaging, although this probably does not contribute significantly to the hydrocephalus (Peach 1965). The third ventricle is rarely enlarged but may take on a narrow-angled appearance, giving rise to the term ‘shark tooth deformity’. The lateral ventricular appearance varies from nearly normal to severely deformed and hydrocephalic. Colpocephaly[20] is common, with the occipital horns disproportionately enlarged compared with the frontal horns. This finding is often present, even in patients with myelomeningocoele who do not have hydrocephalus. It frequently persists in patients in whom a shunt has been placed. ‘Beaking’ of the frontal horns is occasionally seen, when the frontal horns point

[20] Colpocephaly refers to an abnormal appearance of the ventricular system of the brain in which there is asymmetric dilatation of the occipital horns but with normal-sized frontal horns. It is common in Chiari malformation II. It is thought to be related to an intrauterine disturbance that occurs between the second and sixth months of pregnancy. The finding may be indirectly suggested on ultrasound by the so-called lemon sign, which occurs due to depression of the calvarium at the bilateral frontal suture lines, giving the calvarium the appearance of a lemon.

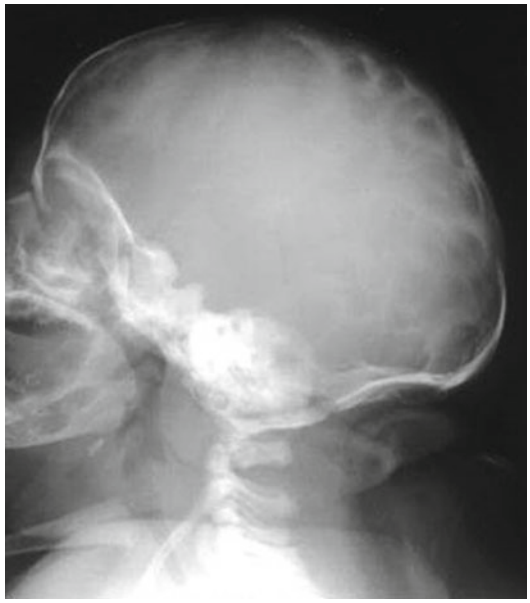

Fig. 4.10 Luckenschadel Also known as lacunar skull, this condition is a dysplasia of the membranous skull vault. Two variants are described. Craniolacunia is the name given when the grooves in the skull are limited to the inner table. In craniofenestrae there are palpable defects involving both the inner and outer tables. It is associated with Chari malformations, particularly Chiari II malformation (up to 80 %). It is believed that the defect is not so much due to pressure from within but rather an abnormality of collagen development and ossification

inferiorly. This finding is attributed to interdigitations of the cerebral hemispheres in the affected region (Rauzzino and Oakes 1995).

In addition to the anomalies of the brain, typical skull malformations are frequently found in association with Chiari II malformation. The foramen magnum is often enlarged, a finding which obviates the need for suboccipital craniectomy in many patients undergoing surgery for symptomatic Chiari II malformation. Luckenschadel scalloping of the petrous pyramid (Fig. 4.10) and shortening of the clivus are common findings on computerised tomography scanning (Naidich et al. 1980).

A description of the pathological and radiological types of Chiari variants is given in Table 4.8. MRI findings are described in Table 4.9.

The widened foramen magnum provides one of the key components of any herniation, which is an incompetent orifice between two compartments. This raises questions regarding the perceived merits of expanding an already widened or incompetent hernia orifice to treat the hindbrain 'hernia'. Indeed the most reasonable treatment of any hernia is to tighten the orifice; release of a constricted orifice is reserved for those cases

Table 4.8 Chiari pathological classification and new radiological variants

Chiari	Description	Association
I	Herniation of the cerebellar tonsils 5 mm below the foramen magnum	Association with craniosynostosis, skull base anomalies and craniocephalic mismatch
II	Herniation of the cerebellar vermis and 4th ventricle Low-lying tentorium with low torcula Occipital lobe often posterior to cerebellum	Associated with myelomeningocele, defect, hydrocephalus syringomyelia and neurological deficits
III	Cerebellum, brainstem, 4th ventricular herniation with occipital or occipito-cervical meningoencephalocoele	Most serious form of Chiari malformation. Hydrocephalus may be present. Severe neurological deficits, incompatible with survival
IV	Cerebellar hypoplasia, 4th ventricle communicates with cisterna magna, no hindbrain hernia	Dandy-Walker-type malformation
Proposed new variants		
0	Patients with headaches and other symptoms of Chiari malformation or syringomyelia and no tonsillar hernia or tonsillar hernia less than 3 mm	Abnormal CSF flow the posterior fossa or foramen magnum as the suspected cause for syringomyelia (Tubbs et al. 2001)
1.5	A Chiari is seen in combination with brainstem herniation through the foramen magnum	Obex below the foramen magnum. Flat medulla oblongata. Mean backward angulation of the odontoid process in relation to the C2 body was 84°. Fifty percent have syringomyelia. Patients may not respond well to posterior fossa decompressive surgery especially if syringomyelia is present

Table 4.9 MRI findings in Chiari II malformation

Location	Abnormality	Cause
Infratentorial	Metencephalon/posterior fossa mismatch	Variably reduced space for the cerebellum and brainstem into a smaller than normal posterior fossa
Inferior vermis	Peg-like cerebellar tonsillar descent	The inferior vermis herniates into the foramen magnum and wraps around the posterior surface of the cord
Medulla	Cervicomedullary kink	The medulla is stretched downwards into the foramen magnum, while the cervical cord is anchored by the dentate ligaments, resulting in the cervicomedullary kink
Cerebellar hemispheres	Cerebellar hemispheres expand around the brainstem, occupying the cerebellopontine angles. Upward cerebellar herniation through the tentorial hiatus	The posterior fossa volume mismatch causes the cerebellum to move forward and be upright creating a distinctive appearance, the 'standing-up' cerebellum
Tentorium cerebelli	Steep angle of the tentorium	
Torcula	Displaced inferiorly	Pushed down nearly into level of foramen magnum along with steep tentorium
Vascular	Venous hypertension	Anomalies of the skull base, tight posterior fossa
Height of posterior fossa	Height from level of foramen magnum to apex of tentorium is increased	
Occipital lobes	Lie posterior to the cerebellum instead of above	
Occipital lobes	Stenogyria[a]	Crowding of the cerebral lobe gyri with loss of sulcal CSF and increased density
4th ventricle	The fourth ventricle is usually small or even completely effaced	
Tectal beaking	The inferior colliculi may be hypertrophied or fused, and point posteriorly to form the tectal beak	
Suprapineal recess of the 3rd ventricle	The suprapineal recess of the third ventricle and the interthalamic mass are especially prominent	
Corpus callosum	Commissural anomalies are commonly associated	
Membranous skull	Lacunar skull or luckenschädel	Disorganisation of the collagenous outer meninges (from which the membranous calvarium forms) produces irregularity of the surfaces of the inner and outer table of the skull
Hydrocephalus	Consistent finding within 48–72 h of repair of the spinal dysraphism	Once the caudal leakage is repaired, the amount of CSF increases in the ventricular system

[a]This is a radiological term describing compaction of otherwise normal gyri, such that they become small, with loss of intervening CSF. This feature is seen commonly in association with Chiari II malformation malformations

of strangulated hernia. It is therefore interesting to learn that performing a posterior, supratentorial calvarial augmentation, in children with craniosynostosis, can lead to regression of an associated Chiari malformation, without recourse to augmentation of the posterior fossa or decompression of the foramen magnum (Solanki et al. 2009, 2011; Farooq et al. 2011; White et al. 2009).

4.6 Morphometric Studies

From the foregoing discussions it may reasonably be suggested that idiopathic Chiari I malformation is the result of mesodermal defects that create a congenitally small posterior fossa (Atkinson et al. 1998; Badie et al. 1995; Nishikawa et al. 1997). A mismatch between the size of the posterior fossa and its contents leads

to neural element compression and herniation through the foramen magnum (Tubbs et al. 2002). In children with Chiari I malformation, the anteroposterior dimension, the width and the volume of the posterior fossa are significantly lower than in controls (Furtado et al. 2009; Milhorat et al. 1999; Rodrigues and Solanki 2008; Rodrigues et al. 2009). So too is the ratio of posterior fossa volume to the overall intracranial volumes. Indeed, posterior fossa volumes may be some 23 % smaller in Chiari I patients compared to controls (Vemaraju et al. 2009; Milhorat et al. 1999). In contrast, a small body of evidence suggests that there is no difference in the size of the posterior fossa in patients with tonsillar ectopia, as compared with controls (Vega et al. 1990). The weight of evidence, however, points to a comparatively smaller size of the posterior fossa, in relation to the supratentorial compartment, in Chiari-affected patients (Badie et al. 1995; Solanki et al. 2009; Frias et al. 1988; Nakai et al. 1995; Vemaraju et al. 2009; Rodrigues et al. 2009; Milhorat et al. 1999).

Morphometric studies also reveal a larger sagittal diameter and a greater area of the foramen magnum compared to controls in both Chiari and Chiari II patients. The shape of the foramen magnum is also altered and expanded, from a normal ovoid to a more rounded opening, particularly in Chiari II malformations (Vemaraju et al. 2009). Contrast this with achondroplasia, a condition where accelerated fusion of the basiocciput and supraocciput occurs. Here the foramen magnum is narrow with a reduced area and sagittal stenosis.[21] Achondroplasia is also associated with macrocephaly, venous hypertension and ventriculomegaly, and yet there is no herniation of the hindbrain. Interestingly, in achondroplasia, the abnormalities often result in upward displacement of the brainstem, sometimes in conjunction with angulation of the pons and medulla oblongata (Nakai et al. 1995; Frias et al. 1988). This may explain the fact that Chiari type I malformation is somewhat rare in the achondroplastic population.

[21] Sagittal stenosis: narrow in the anterior-posterior diameter.

Conclusions

The SHH, HOX and PAX genes are crucial in the normal development of the brain and spinal cord, and many of their influences are mediated through the notochord organiser. It is very probable that both Chiari I and Chiari II malformations have a paraxial mesodermal origin, with a variable expression of their anomaly. It is now seen as less likely that Chiari II malformations are a disorder of neuronal migration, despite the presence of heterotopias[22] in some cases. Indeed, one could argue that Chiari II malformation malformations represent an exaggerated form of Chiari I malformation, resulting from an open neural tube defect that leaks CSF, causing caudal slump of the cerebrum and cerebellum.

The Chiari II malformation first becomes visible by the 10th to 12th weeks on ultrasound imaging. There is now good evidence to suggest that foetal surgery for Chiari II malformation improves motor outcomes, reverses the hindbrain hernia and reduces need for shunting after birth. This does mean, however, that a decision to reverse it must be taken urgently in such cases (Gehweiler et al. 1983).

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[22] Heterotopia refers to normal tissue present at an abnormal site. Heterotopia within the brain is often divided into three groups: subependymal heterotopia, focal cortical heterotopia and band heterotopia.

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