# 5 Embryology and Pathophysiology of the Chiari I and II Malformations

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Although Chiari I and II malformations have hindbrain herniation into the upper cervical spinal canal, both are also often associated with other anomalies of the craniofacial skeleton, vertebral column, and central nervous system (CNS). Table 5.1 lists some of these associated anomalies [1–22]. The herniated hindbrain may include the medulla oblongata, fourth ventricle, and caudal vermis and cerebellar hemispheres (usually tonsils) to varying extents. An efficient theory with high explanatory power should be able to provide a rational basis for the occurrence of not only hindbrain herniation but also that of other associated anomalies. Currently, no single theory explains each of these malformations as the Chiari malformation seems to result from a heterogeneous spectrum of ontogenetic errors and pathological mechanisms, which share some common phenotypical presentations [23]. In this chapter, the theories pertinent to the embryology and pathophysiology of Chiari I and II malformations and their associated anomalies are discussed.

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## Hydrocephalic Brain or Pressure Coning Theory

The question of whether hydrocephalus is the cause or effect of hindbrain herniation has been considered since Chiari's initial description and is complicated by the fact that hydrocephalus may occur without associated hindbrain herniation and vice versa [24]. Therefore, it is reasonable to assume that the developmental or postnatal factors leading to hydrocephalus and hindbrain herniation are mechanistically distinct but also partially overlap. A historical account of the discourses on the relationship between hydrocephalus and hindbrain herniation would best aid in clarifying this concept. In his classic paper of 1891, Hans Chiari wrote:

> Since giving more attention to these relationships [in both type I and II malformations], I have had the impression that the extension of the tonsils and medial side of the inferior lobes [of the cerebellum] *probably* always is the result of chronic and the very early onset of cerebral hydrocephalus. I have found it in a relatively large percentage of cases of chronic congenital hydrocephalus, but never without hydrocephalus or in cases of acute or later developing hydrocephalus. (Quoted from English translation of Radkowski [25])


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**Table 5.1** Some of the anomalies associated with Chiari malformation

| Anomaly | Description | Reference(s) |
|---|---|---|
| Cranium bifidum | Is the cranial counterpart of spina bifida and is likewise comprised of occulta, cystica, and aperta variants | Padget, 1972 [1]; Ingraham and Scott, 1943 [2]; Anegawa et al., 1993 [3] |
| Lacunar skull | Is characterized by rounded (punched-out) defects in the inner table of the skull separated by whorl-like bony ridges | Ingraham and Scott, 1943 [2]; Peach, 1965 [4] |
| Platybasia | Flattening of the angle between the clivus and anterior basicranium; severe form is associated with basilar invagination | Schady et al., 1987 [5]; Smoker, 1994 [6] |
| Small posterior cranial fossa | Reduction in the size of posterior cranial fossa in relation to the cranial dimensions | Schady et al., 1987 [5] |
| Basilar invagination | Abnormal approximation of the odontoid process and skull base | Schady et al., 1987 [5] |
| Proatlas segmentation malformation | Most often present as osseous anomalies around the foramen magnum | Muhleman et al., 2012 [7]; Menezes, 1995 [8] |
| Atlanto-occipital assimilation | Partial or complete fusion of the atlas and occipital bone; is seen in about 8% of pediatric patients with Chiari I malformation | Tubbs et al., 2011 [9] |
| Klippel-Feil syndrome | Fusion of two or more cervical vertebrae; is seen in about 3% of patients with Chiari I malformation | Tubbs et al., 2011 [9] |
| Spina bifida | Is composed of spina bifida occulta, cystica, and aperta variants; the latter two are comprised of meningocele, meningomyelocele, myelocystocele, and myeloschisis; is often but not always associated with hydrocephalus and Chiari II malformation | Pooh and Pooh, 2011 [10]; Russell and Donald, 1935 [11]; Ingraham and Scott, 1943 [2] |
| Dysplastic tentorium cerebelli | Decreased length of the fused tentorium and increased length of the incisura | Peach, 1965 [4] |
| Low-lying tentorium cerebelli | Downward displacement of intracranial attachment of the tentorium; contribute to a small posterior cranial fossa | Gardner, 1973 [12] |
| Hypoplasia or absence of falx cerebri and falx cerebelli | Is related to overcrowding of the intracranial and posterior cranial fossae | Peach, 1965 [4]; Tubbs et al., 2002 [13] |
| Hydrocephalus | Often communicating; may be a primary event or secondary to hindbrain herniation | Ingraham and Scott, 1943 [2] |
| Microgyria | The cerebral gyri are smaller but numerous giving rise to a "wormy" appearance of the cerebral cortex | Ingraham and Scott, 1943 [2] |
| Gray matter heterotopia | Collection of neural cells in abnormal *locations within the white matter*; has been reported in patients with spina bifida and Chiari II malformation | Gilbert et al., 1986 [14] |
| Large massa intermedia | Excessive approximation and adhesion of the thalami and thickening of the interthalamic adhesion | Gardner, 1977 [15]; Naidich et al., 1980 [16]; Peach, 1965 [4] |
| Stenosis of the aqueduct of Sylvius | May be primary or secondary to midbrain compression by hydrocephalus or overcrowded brain | Masters, 1978 [17]; Russell and Donald, 1935 [11] |
| Tectal beaking | The quadrigeminal plate of the midbrain is fused into a conical mass, the apex of which projects between the cerebellar hemisphere | Peach, 1965 [4] |
| Dorsal wedging of the brain stem | Dorsal part of pons and/or upper medulla protrudes into the fourth ventricle | Lichtenstein, 1942 [18] |
| Imperforated rhombic roof | Primary agenesis or secondary occlusion of the outlets of the fourth ventricle by a fibrovascular membrane or arachnoid veil | Gardner, 1965 [19]; Tubbs et al., 2004 [20] |

**Table 5.1** (continued)

| Anomaly | Description | Reference(s) |
|---|---|---|
| "Tight" cisterna magna | The cisterna magna is small or obliterated; is due to overcrowding of the posterior cranial fossa, downward displacement of cerebellum, fibrovascular adhesions of the meningeal layers, or dysgenesis during embryonic and early fetal periods | Gardner, 1973 [12]; Masters, 1978 [17] |
| Low-lying and obliterated fourth ventricle | The fourth ventricle is slit-like and compressed and partly or entirely extends below the foramen magnum | Russell and Donald, 1935 [11] |
| Upslanting cervical spinal nerves | Upper cervical spinal nerves with an ascending intradural course; these spinal nerves normally have a rather horizontal course | Barry et al., 1957 [21] |
| Syringomyelia | The cavitation within the spinal cord tissue; is more common in Chiari II than in Chiari I malformations | Josef and Fehlings, 2011 [22] |
| Hydromyelia | Dilated central canal | Ingraham and Scott, 1943 [2] |

The presence of hydrocephalus was not appreciated by Arnold, but Chiari assumed that it might have been, in some cases, a transient event in the fetal period [26]. The hydrocephalic brain theory, later known as "pressure coning effect" [12], dominated the thoughts and still stands as a plausible—albeit not the sole—mechanism behind hindbrain herniation.

The validity of the pressure coning theory has been questioned by the forerunners of caudal traction, posterior fossa overcrowding, the so-called neural tube overgrowth theory, and inadequate ventricular distension theories (see below). It has been noted that only ~15% of patients with meningomyelocele had externally recognizable hydrocephalus at birth and that a majority of them develop hydrocephalus during the first 3 years of life [27], casting doubt on the presumed role of primary fetal hydrocephalus in Chiari II malformation. The idea that hydrocephalus and hindbrain herniation "may be causally independent of each other" was emphasized by Bell et al. [24]; in their study of 21 human fetuses with spina bifida, 3 of 12 fetuses with Chiari II malformation lacked hydrocephalus. Instead, hindbrain herniation was closely linked with the size and location of the spinal defect: "the more cephalad and extensive the spinal lesion, the more likely it was to be accompanied with Chiari II malformation" [24]. It also has been suggested that a high cerebrospinal fluid (CSF) flow rate through the fistulous communication between the neurocele and amniotic cavity at the level of neural tube defect may induce a high craniospinal pressure gradient (by reducing the pressure of the spinal neurocele without increasing the intracranial pressure), which by itself causes the hindbrain to herniate into the spinal canal [28]. The latter findings indicated that hindbrain herniation may be either a direct or an indirect consequence of the spina bifida defect, shedding light into the plausibility of other theories (e.g., caudal traction, posterior fossa overcrowding and inadequate ventricular distension, etc.), which are mechanistically favored by the spina bifida defect.

The findings of Bell et al. [24] and others could, however, by no means totally exclude the possibility that hydrocephalus is of a direct cause-and-effect relationship with hindbrain herniation at least in some cases. If one accepts the hydrocephalic brain theory, then an account of the etiologies of the *primary* fetal hydrocephalus would deem it inevitable. It has been suggested that CSF absorption pathways are underdeveloped in patients with spina bifida cystica [11]. Atresia of the aqueduct of Sylvius [11], cranial venous outflow insufficiency and venous blood backflow [29], lack of elasticity and reduced permeability of the embryonic rhombic roof [30], primary agenesis of the outlets of the fourth ventricle or occlusion of the rhombic roof foramina by a membrane [11, 19], hyperfunctioning choroid plexus of the lateral ventricles and

overproduction of CSF [15], and dysgenesis of the cisterna magna [15, 17] all hinder normal CSF balance and circulation and are among the known etiologies of primary fetal hydrocephalus in Chiari malformation. In the context of hydrocephalic brain theory, a differentiation should ideally be made between the factors initiating hydrocephalus and those maintaining or aggravating it once it develops. However, such a distinction remains arbitrary in the majority of cases as multiple interrelated anomalies often coexist at the same time in the same subject.

Ultimately, evidence exists for hydrocephalus being either a primary event causing hindbrain herniation (per hydrocephalic brain theory) or a secondary event caused by hindbrain herniation. This may in fact reflect the heterogeneous nature of the pathogenesis of hindbrain herniation across patients with or without spina bifida, and it is safe to assume that the relationship between hydrocephalus and hindbrain herniation is bidirectional, one causing or aggravating the other. Figure 5.1 shows a self-perpetuating cycle; irrespective of the factor(s) initiating the cycle, hydrocephalus reduces the compliance of the intracranial cavity [29]. Therefore, with slight elevation of the CSF and intracranial blood volumes, the intracranial pressure increases quickly, pushing the hindbrain down through the foramen magnum. Obstruction of CSF flow through the foramen magnum aggravates the hydrocephalus, and the cycle continues resulting in increasing hydrocephalus and hindbrain herniation [29]. If hindbrain herniation is the inciting event, then CSF flow blockage would secondarily lead to hydrocephalus, which by itself aggravates hindbrain herniation by increasing intracranial pressure. Several mechanisms have been recognized for CSF blockage in the Chiari malformation. Partial blockage of the foramen magnum with herniated hindbrain is commonly observed in patients with meningomyelocele and Chiari II malformation [11]. Usually, the outlet of the fourth ventricle is below the foramen magnum, and CSF drains into the spinal subarachnoid space. But because of partial blockage at the level of the foramen magnum, an accumulating amount of CSF does not circulate into the cranial subarachnoid space [11]. The spinal compartment has a capacity of CSF absorption that is only one-sixth that of the cranial compartment [31]. Although the dural sac of the spina bifida cystica has abnormally high absorptive capacity [32], this may not compensate for exclusion of the intracranial CSF absorption in severe cases of foramen magnum blockage. Thus, if the accumulated spinal CSF overwhelms the absorptive capacity of the spinal compartment, it reenters the ventricular cavity, leading to a communicating hydrocephalus [11], or penetrates into the substance of the spinal cord, leading to syringomyelia [33]. Alternatively, the outlets of the fourth ventricle may become secondarily obliterated between the impacted cerebellum and brain stem, causing a non-communicating hydrocephalus [2]. Mechanical irritation of the basal cistern can also induce an aseptic inflammatory reaction and fibrosis within the subarachnoid space, which hinders CSF circulation in the posterior cranial fossa [2].

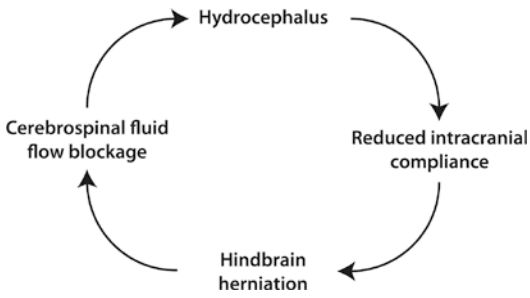


**Fig. 5.1** The self-perpetuating cycle linking hydrocephalus with hindbrain herniation

## External Compression Theory

The external compression theory was proposed by Cameron [34] to provide a mechanical basis for hindbrain herniation aside from hydrocephalus in the fetuses with spina bifida defect. Cameron believed that ontogenetically, the spina bifida cystica is, at the initial stage, an aperta (myeloschisis) lesion, later epithelialized to form a cystic lesion. Thus, in embryonic and early fetal life, there is a fistulous communica-

tion between the neurocele and amniotic cavity. Cameron [34] opined that increased intra-amniotic pressure (perhaps due to fetal and maternal maneuvers) is transmitted onto the developing skull, squeezing the cranial neurocele to drain out through the hydromyelic cord. Leakage of the neurocele fluid into the amniotic space and squeezing of the developing brain would thereby induce a Chiari II malformation and produce a variety of associated anomalies including stenosis of the aqueduct of Sylvius, hypoplasia of the falx cerebri, tectal beaking, large massa intermedia, etc. This theory, however, was refuted by Peach [35] on the grounds that according to Pascal's law, the pressure exerted by the amniotic fluid on the embryo or fetus is equal at the skull and defective spinal lesion. Thus, the intra-amniotic pressure cannot induce a pressure gradient between the cranial neurocele and the hydromyelic cord. Moreover, in a study of infants less than 3 months of age with lumbar meningomyelocele, about half of them were found to have amniotic fluid debris (squama, lanugo hair, and mucin) in the spinal cord tissues, central spinal cord canal, and spinal subarachnoid space, i.e., vernicomyelia [36]. The presence of vernicomyelia in meningomyelocele infants implies that the direction of flow between the amniotic cavity and neurocele is not always caudad and that a degree of rostral flow from the amniotic cavity to the neurocele also exists in some if not all of the affected fetuses [36].

Although the external compression theory has not been accepted, its invalidation does not contradict the hydrodynamic theory or other theories, which emphasize that hindbrain herniation is a consequence of neurocele fluid leaking through the defect in the neural tube. This leakage could instead be mechanically favored by a normally higher neurocele pressure than amniotic pressure in the embryonic and early fetal neural tube [15]. However, when the hindbrain herniates, the spinal compartment is isolated—partially or completely—from the cranial compartment and becomes in equilibrium with the amniotic cavity. As a result, a to-and-fro flow through the spina bifida defect is established: The in utero maneuvers compressing the head cause caudad egress of the fluid through the defect, while subsequent release of head compression causes the amniotic fluid to pass rostrad into the spinal compartment [36].

## Crowding of the Posterior Fossa in Chiari Malformation

The phenomenon of posterior cranial fossa overcrowding is an integral part of the modified hydrodynamic theory of Gardner, occipital dysplasia theory, disorganized neural tube growth theory, and inadequate ventricular distension theory (see below). In fact, these theories have been proposed to explain the overcrowding phenomenon on the grounds of either a small posterior cranial fossa or increased size of the hindbrain (see below). Accordingly, normal growth of the posterior fossa brain within a confined, unyielding fossa or abnormally large size of the posterior fossa brain in an apparently normal fossa results in the state of "overcrowding." The overcrowded posterior fossa brain herniates upward through the tentorial incisura and downward through the foramen magnum and also hinders CSF circulation, leading to the hydrocephalus. A point of importance here is that the relative ratio of the posterior fossa brain volume to total fossa volume is above normal but less than one in this state, and overcrowding by no means indicates that the posterior fossa brain volume is greater than the total posterior fossa volume. In one study, the posterior fossa brain occupied 83.3% of the posterior fossa space in adult patients with Chiari I malformation and 79% of the fossa space in healthy individuals [37]. Whether such a degree of posterior fossa overcrowding (~5%) is by itself sufficient to cause hindbrain herniation or not is not clear. However, it is more likely that the overcrowding phenomenon works in concert with other factors to induce hindbrain herniation.

### Hydrodynamic Theory

The hydrodynamic theory was suggested by Gardner et al. in 1957 [30], and in 1977 [15], he

modified it to explain the smallness of the posterior cranial fossa as well as formation of the neural tube defect in Chiari II malformation. Consulting the works of Weed [38], Padget [39], and Bering [40], Gardner [15] attested that (1) development of the area membranacea superior of Weed coincides with development of the posterior choroid plexus of the rhombic cavity, and that of the area membranacea inferior of Weed coincides with development of the anterior choroid plexus of the lateral ventricles; (2) the area membranacea superior and inferior filter the CSF out of the brain ventricles in normal fetuses; and (3) the anterior choroid plexus expands rapidly and out of proportion to the posterior choroid plexus; thus, the CSF pressure generated by the anterior choroid plexus in the supratentorial space overrides the pressure generated by the posterior choroid plexus, and this pressure gradient pushes the tentorium downward. If the second mechanism fails due to abnormal thickening or reduced permeability of the rhombic roof [30], then the CSF cannot egress from the ventricular cavity through the rhombic roof. If the third mechanism becomes exaggerated due to hyperfunctioning or markedly enlarged anterior choroid plexus [12, 15], the filtering capacity of the rhombic roof is overwhelmed, and the neural tube expands to a greater extent than normal. Under both these circumstances, a state of fetal hydrocephalus and hydromyelia ensues. The fetal hydromyelia leads to rupture of the weakest part of the closed neurocele in the caudal region (or occasionally in the cephalic region such as in the mesencephalon) leading to a variety of neural tube defects [15]. When the caudal neurocele opens, CSF drains out of the fourth ventricle through the hydromyelic central spinal cord canal and from the spina bifida defect into the amniotic cavity; this results in dissipation of the CSF pressure generated by the posterior choroid plexus within the infratentorial space. The supratentorial CSF pressure generated by the anterior choroid plexus and the hydrocephalic cerebrum push the tentorium downward to a greater extent than in normal, leading to a small posterior cranial fossa. Ultimately, the growing hindbrain herniates out of the small posterior fossa [15].

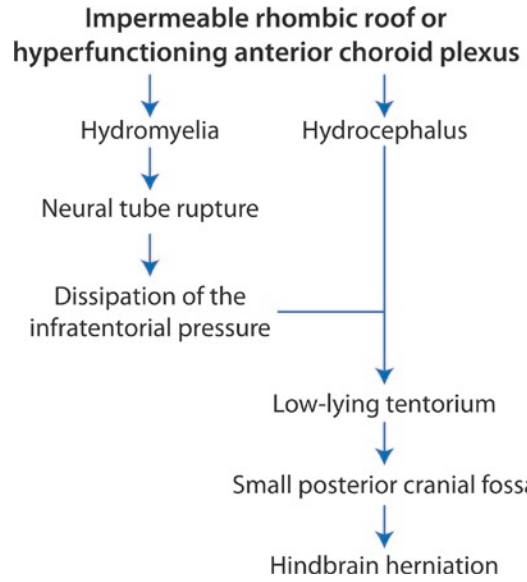


**Fig. 5.2** A flow diagram depicting Gardner's hydrodynamic theory

The sequence of the events per Gardner's hydrodynamic theory (Fig. 5.2) occurs in the embryonic and early fetal period when the otic capsule is still cartilaginous and tentorial rotation is feasible. Gardner [19] outlined the differences in pathogenesis of the Chiari I and II malformations in an interesting manner: "if the size of the posterior fossa is severely reduced by this process, the cerebellar portion of the resulting hernia will consist of the earlier developing vermis (Chiari II); if its size is reduced to a lesser degree, the cerebellar hernia will consist of the later developing tonsils (Chiari I)."

Gardner [19] elaborated upon the hydrodynamic theory to explain the co-occurrence of hydromyelia and syringomyelia with Chiari malformation and hydrocephalus. He postulated that with any restriction in the outflow of the fourth ventricle, either due to complete or partial obstruction of the foramen of Magendie, the CSF pulse wave generated by the pulsating choroid plexus (synchronous with cardiac beat) cannot be dissipated at the level of the foramen of Magendie but is directed downward toward the obex of the medulla and central canal. The "water hammer effect" of the CSF pulse pressure causes funnel-shaped dilation at the obex, dilation of the central

canal, and/or hydrodissection of the lower medulla or spinal cord along the nerve fiber tracts. Notably, the foramen of Magendie was completely obliterated by an arachnoid veil in at least 30% of patients with syringomyelia and Chiari malformation examined by Gardner [19] and was also partially closed in more than 10% of patients.

Ultimately, in the hydrodynamic theory of Gardner, overdistension of the supratentorial ventricles and/or imperforation of the roof of the fourth ventricle is an inciting event, which independently leads to hydrocephalus, hydromyelia, and syringomyelia. The induction of hindbrain herniation is secondary to the *early fetal* hydrocephalus and growth of the hindbrain within a small posterior cranial fossa. Moreover, this theory maintains that the expansion of the syrinx is due to a pulsatile CSF flow wave (hammer effect), which is transmitted into the syrinx through a patent upper cervical central canal. Hence, it predicts that the syrinx should expand during cardiac systole and should constrict during diastole. The latter assumption has been invalidated by Oldfield et al. [33] who put forth another theory for the pathogenesis of the syringomyelia (see below).

## Occipital Dysplasia Theory

The size of the posterior cranial fossa is determined by several factors effective in fetal and postnatal life, including (1) ventricular distension, (2) rotation of the intracranial attachment of the tentorium cerebelli, (3) rotation of the otic cartilage and petrous temporal bone, (4) growth of the basicranial synchondroses, (5) upward reflection of the tentorium cerebellum, and (6) various hormonal influences (see Chap. 4 "Embryology of the Craniocervical Junction and Posterior Cranial Fossa" for details). The occipital dysplasia theory implies that failure of the occipital bone to develop normally, primary axial skeletal defect, paraxial mesodermal insufficiency, or altered morphogenesis of the occipital bone gives rise to a small posterior cranial fossa and contributes to the overcrowding phenomenon.

This theory was emphasized by Marin-Padilla and Marin-Padilla [41] in an animal embryo model of Chiari I and II malformations induced by maternal administration of vitamin A and was later supported by the morphometric data obtained from patients with Chiari malformation. Marin-Padilla and Marin-Padilla's model expressed a constellation of craniofacial anomalies and dysraphic states. In this model, (1) there was a reduction in the length of the skull base essentially as a result of an underdeveloped occipital region; underdevelopment and shortening of the basiocciput were more pronounced in animal fetuses with a spina bifida defect (corresponding to Chiari II malformation) than in those without a spina bifida defect (corresponding to Chiari I malformation); (2) the odontoid process was apparently protruded into the posterior fossa with its tip located above the plane of the depressed basion of the underdeveloped basiocciput; and (3) shortening of the basiocciput resulted in a small posterior cranial fossa and subsequent compression of the brain stem and cerebellum and partial reduction in the ventricular size and slight compression of the aqueduct of Sylvius. Therefore, Marin-Padilla and Marin-Padilla [41] suggested that Chiari I and II malformations are "complex developmental disorders" or sequence anomalies initiated by "primary axial skeletal defects" (invariably involving the craniocervical junction and occipital region) leading to "secondary neurological anomalies."

The nature of occipital dysplasia leading to a small posterior cranial fossa in Chiari I malformation is already discussed (see Chap. 4 "Embryology of the Craniocervical Junction and Posterior Cranial Fossa"). In brief, the supraocciput is affected more than the basiocciput, the foramen magnum tends to enlarge, and the height of the posterior fossa is reduced. There may be a compensatory increase in the length of the posterior fossa in adults. Further studies comparing adult and pediatric patients are required to fully elucidate the dynamic and potentially age-related pattern of the occipital dysplasia in the Chiari I malformation. Patients with Chiari II malformation also have a small

posterior cranial fossa, but the pattern of occipital dysplasia shows some differences from that of the Chiari I malformation. A reduced clivus-supraocciput angle (the angle formed between the lines drawn along the axes of the clivus and supraocciput) has been reported among Chiari II patients [42]. The following equations reflect the morphological significance of the clivus-supraocciput angle:

$$\text{Basicranial angle} + \text{Clival angle} = 180^{\circ} \quad (5.1)$$

The clival angle is between Twining's line and axis of the clivus, and the basicranial angle is formed between the axis of the clivus and horizontal plane of the anterior basicranium.

$$\text{Supraoccipital angle} + \text{Clival angle} + \text{Clivus Supraocciput angle} = 180^{\circ} \quad (5.2)$$

The supraoccipital angle is between Twining's line and the axis of the supraocciput. Based on Eqs. 5.1 and 5.2, Eq. 5.3 can be obtained.

$$\text{Clivus Supraocciput angle} = \text{Basicranial angle} - \text{Supraoccipital angle} \quad (5.3)$$

Equation 5.3 indicates that a decrease in the clivus-supraocciput angle is associated with (and, in a mechanistic term, caused by) a reduction in the basicranial angle and an increase in the supraoccipital angle. Therefore, the clivus and supraocciput tend to lie perpendicular to Twining's line when the clivus-supraocciput angle is reduced. Figure 5.3 shows the three morphological changes in the posterior cranial fossa, which can potentially explain a reduced clivus-supraocciput angle. These include increased size of the foramen magnum as well as an increased height and reduced length of the posterior fossa. The possibility of an increase in the posterior fossa height in Chiari II malformation is not supported by the literature as the reduction in the posterior fossa volume is recognized as an etiopathogenic factor. Thus, a combination of increased foraminal size and reduced length of the posterior fossa can best explain the co-occurrence of small posterior fossa with the reduced clivus-supraocciput angle in the Chiari II malformation.

## The Neural Tube Overgrowth or Disorganized Neural Tube Growth Theory

This theory was proposed by Barry, Patten, and Stewart [21] in an attempt to link the co-occurrence of neural tube non-closure, Chiari malformation, and other cerebral anomalies with an earlier observation by Patten [43] of a curious neural tube maldevelopment, the so-called overgrowth of the neural tube. The neuroepithelium in such cases was characterized by an enhanced growth, folding and refolding on itself and crowding into the apparently normal surrounding space and ventricular cavity [43]. Later, Patten [44] reported that a local overgrowth may lead to non-closure of the neural tube. Examining the fetuses with caudal neural tube defects and Chiari II malformation, Barry and colleagues observed that (1) the spinal cord segments immediately proximal to the defect were larger than normal; (2) the cerebrum and hindbrain were enlarged; and (3) the proximal cervical spinal cord segments were also larger but were compressed cephalocaudally [21]. They subsequently posited that the neural tube overgrowth phenomenon observed in the fetuses with spina bifida involves distant regions of the developing central nervous system as well and occurs before differential growth of the vertebral column begins. Such a phenomenon, Barry et al. [21] opined, leads to neural tube non-closure (spina bifida), downward displacement of the overgrown hindbrain into the cervical spinal canal (Chiari II malformation), and multiplicity of the cerebral cortical gyri (microgyria). In a rat fetal model of Chiari II malformation induced by maternal dose of ethylenthiourea, hydrocephalus was absent, but overgrowth of the neural tube was evident, indicating that Chiari malformation can develop without hydrocephalus and with crowding of the cranial space by the overgrown brain [45]. The neural overgrowth theory was faced with skepticism as the cerebellum in the Chiari II malformation has often been found atrophied and small postnatally. However, an unbiased revisit of this theory in the light of earlier accounts and most recent observations implies that this theory

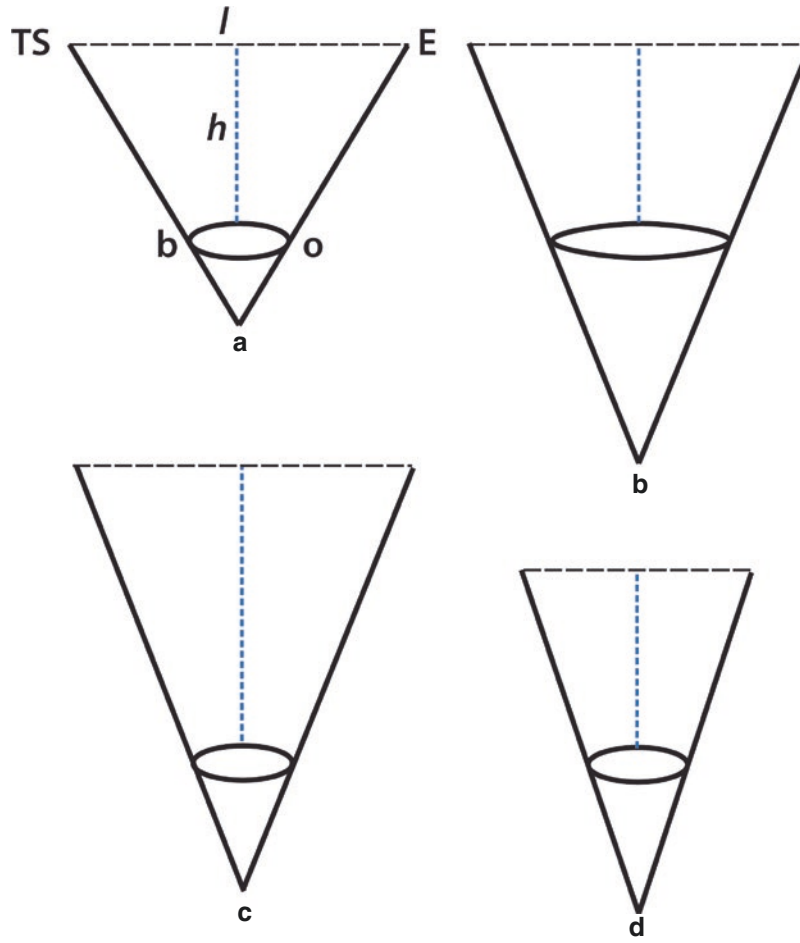


**Fig. 5.3** Line diagrams showing the morphological implications of the reduced clivus-supraocciput angle in the posterior cranial fossa of patients with Chiari II malformation. *TS* tuberculum sellae, *E* endinion, *b* basion, o opisthion. *l* and *h* indicate the length and height of the bony posterior cranial fossa. The oval circle represents the foramen magnum. (**a**) Is the reference diagram representing the normal condition; (**b**), increase in the size of foramen magnum; (**c**), increase in the height of the posterior fossa; (**d**) decrease in the length of the posterior fossa

may indeed be relevant and has the power of explaining such associated anomalies as microgyria, neural dysgenesis, and gray matter heterotopia in the cerebrum and cerebellum of patients with Chiari II malformation. The so-called neural tube overgrowth theory is supported by findings that the brain in the Chiari II malformation is heavier than normal despite the presence of hydrocephalus [36].

Perhaps, the main barrier to the popularity of the neural overgrowth theory is its name, giving rise to a misunderstanding of its pathological nature. Barry and colleagues stated that this term is "a purely descriptive morphological term," thus testifying that it may or may not reflect the underlying histopathogenesis. Experimentally, this phenomenon can be induced by manipulation or extirpation of the notochord, hypoxia, and various non-specific chemical insults in animal embryos [46] and is characterized by disorganized neuroepithelial cell migration and formation of the rosette-like accumulation of cells within the overgrown regions [47] as well as shrinkage of the brain vesicles [48]. Splotch-delayed mouse embryos harboring Pax-3 gene mutation [49] are predisposed to neural tube defects and also demonstrate features of an overgrown neural tube [50]. The so-called overgrowth is associated with mesodermal insufficiency, notochordal abnormality, alterations in the neuroepithelial basal lamina, loss of cellular polarity, disorganized cell orientation, and increased neuroepithelial intercellular space rather than true neuroblast proliferation [51, 52]. Overgrowth of the neural tube in the chicken embryo overexpressing the forkhead transcription factor *FoxG1*

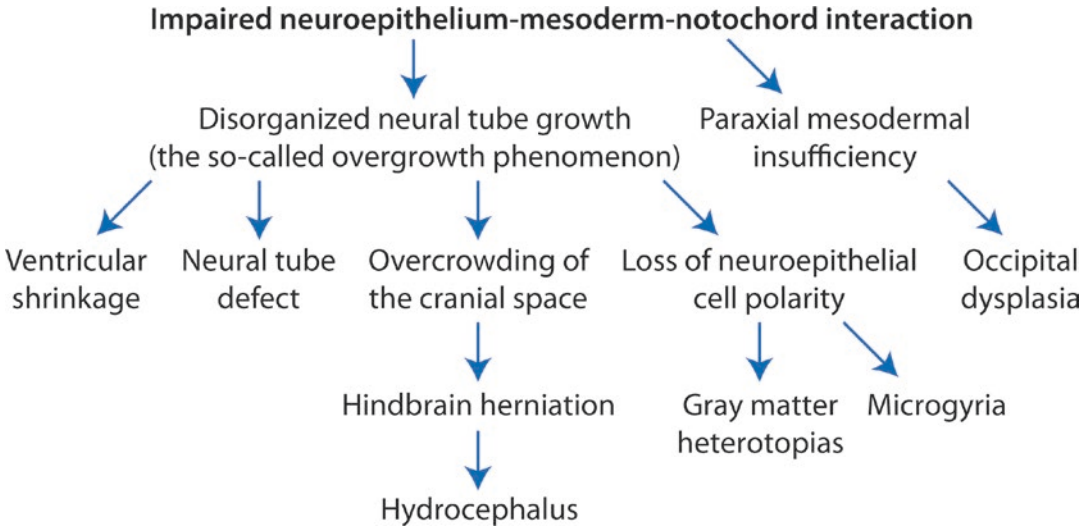


**Fig. 5.4** The proposed sequence of events in the disorganized neural tube growth theory. In splotch-delayed animal models, impaired neuroepithelium-mesoderm-notochord interaction was associated with mesodermal insufficiency and disorganized neural tube growth [52]

is also associated with decreased neuroepithelial apoptosis mainly in the telencephalon and mesencephalon [53].

The data above imply that the phenomenon of "neural tube overgrowth" mentioned by Patten [43] and Barry et al. [21] is in fact a generalized disorder of neuroepithelial organization manifesting as an enlarged, folded, or crowded neural tube in the embryonic or early fetal periods. The manifestation of *disorganized neural tube growth* in late fetal and postnatal life, especially in connection with hindbrain development, remains to be elucidated in experimental studies or studies of aborted human fetuses. If *disorganized neural tube growth* is the underlying factor in the pathogenesis of a neural tube defect (as suggested by Patten [44]), one should look for distant abnormalities in the central nervous system derived from a fused but still disorganized neural tube in patients with a spina bifida defect. Barry et al. [21] proposed that such a pathological phenomenon leads to hindbrain enlargement and herniation and microgyria. It is not unlikely that the structures similar to rosette-like neuroepithelial cell accumulations seen in animal embryos with a disorganized neural tube give rise to the masses of gray matter heterotopia, which are often located periventricularly in patients with Chiari II malformation. There is no direct evidence in the literature as to whether the mesodermal and notochordal abnormalities seen in the experimental models of a disorganized neural tube also contribute to the constellation of axial skeletal anomalies and occipital dysplasia in human fetuses with Chiari II malformation. However, such a possibility is likely, and further studies should address this aspect of maldevelopment. Figure 5.4 shows the proposed sequence of events per the disorganized neural tube growth theory leading to hydrocephalus and hindbrain herniation [52].

## Neuroschisis Theory

This theory was formulated by Padget [1] and, in fact, represented an early attempt to put forth the foundations of an inadequate ventricular distension theory and merge it with the disorganized neural tube growth theory. The neuroschisis or neural cleft is the splitting open of the neural plate. The mesencephalon is the most common site of the cleft. The irregular margins of the cleft are composed of pyknotic cells and occasionally tend to join in an end-to-end manner sometimes with an everted or inverted fusion of the cleft walls. A neuroschisis bleb is formed at the site of the cleft by escape of neurocele fluid into the surrounding mesoderm; this bleb is walled by a

membrane and mesoderm and is often covered by an intact cutaneous ectoderm (primitive skin), but occasionally the skin is also damaged and interrupted by pyknotic, degenerated cells. Padget [1] noted that the process of neuroschisis was associated with folding of irregularly widened neural tube walls into the neurocele cavity and secondary fusion of these folds as well as narrowing of the neurocele cavity. These features are reminiscent of disorganized neural tube growth and, according to Padget [1], are most prominent at the mesencephalon and hindbrain regions, which are relatively voluminous in normal embryos. Padget [1] added that narrowing of the neurocele cavity arises from abnormal folding and fusion of the neural tube walls and partial collapse of the neurocele following rupture of the neural clefts.

Padget [1] postulated that the neuroschisis blebs (1) may undergo healing with some scarring left at the site of the healed neuroschisis, (2) may remain intact as a loculated fluid collection with a mesodermal periphery, or (3) may rupture with eversion of the neural cleft margins, leading to the spectrum of cranium bifidum and spina bifida anomalies, respectively, comprising occulta, cystic, and aperta variants. Reduction in the size of the neurocele secondary to partial neurocele collapse and folding and fusion of the neural tube walls results in micrencephaly. Subsequently, a small posterior cranial fossa ensues as the neural tube folding process is more conspicuous in the voluminous mesencephalic and hindbrain regions of the embryonic neural tube. Neural wall folding and fusion at the mesencephalon lead to stenosis and forking of the aqueduct of Sylvius, and crowding of the meten-myelencephalic junction blocks the outlets of the fourth ventricle, leading to hydrocephalus. Subsequent development of the crowded cerebellum within a small posterior cranial fossa results in a Chiari malformation. Figure 5.5 shows the sequence of events proposed by the neuroschisis theory.

## Cord Traction or Tethered Cord Theory

This theory was proposed by Penfield and Coburn [54] based on surgical and autopsy findings in an adult patient with hindbrain herniation and a history of operation for a thoracic meningomyelocele in childhood. At the level of the bifid vertebral arch, the dura mater and spinal cord were dorsally attached to the soft tissues by fibrous adhesions. The brain stem was elongated, and the lower brain stem and cerebellum were herniated downward through the foramen magnum. The cisterna magna was obliterated, and the space between the cerebellum and tentorium was enlarged to form a supracerebellar cisterna. The lower cranial nerves and cervical nerves demonstrated a prominent ascending course rather than their expected descending or horizontal course. The tip of the herniated cerebellum was firmly adherent to the spinal cord by meningeal adhesions, and upon release of these adhesions, the herniated cerebellum retracted upward for a significant distance. Penfield and Coburn [54] then proposed that spinal cord fixation at the level of the bifid vertebral arch produces traction on the cord during vertebral growth. This traction interrupts the normal ascent of the spinal cord and results in downward traction of the brain stem and spinal cord and nerves above the point of fixation.

Lichtenstein [18] expounded upon the cord traction theory to explain the co-occurrence of Chiari II malformation with hydrocephalus and syringomyelia. He posited that spinal cord stretching secondary to various dysraphic conditions results in hindbrain herniation early in life and spinal cord degeneration later in life. Secondary to spinal cord stretching, the brain stem is elongated. The medulla oblongata, fourth ventricle, choroid plexus, and vermis are pulled downward. Midbrain traction results in the elongation, flattening, and stenosis of the aqueduct of Sylvius, which subsequently leads to the hydrocephalus of the third and lateral ventricles. The herniated choroid plexus produces CSF. As the fourth ventricle is collapsed and restricted at the foramen magnum, the CSF escapes into the substance of the upper cervical spinal cord through a diverticulum or fissure along the intramedullary path of least resistance, leading to syringomyelia. Penfield and Coburn [54] and Lichtenstein [18] noted that with distal cord tethering, the fourth ventricle is obliterated by a wedge-shaped pro-

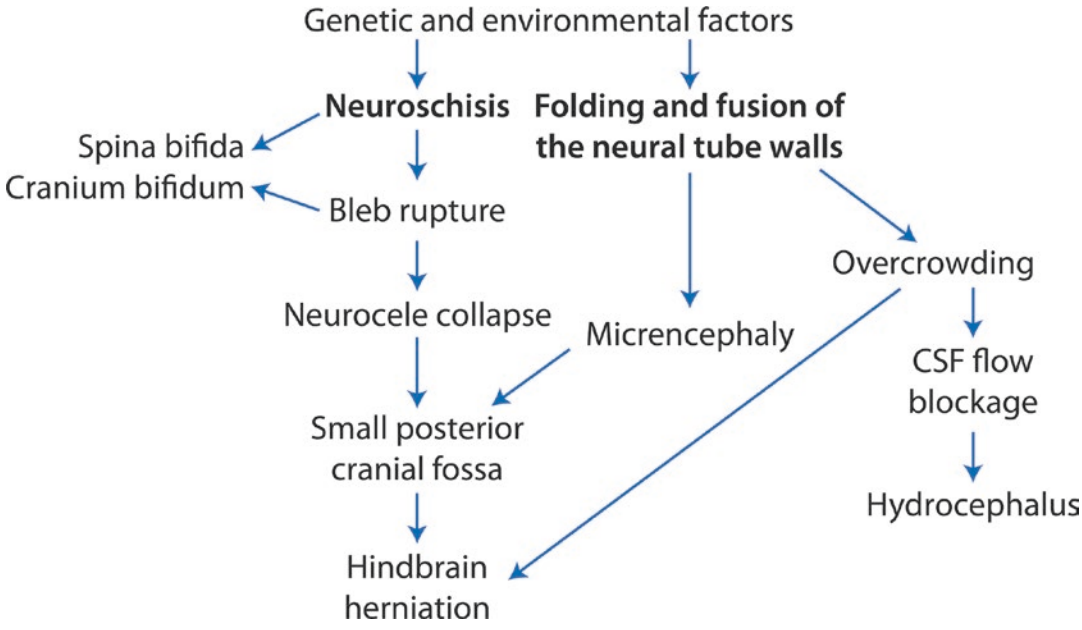


**Fig. 5.5** The sequence of events in the neuroschisis theory of Padget leading to a neural tube defect, hindbrain herniation, and hydrocephalus

trusion of the upper medulla or pons into the ventricle. Such brain stem deformation also blocks the fourth ventricle leading to hydrocephalus. In order to explain this finding, Lichtenstein [18] proposed that the dorsal part of the spinal cord is often fixed in the midline in case of tethering. Thus, the ventral part of the spinal cord and hindbrain ascends to a greater extent than does the dorsal part. This results in a relative overcrowding of the ventral hindbrain, which wedges backward into the fourth ventricle.

Ultimately, the cord traction theory states that hindbrain elongation/herniation is due to impediment of normal ascent of the spinal cord during axial growth and subsequent downward pulling of the cord. Protracted spinal cord traction should be present since the fetal or early postnatal growth period to sufficiently interfere with spinal cord ascent and cause hindbrain herniation [55]. The spinal ascent is a passive process related to the disproportionate growth rates of the vertebral column and spinal cord. Failure of cord ascent is due to the fixation of the spinal cord against the elongating vertebral column. This theory is able to explain the occurrence of brain stem gross abnormality, stenosis of the aqueduct of Sylvius, hydrocephalus and syringomyelia in patients with spinal dysraphism, and a tethered cord. However, the validity of the caudal traction theory was doubted by Barry et al. [21] as they noted that the tension exerted by the anchorage of the spinal cord at the level of the spina bifida defect is dissipated within five spinal cord segments. The ascending course of the upper cervical spinal nerves attributed to caudal cord traction by Penfield and Coburn [54] and Lichtenstein [18] was instead attributed to the compression of the cervical cord by the enlarged and herniated hindbrain (Barry et al. [21]).

## Developmental Arrest Theory

This theory was suggested by Daniel and Strich [56]. They postulated that hindbrain abnormalities in Chiari malformations are a consequence of failure in normal development of the pontine flexure. The pontine flexure together with the mesencephalic and cervical flexures develops late in the first month of embryonic life as the brain grows rapidly [57]. Therefore, the flexures reduce the length of the neural tube along the longitudinal axis of the body. According to Daniel and Strich [56], if the pontine flexure does not

develop, the vascularized rhombic roof fails to normally invaginate into the rhombic cavity. Therefore, it is retained as a thick fibrovascular band connecting the caudal vermis to the obex and dorsal medulla. The cerebellum wraps around the brain stem, and the elongated hindbrain herniates through the foramen magnum. In this theory, the elongated brain stem is a primary event central to the pathogenesis of Chiari malformation. In contrast, brain stem elongation is secondary to tethering of the cord in the caudal traction theory. This theory has major shortcomings. Firstly, formation of the pontine flexure is necessary for cerebellar anlages and primordium to come into a horizontal plane securing the normal development of the cerebellum in such a way that in the mature cerebellum, the vermis is located medially and the hemispheres laterally. If the pontine flexure does not develop normally, then it is reasonable to assume that the cerebellar anlages would retain a rather angular position. Therefore, in the mature cerebellum, the cerebellar vermis and hemispheres would, respectively, be superiorly and inferiorly positioned. This pattern is not appreciated in cases of Chiari malformation. Secondly, the fibrovascular adhesions between the cerebellum and medulla are in fact due to failure of the area membranacea inferior to differentiate and thin out. As a result, the choroid plexus does not normally grow into the rhombic cavity but infiltrates the thickened rhombic roof [58]. Finally, like the mesencephalic and cervical flexures, the pontine flexure straightens during brain development [57]. Although the pontine flexure initially leads to invagination of the rhombic roof, it could not be a main factor in maintaining the intraventricular position of the choroid plexus. Instead, it has been shown that intorsion of the choroid plexus is associated with inward rotation of the caudal vermis favored by regression of the area membranacea inferior and perforation of the rhombic roof [58].

## Inadequate Ventricular Distension Theory

This theory was suggested by McLone and Knepper [59] and was based on the observation that the spinal neurocele undergoes a transient and partial collapse early in the developing embryo. McLone and Knepper [59] found a temporal association of this partial neurocele occlusion with distension of the cranial vesicles in a mouse embryo model. They attested that in the embryo with a neural tube defect, the occlusion process is defective in a way that the ventral portion of the spinal neurocele fails to collapse in the midline and the medial walls do not come into opposition. The latter results in less-than-normal distension of the cranial vesicles, which leads to the formation of a small posterior fossa from lack of the adequate forces necessary to expand the surrounding mesenchymal primordia of the chondrocranium. Subsequently, the development of the rhombencephalon in an inadequate and fixed space results in the downward displacement of the brain stem and cerebellum.

McLone [60] further expounded upon this theory in an attempt to link the co-occurrence of pan-brain and calvarial anomalies with the Chiari II malformation. Figure 5.6 shows the sequence of events led by an inadequate ventricular distension. Hydrocephalus is not a primary event in this theory, but is secondary to hindbrain herniation and overcrowding of the intracranial cavity resulting in blockade of CSF flow through the restricted foramen magnum and obliterated subarachnoid space as well as occlusion of the fourth ventricular outlet and aqueduct of Sylvius. The cortical dysplasia and gray matter heterotopias are attributed to lack of the inductive ventricular forces necessary for normal development and organization of the telencephalon. A large massa intermedia is due to abnormal approximation and fusion of the thalami in a collapsed third ventricle. McLone [60] also posited that normal orientation of calvarial ossifying collagen bundles requires distension of the lateral ventricles; the inadequate ventricular distension causes these ossifying bundles to abnormally whorl, leading to the appearance of the lacunar skull (craniolacunia). The inadequate ventricular distension theory has been supported by experimental data. In the fetal rat model of dysraphism induced by a midline dorsal incision deep into the medulla oblongata during late pregnancy, hindbrain herniation consistent with Chiari type II malforma-

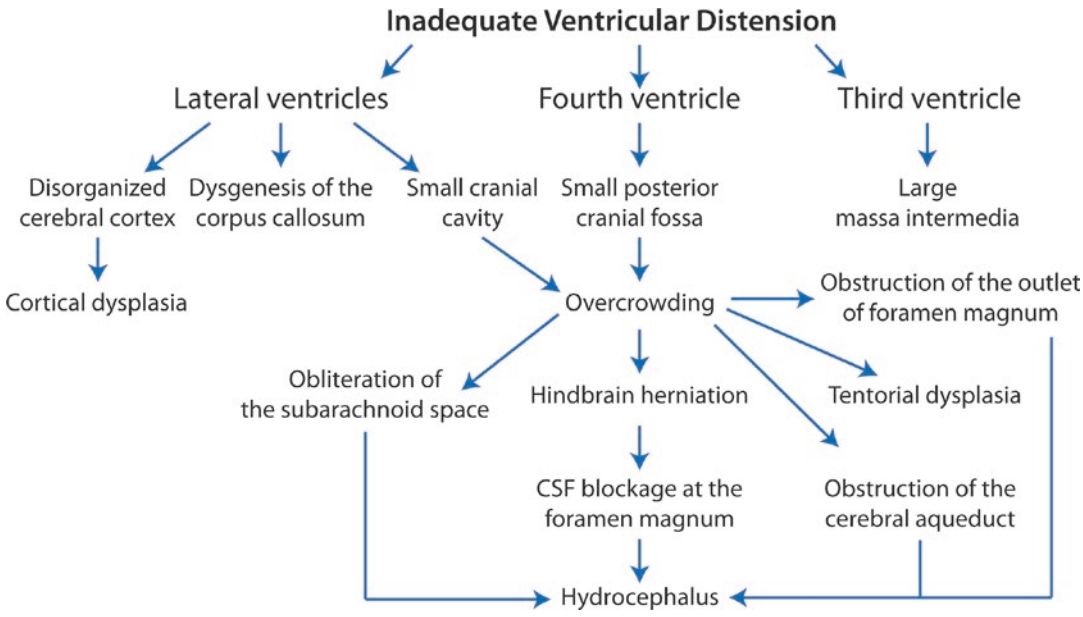


**Fig. 5.6** A flow diagram showing the sequence of pathological events favored by inadequate distension of the lateral, third, and fourth ventricles

tion was noted in surviving animals [61]. This observation indicated that *significant* leakage of CSF distal to the brain stem is sufficient to result in hindbrain herniation. Although this theory explains the small posterior cranial fossa in Chiari II malformation, it fails to provide a clue to the pathoembryogenesis of Chiari I malformation.

## Craniocervical Growth Collision or Caudocranial (Reversed) Vertebral Growth Theory

This theory, suggested by Roth [62], is pertinent to the pathogenesis of Chiari malformation in the case of lumbar tethering of the spinal cord such as observed in patients with a caudal meningomyelocele. Craniocervical growth collision theory claims that hindbrain herniation is essentially secondary to maldevelopment of the vertebral column. Roth maintained that:

1. The developing neurocele is always separated from the surrounding skeletogenic tissues (primordia of axial skeleton) as the subarachnoid space is apparent as early as when chondrification takes place.
2. The availability of space along the developing central nervous system determines the distribution of and relative quantity of the skeletogenic mesoderm.
3. With the onset of a neuro-vertebral growth differential, the relatively faster growth of the vertebral column overrides the growth of the spinal cord.
4. With upward retraction of the spinal cord, more space is available caudally for distribution of skeletogenic tissue; thus, the vertebral column grows caudally below the level of the spinal cord.

This pattern is referred to as cranio-caudal direction of vertebral growth, which, according to Roth, is a "basic growth law." With fixation of the spinal cord to the caudal vertebrae, upward ascent of the cord is restricted. Therefore, skeletogenic materials are distributed cranially, colliding with the developing skull base. This pattern is referred to as a caudocranial direction of vertebral growth (reversed cervical growth or reversal of cranio-caudal vertebral growth), which,

according to Roth, leads to the following abnormalities:

1. "Sucking up" of the hindbrain into the upper cervical spinal canal
2. Upward rather than downward slanting of the upper cervical spinal nerves, giving rise to the impression of a "cervico-cranial cauda equina"
3. Funneling of the upper cervical spinal canal and widening of the foramen magnum
4. Secondary hydrocephalus
5. Basilar invagination

Per this theory, the sequence of events leading to Chiari malformation begins with a primary neural tube defect, which then alters the development of the vertebral column, secondarily leading to the malformation of the hindbrain at the craniocervical junction. Although the craniocervical growth collision theory essentially associates Chiari malformation with dysraphism, Roth attempted to attribute the Chiari malformation of non-dysraphic states to a "genuine" (i.e., primary or intrinsic) abnormality of axial growth. Roth further mentioned the phenomenon of "postembryonic neural growth" (especially that of the cerebellum), which contributes to the pathogenesis of hindbrain herniation by caudal displacement of the growing neural tissue within the collided craniocervical junction. Not mentioned by Roth, however, is the adaptability of the craniocervical growth collision theory for explaining the occurrence of atlanto-occipital or cervical vertebral fusion in Chiari patients. These abnormalities may represent a reaction to the cranially directed colliding force stimulating abnormal osteogenesis and fixing the derivatives of the occipital and cervical somites.

## Theory of "Suck and Slosh" Effect as the Cause of Origin and Expansion/Maintenance of a Spinal Cord Syrinx

This theory was formulated by Williams [63, 64] to provide a mechanism for formation and maintenance of communicating and non-communicating spinal cord syrinx seen with Chiari malformations. This theory maintains that under physiologic conditions and at rest, the pressure within the spinal canal is equal to the intracranial pressure. With maneuvers that increase thoracoabdominal pressure, the spinal CSF pressure initially goes up but soon equalizes with the intracranial pressure by the shift of CSF from the spinal to the intracranial compartment. Following the cessation of the straining maneuver, the spinal CSF pressure goes down, which also rapidly equalizes with the intracranial pressure by the shift of CSF between the two compartments. If the pressure within the spinal canal becomes substantially lower than the intracranial pressure for a prolonged time (the so-called phenomenon of craniospinal pressure dissociation), the relative negative pressure within the spinal cord tends to "suck" the CSF from the fourth ventricle down into the spinal cord central canal and tissues, leading to the formation of hydromyelia and syringomyelia. This "suck" effect occurs in Chiari patients and causes further downward displacement of the hindbrain through the foramen magnum. Once a significant hindbrain (tonsillar) herniation is established and the upper cervical spinal cord central canal is secondarily impacted at or below the level of the foramen magnum by the herniated tonsils, the anatomical communication between the fourth ventricle and syrinx closes off. Next, the maintenance or further expansion of the syrinx takes place by another mechanism, the so-called "slosh" effect. Accordingly, the fluctuation in the CSF pressure within the spinal subarachnoid space is transmitted to the spinal cord and the wall of the syrinx externally. The increased spinal CSF pressure compresses the syrinx leading to the egress of the intrasyrinx fluid rostral and/or caudal to the site of its maximum compression. This potentially forceful pulsatile and bidirectional movement of intrasyrinx fluid extends the syrinx at its proximal and distal ends without the need for any anatomical communication between the syrinx cavity and the intracranial ventricular system. Expansion and maintenance of the syrinx are further contributed to by the perivascular transport of spinal CSF into the syrinx cavity.

Thus, the "suck" effect is driven by the craniospinal pressure dissociation, and the "slosh" effect is driven by the isolated spinal CSF pressure fluctuation. In an attempt to explain the mechanism underlying the fluctuations in the spinal CSF pressure, Williams stressed that the spinal CSF pressure is mainly a result of extradural spinal venous pressure. Increases in the extradural spinal venous pressure with Valsalva maneuver lead to an increase in spinal CSF pressure. Following the cessation of the restraining maneuver, an abrupt increase in the spinal venous outflow leads to a rebound decrease in the spinal CSF pressure. In this way, fluctuations in the spinal CSF pressure reflect the pressure fluctuations of the spinal venous system. The mechanism behind the "suck" effect and craniospinal pressure dissociation is slightly more complex. In patients with hindbrain herniation not significant enough to cause impaction of the cord, the herniated hindbrain (tonsils) acts as a unidirectional valve. The CSF can move in an upward direction from the spinal to the cranial compartments; however, downward movement of CSF from the cranial to the spinal compartment is dampened by the synchronous downward movement of the herniated hindbrain and partial obstruction at or below the level of the foramen magnum. Such dampening of CSF flow in the craniospinal direction results in an aggravated and protracted (rebound) decline in spinal CSF pressure in relation to the intracranial pressure.

The "suck and slosh" effect of Williams is pervasive and can explain the occurrence of communicating and non-communicating syringomyelia as well as their temporal relationship. In this theory, the communicating syringomyelia is the precursor for the non-communicating syringomyelia, and temporally, these two are separated by the timing of *significant* hindbrain herniation through the foramen magnum. At first, the *internally* acting "suck" effect leads to formation of syringomyelia, and once a significant hindbrain herniation occurs, the syrinx is maintained or expanded by the *externally* acting "slosh" effect. However, this theory cannot explain and was not proposed to explain the events leading to the occurrence of initial hindbrain herniation, which are necessary to generate the "suck" effect. Notably, in patients with Chiari I malformation, syringomyelia is more commonly found in patients with moderate cerebellar herniation (9–14 mm) than in those with smaller or larger herniation [65]. Thus, it is reasonable to assume that the valve-like mechanism imposed by the herniated hindbrain is more efficient at the moderate degrees of herniation. While the smaller herniation may not be sufficient enough to induce a valve-like mechanism, the larger herniation hinders this mechanism by blocking the CSF flow through the foramen magnum in both upward and downward directions and eliminating the "suck" effect.

## Exaggerated Spinal CSF Systolic Wave Theory of Syringomyelia

This theory proposed by Oldfield et al. [33] only deals with the pathogenesis of syringomyelia in patients with Chiari malformation. The theory stresses the earlier observations of du Boulay et al. [66, 67] that in normal individuals and during the cardiac systole, CSF moves downward from the cranial into the spinal subarachnoid space through the foramen magnum to accommodate for the increased intracranial blood volume. During diastole and when blood rushes out of the cranial cavity, the CSF flow is reversed back into the cranial subarachnoid space. This waveform or pulsatile flow of CSF across the foramen magnum is approximately ten times greater than the synchronous CSF flow through the fourth ventricle. In the cases examined by Oldfield et al. [33], they noted that the communication between the spinal syrinx and fourth ventricle (i.e., upper cervical spinal cord central canal) in Chiari I patients was invariably closed. Contrary to the prediction of Gardner's theory, they also noted that, in fact, the syrinx constricts during cardiac systole and expands during diastole. The systolic constriction of the syrinx was synchronous with the downward excursion of the herniated tonsils. The CSF "to-and-fro" flow between the cranial and spinal compartments was dampened as a result of partial occlusion of the

subarachnoid space at the level of the foramen magnum (secondary to hindbrain herniation). Based on these findings, Oldfield et al. [33] concluded that (1) the sudden, pistonlike excursion of the herniated tonsils transmits an accentuated pressure wave on the spinal CSF and creates an exaggerated CSF pulsatile pressure in the spinal canal during systole, (2) the exaggerated spinal CSF pulse pressure acts on the syrinx externally causing its compression, and (3) by diastole, the spinal CSF pressure suddenly ceases, leading to sudden expansion of the syrinx during diastole. Ultimately, Oldfield et al. [33] formulated a new theory to compensate for the inadequacy of Gardner's hydrodynamic theory of syringomyelia: The exaggerated CSF wave pressure during cardiac systole leads to a greater than normal passage of CSF along the perivascular spaces of the spinal cord into the cord substance. Intramedullary accumulation of CSF leads to the formation of syringomyelia. The pathophysiology of syringomyelia in Chiari I malformations is further discussed in Chap. 12 ("Research on the Pathophysiology of Chiari I-Related Symptoms and Syringomyelia, with Emphasis on Dynamic MRI Techniques").

## Peri-Odontoid Pannus

We recently hypothesized that inflammatory reactions—e.g., pharyngitis in the peri-odontoid region—might result in inhibition of CSF flow at the craniocervical junction with resultant raised intracranial pressure [68]. Such raised pressure above the foramen magnum might then result in hindbrain herniation (Fig. 5.7). Our experience with the pediatric CIM has shown that almost 1 in 20 patients who present with symptoms is found to have a peri-odontoid pannus (Fig. 5.8).

These masses ranged in size from 4 to 11 mm in diameter (Fig. 5.8). Forty percent had a history of clinically significant pharyngitis or pharyngeal abscess. Pannus formation around the odontoid process resulted in ventral compression of the craniocervical junction in each of these patients. Highlighting the hypermobility that causes such lesions, following fusion, the pannus and symptoms in several patients were diminished.

Pharyngeal inflammatory conditions are known to cause disorders of the craniocervical junction. Non-traumatic atlanto-axial subluxation following an upper respiratory tract infection or surgical intervention in the head and neck region, also referred to as Grisel's syndrome, is the prime example. The syndrome is named after Pierre Grisel, a French ENT specialist who described three such cases of patients with pharyngitis associated with torticollis and atlanto-axial subluxation. It was Bell [69], however, who first reported a patient who suffered from pharyngitis that consequently died from spinal cord compression from atlanto-axial subluxation. His report underlines the potential consequences of this rare condition that affects primarily the pediatric population. Even though the precise pathogenesis of Grisel's syndrome remains unknown, the condition is attributed to spread of septic emboli from an infection nidus via the pharyngovertebral veins to the peri-odontoid vascular plexus, resulting in ligamentous laxity.

The vascular supply of the pharynx, peripharyngeal space, and odontoid process illustrate their close relationship. Parke [70] demonstrated that small venous branches drain the posterior nasopharyngeal region into two sets of pharyngovertebral veins. These pharyngovertebral veins pass through the upper posterior pharyngeal wall, penetrate the anterior atlanto-occipital membrane, and drain into the peri-odontoidal plexus, providing the anatomical correlate for the hematogenous spread of septic exudates thought to occur with Grisel's syndrome. The theory of direct spread of infectious material via the aforementioned route is complemented by Battiata and Pazos' [71] two-hit hypothesis. According to the hypothesis, patients with baseline laxity of the atlanto-axial joint (first hit), such as children or patients with Down syndrome, are more susceptible to muscle spasm that is triggered by inflammatory mediators transported to the cervical muscles by the pharyngovertebral venous plexus (second hit) and consequently develop Grisel's syndrome.

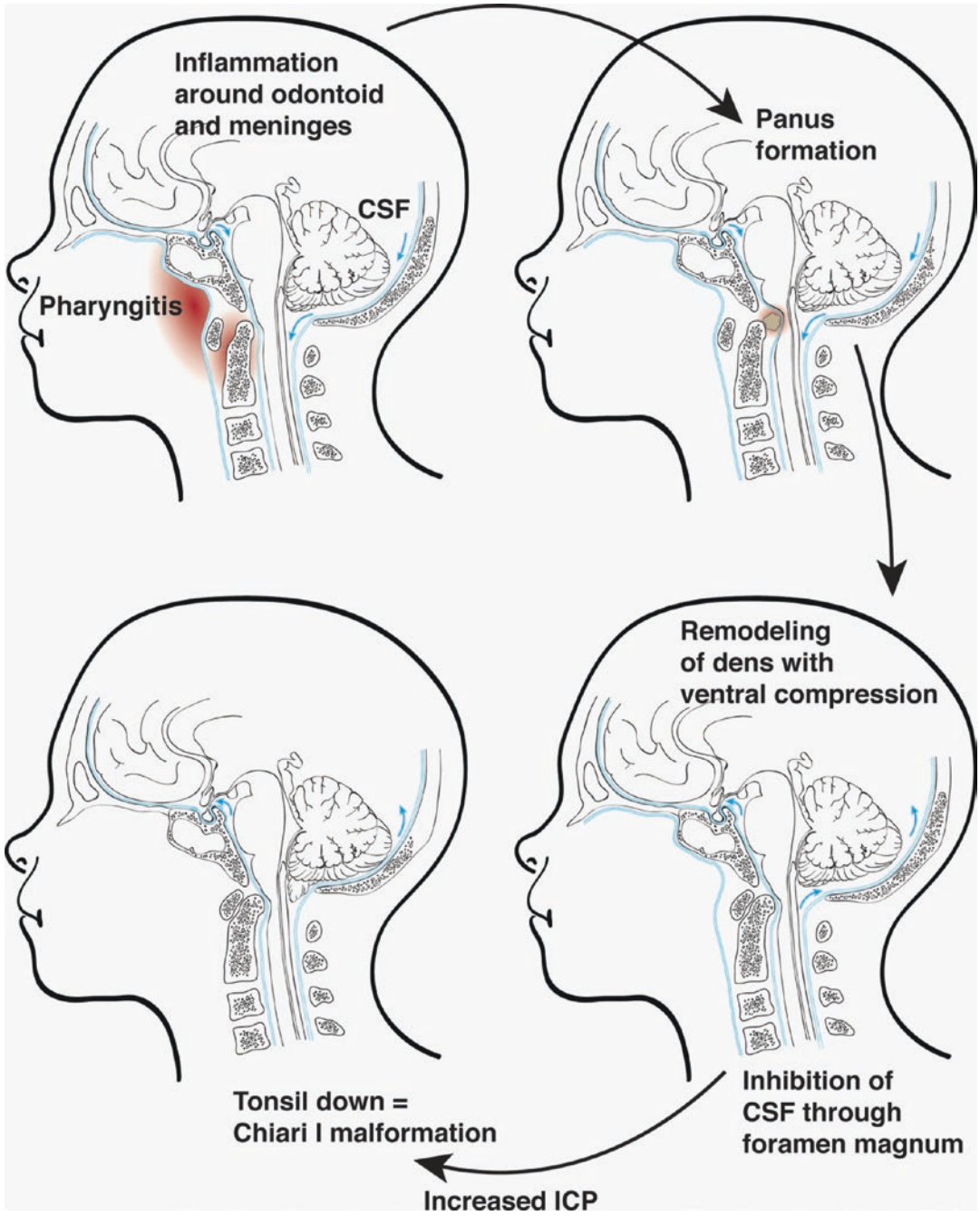


**Fig. 5.7** Hypothetical process of peri-odontoid pannus formation with resultant Chiari I malformation

Chiari malformations are dynamic processes that may change with time. While they are generally considered a congenital condition, acquired Chiari malformation as a result of various causes is well described. The pathophysiology responsible for the development of a CIM seems to involve impaired CSF circulation out of the fourth ventricle and across the craniocervical junction. We hypothesize that inflammatory pharyngeal conditions attribute to the impendence of CSF circulation and to the formation and progression of CIM.

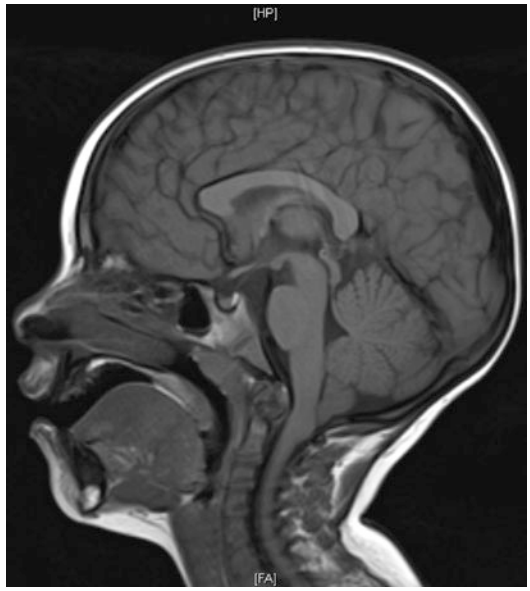


**Fig. 5.8** MRI of patient with peri-odontoid process pannus and CIM

Abnormalities of the bony elements of the craniocervical junction are common in patients with CIM. Up to a quarter of all patients with CIM have an increased incidence of a retroflexed odontoid process. A smaller percentage have concomitant atlanto-occipital fusion and basilar invagination. Associated abnormalities of the craniocervical junction contribute to the impairment of CSF circulation, as evidenced by the observation that a higher grade of odontoid retroflexion is more frequently associated with syringomyelia and holocord syrinx [72].

Hypermobility of the occipitoatlantal and atlanto-axial joints is a well-established cause of retro-odontoid pannus formation in patients with hereditary connective tissue disorders. While those patients may be particularly susceptible, pannus formation is also frequently observed in CIM patients not possessing underlying connective tissue disorders. In patients with underlying

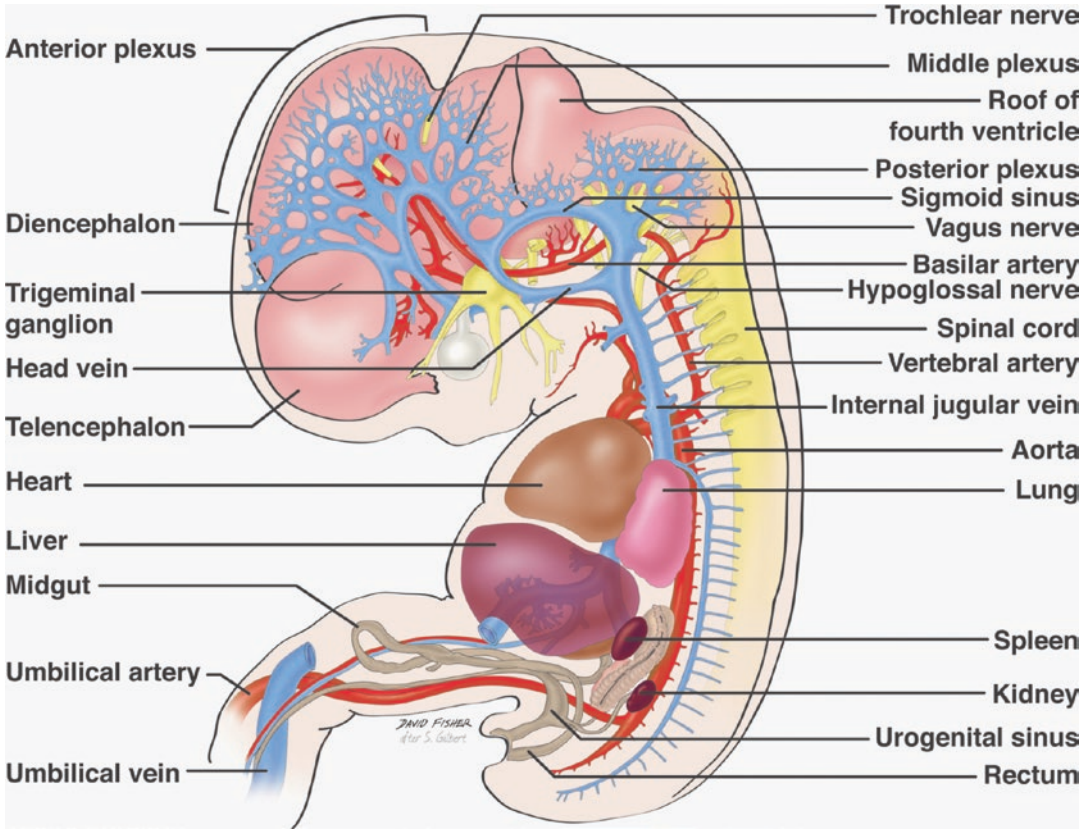


**Fig. 5.9** Schematic drawing of the developing human and noting the complexity of the developing brain and posterior cranial fossa

craniocervical junction abnormalities, such as odontoid retroflexion and pre-existing CIM, acceleration of pannus formation may have profound radiographic and clinical consequences. One extreme example of an association of pharyngeal infection and CIM is a reported case of mononucleosis resulting in transient, highly symptomatic CIM that completely resolved with treatment of the infection [73].

## Conclusion

The development of the hindbrain and craniocervical junction is a complicated process resulting in eloquent structures (Fig. 5.9). Derailment of this process can result in Chiari malformations. However, the exact reason for these hindbrain hernias remains elusive but is multifactorial.

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