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3.1 Introduction

Syringomyelia and hydrocephalus, from whatever cause, are characterised by the abnormal accumulation of fluid within cavities in the central nervous system (CNS), suggesting that there is a failure of fluid drainage systems in these conditions.

Extracellular fluid in the CNS consists of cerebrospinal fluid (CSF) and interstitial fluid (ISF). CSF is produced by the choroid plexuses and circulates through the ventricular system and the subarachnoid spaces of the brain and spinal cord. Drainage of CSF is partly into the blood through arachnoid granulations and villi and partly along lymphatic drainage pathways, mostly associated with the cribriform plate of the ethmoid bone (Johnston et al. 2004). Interstitial fluid is larger in volume than CSF: in humans 250 mL compared with 140 mL of CSF (Bergsneider 2001). Derived from the blood, ISF and solutes circulate through the narrow extracellular spaces of the CNS and drain out with soluble brain metabolites, along basement membranes of capillaries

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and arteries to lymph nodes (Carare et al. 2008; Weller et al. 2009b). Disturbances of CSF drainage result in hydrocephalus and syringomyelia, whereas failure of ISF drainage appears to play a role in the aetiology of neurodegenerative diseases, particularly Alzheimer's disease (Weller et al. 2009c, 2011).

This chapter reviews the production, circulation and drainage of cerebrospinal fluid and interstitial fluid from the central nervous system and how the balance between the two fluids is disturbed in hydrocephalus and syringomyelia. Some attention is also given to pathologies not directly related to syringomyelia but which serve to illustrate how metabolic consequences of altered CSF and water movement in the CNS might account for some of the hitherto unexplained phenomena relating to syringomyelia.

3.2 Choroid Plexus and the Production of CSF

Cerebrospinal fluid is produced by the choroid plexuses at the rate of approximately 350 $\mu\text{L}/\text{min}$ in humans (Davson et al. 1987). The major choroid plexuses are in the lateral and third ventricles and in the fourth ventricle, from which the plexuses protrude through the foramina of Luschka into the subarachnoid space. Microscopic examination of the choroid plexus reveals two

major components, namely the stroma and the choroid plexus epithelium (Fig. 3.1) (Wolburg and Paulus 2010). The stroma contains blood vessels, meningeal cells and sheaths of collagen (Alcolado et al. 1986). In contrast with the brain, there is little barrier in the plexus blood vessels to the passage of macromolecules into the stroma itself. This is reflected in the entry of contrast media into the choroid plexus and its resultant visualisation by imaging techniques. Leptomeningeal cells in the choroid plexus generate the collagen bands that constitute the major bulk of the stroma. With advancing age, these leptomeningeal cells produce spheres of collagen that become calcified (Alcolado et al. 1986), to such an extent that they are visible in skull x-rays of older individuals.

The anatomical substrate of the blood-CSF barrier is the choroid plexus epithelium, which is derived from the ependymal lining of the ventricles (Johanson et al. 2008). Choroid plexuses are formed by the invagination of leptomeninges into the ventricular cavities and by modification of the ventricular ependymal lining into choroid plexus epithelium. Histological and ultrastructural techniques have shown that the choroid plexus epithelium is composed of cuboidal cells. These are coated by basement membrane on their basal surface, which abuts onto the stroma, and by microvilli on the ventricular surface (Wolburg and Paulus 2010). Tight junctions bind the apical

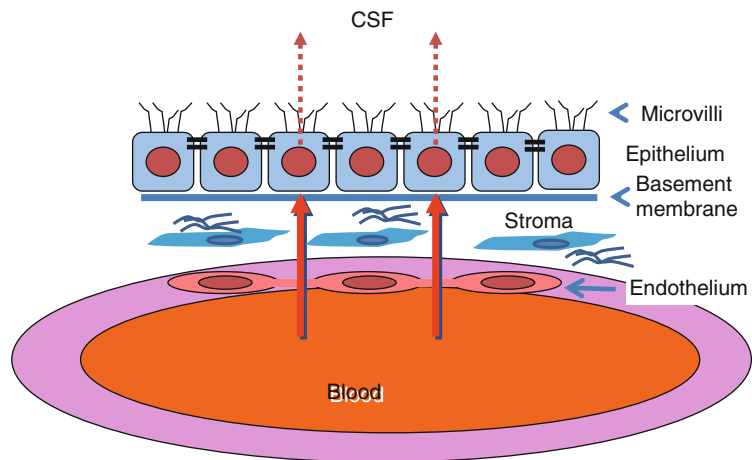


Fig. 3.1 Choroid plexus and the formation of CSF. Fluid and solutes pass freely from the blood through the fenestrated epithelium of choroid plexus capillaries into the stroma (red arrows). CSF is produced by filtration through the choroid plexus epithelial cells

Choroid plexus and the formation of CSF

portions of these epithelial cells together. CSF is formed by the net transport of water, sodium chloride, potassium and bicarbonate ions from the choroid plexus stroma, through the epithelial cells, into the ventricles (Fig. 3.1) (Johanson et al. 2008). This process involves the enzymes carbonic anhydrase C, sodium and potassium ATPases, and aquaporin-1 (AQP1), which reside in the choroid plexus epithelial cells (Johanson et al. 2008; Wolburg and Paulus 2010; Yool 2007). Acetazolamide reduces CSF production by inhibiting carbonic anhydrase C and by reducing the amount of AQP1 through an alteration in protein transcription (Ameli et al. 2012). CSF in humans is produced at a rate of 0.3–0.6 mL/min, or 500–600 mL/day. In those smaller mammals that have been studied, CSF is replaced approximately four times per day (Johanson et al. 2008). A small proportion of CSF appears to be derived, additionally, from brain interstitial fluid (Johanson et al. 2008).

3.3 Circulation and Drainage of the CSF

CSF leaves the ventricular system via the foramina of Luschka and Magendie and flows into the basal cisterns and the cisterna magna. It circulates through the ventricles and the basal cisterns and across the foramen magnum in a pulsatile manner (see Sect. 3.5.2), the pulses being derived from the vascular system (Weller 1995).

There are two major routes of drainage of CSF from the subarachnoid channels (Johnston et al. 2004): (a) alongside cranial and spinal nerve roots, particularly the olfactory nerves as they pass through the cribriform plate of the ethmoid bone, and (b) directly into the blood via arachnoid granulations and villi associated with major cranial venous sinuses.

3.3.1 The Ventricular System and Ependyma

The cerebral ventricular system is lined by ependyma, which develops during foetal life. In the postnatal brain and in the adult brain, ependyma

consists of a single layer of ciliated cuboidal epithelial cells (Del Bigio 1995), but in the adult human brain, there are frequently areas of the ventricular walls that are devoid of ependyma, leaving the subependymal glia exposed to ventricular CSF. Ependymal cells are joined by gap junctions and lack the tight barrier function of choroid plexus epithelium so that, even in brains with intact ependyma, tracers injected into the ventricles pass freely into the periventricular tissue, particularly into the white matter (Abbott 2004). The central canal of the spinal cord is well defined in the foetus and is also lined by ependyma. However, in the adult human spinal cord, the central canal is usually very small or obliterated and marked only by a small, closely packed nest of ependyma cells.

3.3.2 Leptomeninges and the Subarachnoid Space

The human brain and spinal cord are encased in layers of meninges. On the outer surface, and abutting the bones of the skull and spine, is the tough collagenous dura mater, the outer layer of which forms the inner periosteum of the skull. Within the dura, the leptomeninges consist of two major layers; the outer is the arachnoid mater and is applied to the inner aspect of the dura mater. Separated from the arachnoid by the subarachnoid space is the pia mater. The arachnoid and pia are connected by many sheetlike trabeculae of arachnoid-coated collagen that traverse the subarachnoid space and suspend the leptomeningeal arteries and veins within the CSF (Fig. 3.2) (Weller 2005). As arteries penetrate the surface of the cortex, the arachnoid coating is reflected onto the surface of the brain as the pia mater and a single layer of pia mater also accompanies the artery into the surface of the brain (Fig. 3.2) (Zhang et al. 1990). Scanning electron microscope studies have also shown that the pia mater on the brain and spinal cord is reflected onto blood vessels in the subarachnoid space and thus separates CSF in the subarachnoid space from the brain and spinal cord (Figs. 3.2 and 3.3) (Hutchings and Weller 1986; Nicholas and Weller 1988; Weller 2005). The pia mater is usually only one cell

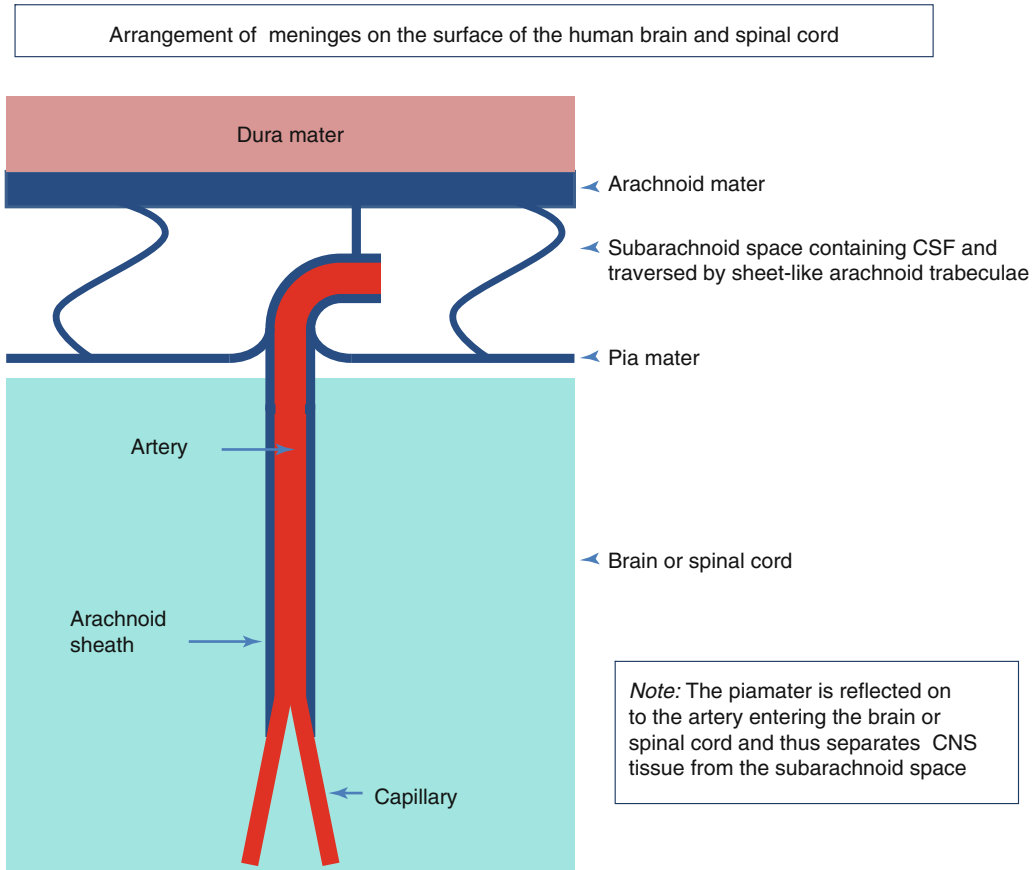


Fig. 3.2 A diagram summarising the arrangement of meninges on the surface of the human brain and spinal cord. Arachnoid mater is closely applied to the dura mater; sheetlike trabeculae cross the subarachnoid space to link arachnoid to the pia mater on the surface of the brain or spinal cord. Pia mater is reflected from the surface

of the brain onto the surface of arteries and veins in the subarachnoid space, thus separating CSF in the subarachnoid space from the brain and spinal cord. A thin layer of pia mater extends alongside arteries as they penetrate the brain or spinal cord

thick and contains intercellular junctions, but it is uncertain how impermeable the pia mater is to the passage of water and macromolecules. Larger particles, such as erythrocytes in subarachnoid haemorrhage, do not penetrate the intact pia mater although inflammatory cells can migrate through this thin cell layer (Hutchings and Weller 1986). Underlying the pia mater, there are bundles of collagen that surround arteries and veins in the subpial space (Alcolado et al. 1988).

The layout of leptomeninges coating the spinal cord differs somewhat from the arrangement of the leptomeninges surrounding the cerebral

hemispheres and the brain stem. Arachnoid mater coating the spinal cord is composed of several layers (Nicholas and Weller 1988) (Fig. 3.4). The outer arachnoid is firmly applied to the inner surface of the dura mater. A series of intermediate layers of arachnoid mater are attached to this parietal layer, and they either spread out over the dorsal and ventral aspects of the spinal cord or form the dorsal, dorsolateral and anterior ligaments. Dentate ligaments on the lateral aspect of the spinal cord (Fig. 3.4) are formed of collagenous sheets that connect the dura to the substantial layer of subpial collagen that surrounds the

Fig. 3.3 Scanning electron micrograph of the surface of the brain as viewed from the subarachnoid space. A leptomeningeal artery spreads its branches over the surface of the pia mater, and before the branches penetrate the brain, the pia mater is reflected on to the surface of the artery (*arrow*) (Reproduced with permission from Hutchings and Weller (1986)). $\times 75$

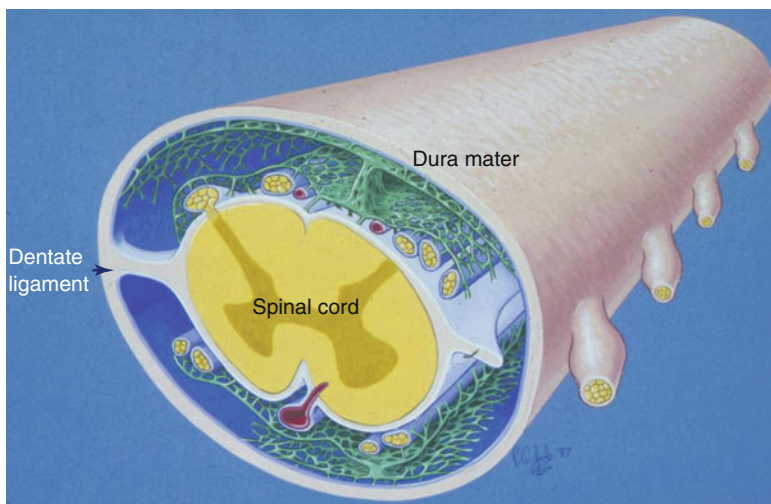
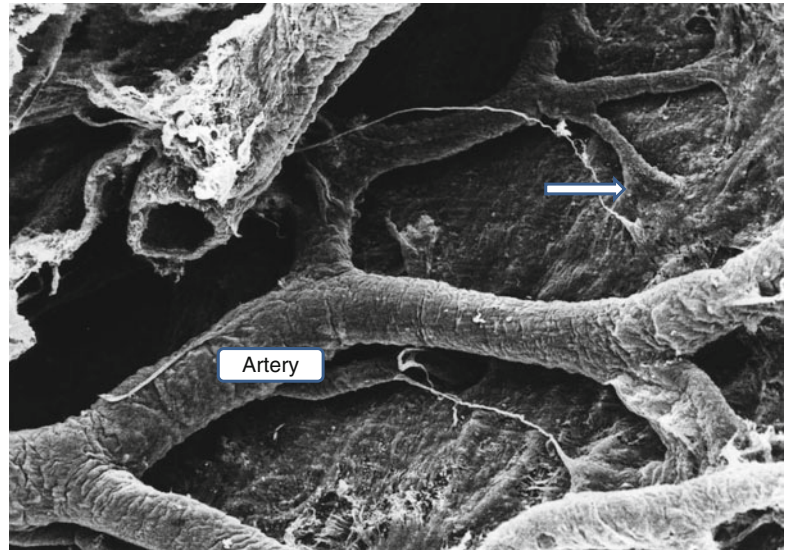


Fig. 3.4 Diagram showing the arrangements of the leptomeninges surrounding the spinal cord. An outer layer of arachnoid mater (*blue*) is applied to the inner aspect of the dura mater. Highly perforated intermediate layers of arachnoid (*green*) arise from the outer arachnoid to coat the dorsal

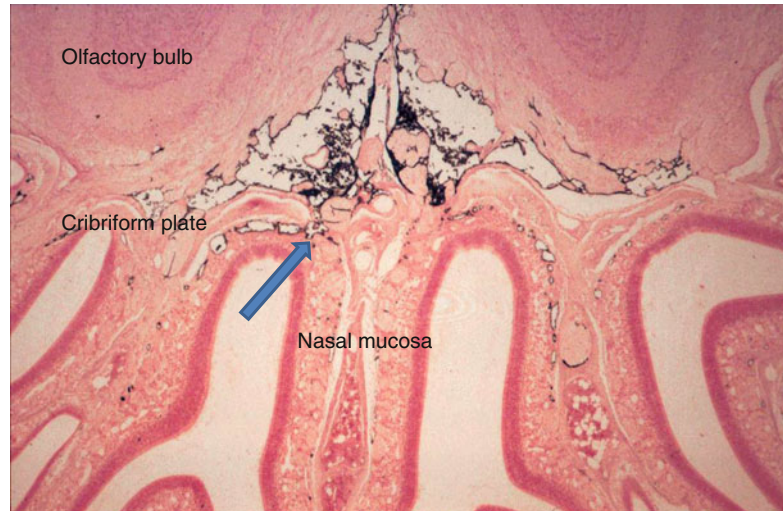
and ventral surfaces of the spinal cord. There is a prominent dorsal ligament and less robust dorsolateral ligaments are also present. The dentate ligaments connect the layer of subpial collagen (*white*) with the collagenous dura (Reproduced with permission from Nicholas and Weller (1988))

spinal cord. The surface of the dentate ligaments is coated by arachnoid mater (Nicholas and Weller 1988). Functionally, the intermediate layers of arachnoid around the spinal cord may act as baffles, modifying the propagation of pressure waves within the CSF passing up and down the spinal subarachnoid channels.

3.3.3 Lymphatic Drainage of the Cerebrospinal Fluid

In smaller mammals such as rats, mice and rabbits and even in larger mammals such as sheep, the major pathways for drainage of CSF appear to be alongside cranial and spinal nerve roots to

Fig. 3.5 Coronal section through the olfactory bulbs, cribriform plate and nasal mucosa of a rat that had received an injection of Indian ink into the CSF. Black Indian ink is seen in the subarachnoid space inferior to the olfactory bulbs. Channels cross the cribriform plate adjacent to branches of the olfactory nerve and allow Indian ink to drain into the lymphatics of the nasal mucosa (*arrow*) (Reproduced with permission from Kida et al. (1993)). Haematoxylin and eosin $\times 40$



regional lymph nodes. This lymphatic drainage of cranial CSF is via well-defined channels that run alongside branches of the olfactory nerves, as they pass through the cribriform plate of the ethmoid bone to nasal lymphatics (Fig. 3.5) (Johnston et al. 2004; Kida et al. 1993). Channels formed by leptomeningeal cells in the subarachnoid space join nasal lymphatics, and when tracers are injected into the cisterna magna in the rat, they drain to lymph nodes in the neck in less than 1 min (Kida et al. 1993). Although there are arachnoid villi in the rat, they are small and mostly associated with the dorsal aspect of the olfactory bulbs (Kida et al. 1993). It is estimated that at least 50 % of cranial CSF in the rat drains to cervical lymph nodes by the nasal route, and this has implications for immunological reactions in the central nervous system (Cserr and Knopf 1992; Weller et al. 2010).

3.3.4 Drainage of Cerebrospinal Fluid via Arachnoid Villi and Granulations

In humans, the brain is much larger than in other mammals and the volume of CSF is much greater. Similarly, the sizes of arachnoid granulations and villi associated with the superior sagittal sinus and other cerebral and spinal sinuses are also much greater (Upton and Weller 1985). In humans, therefore, CSF drains directly back into

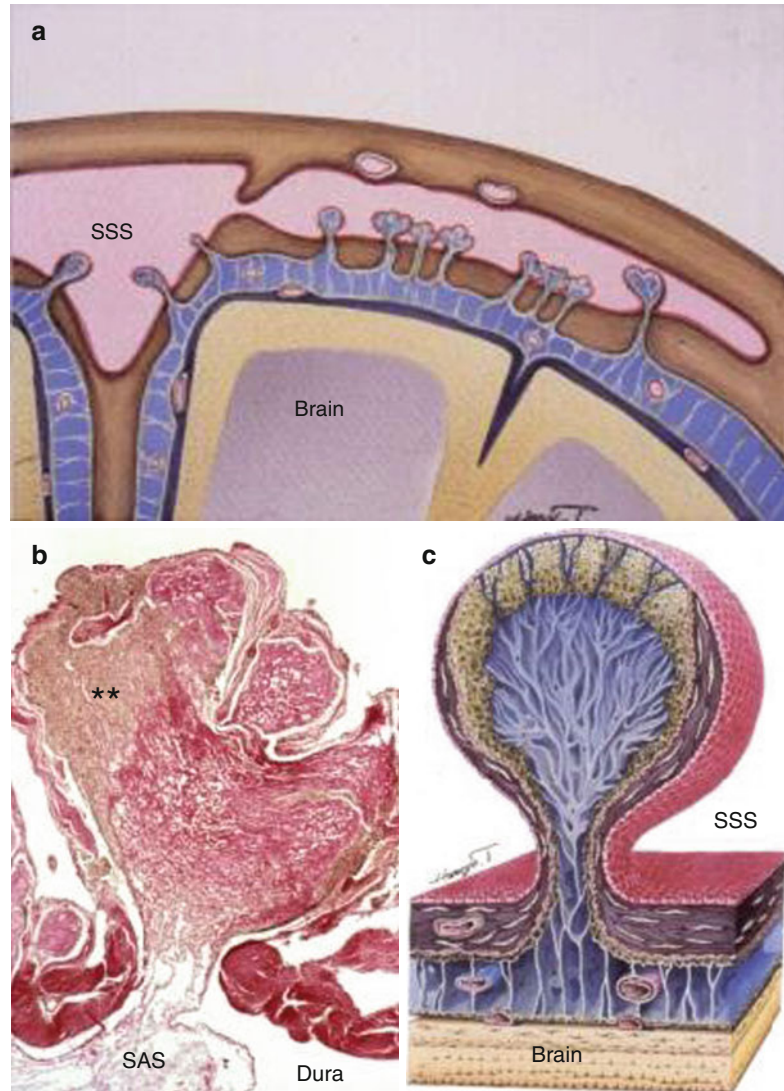
the blood, via arachnoid granulations and villi, as well as through the cribriform plate and nasal lymphatics. However, the balance of amounts of CSF draining via these two routes is still unclear (Johnston et al. 2004).

Structurally, arachnoid granulations and villi are extensions of the leptomeninges, protruding through perforations in the dura mater, into venous sinuses (Fig. 3.6a) (Kida and Weller 1993; Kida et al. 1988). CSF appears to percolate through a mesh of collagenous trabeculae, which is coated by arachnoid cells and located in the centre of the villus or granulation. The CSF finally reaches the venous endothelium via channels in a compacted layer of leptomeningeal cells that caps each granulation or villus (Upton and Weller 1985) (Fig. 3.6b, c). Tracer studies in monkeys suggest that CSF then drains through the venous endothelial cells by a bulk flow mechanism that entails the transport of macrovacuoles across the endothelial cells (Tripathi and Tripathi 1974). Despite the large size of some arachnoid granulations, drainage of CSF appears to be restricted to an apical area some 300 μm in diameter (Upton and Weller 1985).

3.3.5 Other Routes of Drainage of the Cerebrospinal Fluid

In addition to these major drainage pathways for CSF, through venous endothelium and via

Fig. 3.6 Arachnoid granulations in the human brain. (a) Diagram showing the relationship between the brain, subarachnoid space (blue) and the superior sagittal sinus (SSS). Arachnoid granulations extend through the dura from the subarachnoid space into the superior sagittal sinus and its lateral extension. (b) Histological section through the length of an arachnoid granulation. CSF from the subarachnoid space (SAS) passes into channels in the collagenous core (red) of the granulation and then through channels in the arachnoid cap of the granulation (***) to reach the endothelium lining the venous sinus. Haematoxylin van Gieson $\times 40$. (c) Diagram showing the main features of an arachnoid granulation with channels leading from the subarachnoid space to the endothelium (red) of the superior sagittal sinus (SSS) (Reproduced with permission (a, c) from Dr. Shinya Kida and (b) from Upton and Weller (1985))



nasal and spinal lymphatics, some may also be absorbed directly into blood vessels in periventricular tissue (Johnston et al. 2004).

3.4 Interstitial Fluid (ISF)

In common with most other tissues of the body, the central nervous system has interstitial fluid within the extracellular spaces. In contrast with most other tissues, there are no conventional lymphatics in the central nervous system to drain interstitial fluid to regional lymph nodes. However, there are well-defined perivascular

lymphatic pathways in the CNS by which interstitial fluid and solutes drain from the brain and spinal cord. These run along the basement membranes in the walls of capillaries and arteries, to reach regional lymph nodes (Weller et al. 2009b). Perivascular lymphatic drainage of interstitial fluid appears to be largely separate from the CSF drainage, with only 15 % of ISF leaking into the CSF (Szentistvanyi et al. 1984). This is contrary to some established concepts that the CSF acts as a sink for metabolites from the brain, a concept that needs to be re-examined in the light of more recent work on the drainage of interstitial fluid (Carare et al. 2008; Weller et al. 2009b).

3.4.1 The Blood–brain Barrier and Production of Interstitial Fluid

The blood–brain barrier (BBB) is one of the major systems that regulate homeostasis and the constancy of the neuronal environment in the CNS. The BBB is located in the capillary endothelial cells of the brain and spinal cord and appears to be induced by the presence of perivascular astrocytic and neuronal processes; it is characterised by the tightness of intercellular junctions and the relative absence of trans-endothelial vesicular transport (Fig. 3.7a) (Abbott et al. 2006; Nag et al. 2011). Although water may pass freely across the blood–brain barrier, other molecules are actively transported from blood to brain; many substances are blocked from entering the CNS by the blood–brain barrier.

The volume of interstitial fluid in the human brain has been estimated at approximately 280 mL (Bergsneider 2001). It is produced partly from the blood and partly from the metabolites produced by the CNS tissue itself. The estimated range of drainage of ISF is 0.11–0.29 $\mu\text{L}/\text{min}/\text{g}$ of tissue (Abbott 2004); this is comparable with the drainage of ISF from other organs (Szentistvanyi et al. 1984). Although the study of ISF has been largely overshadowed by concentration of research on CSF, the production and drainage of ISF has implications particularly for neurodegenerative disorders, neuroimmunological diseases (Weller et al. 2010), hydrocephalus and syringomyelia.

Fluid in the central nervous system is increased in three main types of oedema. *Cytotoxic oedema* occurs in the very early stages of damage to the CNS, particularly in grey matter, when cells are deprived of oxygen or glucose and die (Marmarou 2007). As ATP production ceases, ion pumps at the cell membrane no longer function and allow the influx of sodium and other electrolytes into the cell, followed by water, with the result that cells swell and burst. *Vasogenic oedema* results from the breakdown of the blood–brain barrier following tissue damage in the CNS and the outpouring of fluid, proteins and other solutes into the brain tissue (Marmarou 2007; Nag et al. 2011). The third type is *interstitial oedema*

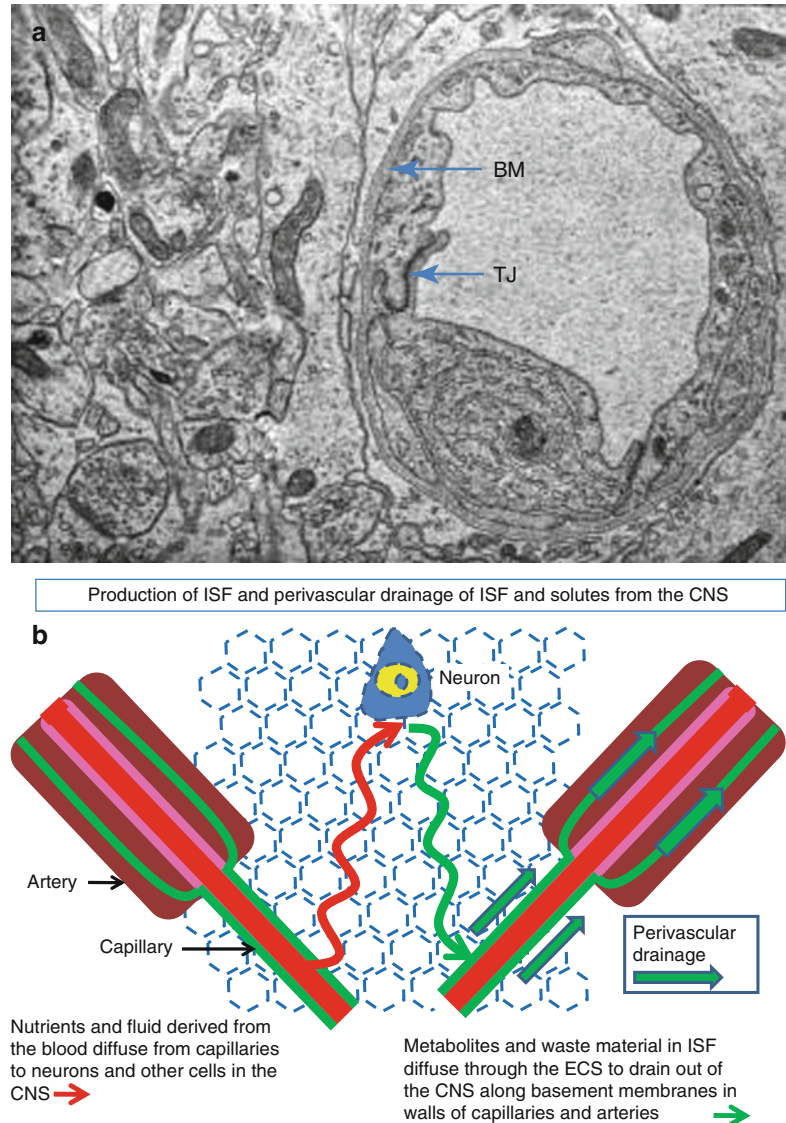
(Weller 1998) due to the infusion of CSF into the white matter in hydrocephalus and syringomyelia (see Sects. 3.4.2 and 3.5.2). Accumulation of interstitial oedema fluid reflects the failure of interstitial fluid drainage pathways to accommodate increased ISF in the extracellular spaces of the CNS.

3.4.2 Circulation and Drainage of Interstitial Fluid

Fluid and nutrients cross the blood–brain barrier at the capillary endothelial cells and diffuse through the narrow extracellular spaces of the brain to supply neurons and glial cells (Abbott 2004; Abbott et al. 2006; Marmarou 2007) (Fig. 3.7a, b). Interstitial fluid and soluble metabolites then diffuse through the extracellular spaces (Syková and Nicholson 2008) to drain by bulk flow along the basement membranes in the walls of capillaries and arteries (Fig. 3.7b) within CNS tissue and leptomeninges (Carare et al. 2008; Weller et al. 2009b).

Evidence for perivascular lymphatic drainage pathways is derived from a series of experimental studies, initially using radioactive tracers that showed rapid elimination of interstitial fluid and solutes from the brain to cervical lymph nodes (Szentistvanyi et al. 1984). The detailed anatomy of the drainage pathway was later elucidated using fluorescent tracers and confocal microscopy (Carare et al. 2008). When fluorescent dextran is injected into grey matter of the mouse brain, it initially spreads diffusely through the extracellular spaces and then, within 5 min, is present in the basement membranes in the walls of capillaries and arteries in the brain and leptomeninges (Carare et al. 2008). It appears that interstitial fluid and solutes drain to the lymph nodes at the base of the skull from the walls of the carotid artery (Weller et al. 2009b). The motive force that drives perivascular drainage is thought to be the contrary, or reflection, wave that follows the pulse wave passing along cerebral artery walls; in this model, the contrary wave drives interstitial fluid out of the brain in the reverse direction to the flow of blood (Schley et al. 2006).

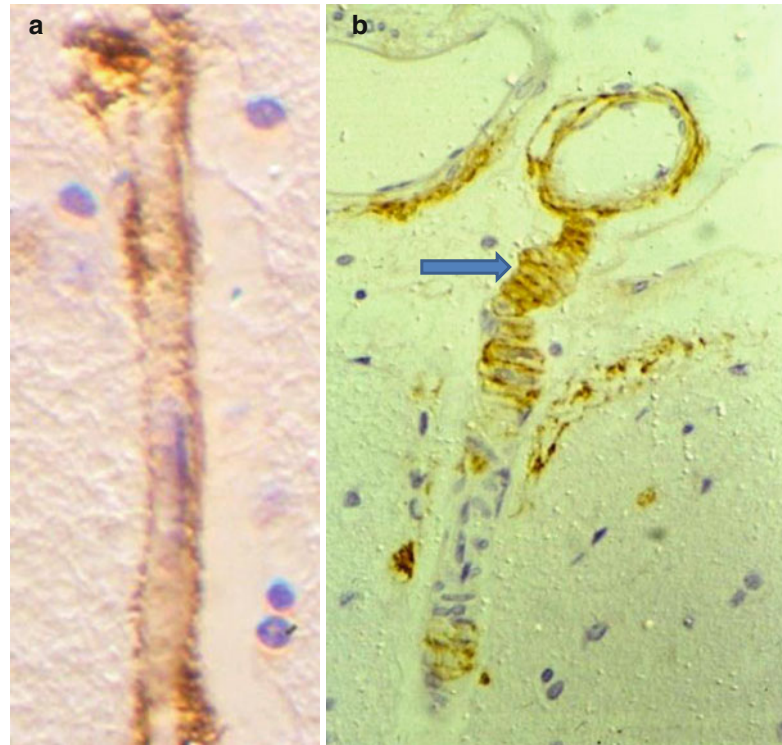
Fig. 3.7 Production and drainage of interstitial fluid. (a) Transmission electron micrograph of a capillary and surrounding brain tissue in the human cerebral cortex. Endothelial cells, joined by tight junctions (*TJ*), surround the lumen of the capillary and are coated on the abluminal surface by basement membrane (*BM*). Neuronal and glial processes are tightly packed together and separated by a very narrow extracellular space. $\times 14,000$. (b) Diagram to show the passage of fluid and soluble nutrients from a capillary, through the narrow extracellular spaces, to neighbouring neurons (*red line*) and the drainage of fluid and soluble metabolites out of the brain along perivascular basement membranes in the walls of capillaries and arteries (*green line*) (Reproduced with permission (a) from Preston et al. (2003))



Although it is not possible to perform tracer studies in humans, there is one natural tracer that strongly indicates the presence of a perivascular lymphatic drainage pathway in the human brain, similar to that in the mouse. Amyloid- β ($A\beta$) is derived from amyloid precursor protein and is one of the peptides that accumulate within the brain in Alzheimer's disease (Duyckaerts and Dickson 2011). $A\beta$ also accumulates in the walls of capillaries and arteries in the brain and leptomeninges as cerebral amyloid angiopathy (Biffi and Greenberg 2011; Weller et al. 2009c, 2011)

(Fig. 3.8a, b). The pattern of perivascular accumulation of $A\beta$ is exactly the same as the distribution of fluorescent tracers defining interstitial fluid drainage pathways (Carare et al. 2008; Weller et al. 2009b). This strongly suggests that soluble $A\beta$ is draining out of the brain along perivascular interstitial fluid drainage pathways (Biffi and Greenberg 2011; Weller et al. 2011). Furthermore, biochemical studies have shown that the accumulation of $A\beta$ in the walls of the carotid arteries ceases at the base of the skull (Shinkai et al. 1995), suggesting that interstitial

Fig. 3.8 Amyloid- β is deposited in the perivascular interstitial fluid drainage pathways in human brain as cerebral amyloid angiopathy. (a) Deposition of amyloid- β (brown) in the basement membrane surrounding a cortical capillary. Immunocytochemistry for amyloid- β $\times 750$. (b) Leptomeningeal artery (top) extends a branch into the cerebral cortex. Amyloid- β (brown) is deposited in the basement membranes between the smooth muscle cells of the tunica media (arrow) suggesting that soluble amyloid- β drains out of the brain along perivascular pathways. Immunocytochemistry for amyloid- β $\times 200$ (Reproduced with permission (a) from Preston et al. (2003) and (b) from Weller et al. (1998))



fluid with soluble A β drains from the artery wall to adjacent cervical lymph nodes in a similar way to that observed in experimental animals.

Although it is mainly the brain that is affected by amyloid angiopathy in Alzheimer's disease, amyloid also accumulates in artery walls in the spinal cord in the familial British dementia (Revesz et al. 2009). This suggests that interstitial fluid and solutes drain from the spinal cord along perivascular pathways by a system similar to that observed in the brain.

3.5 Pathology of the Cerebrospinal Fluid

Pathology of the CSF falls into two main categories (Weller 1998):

(a) Meningitis and haemorrhage in which inflammatory cells, erythrocytes or tumour cells are released into the CSF following infection, subarachnoid haemorrhage and invasion of the subarachnoid space by primary or metastatic tumours.

(b) Obstruction to the flow of CSF that results in hydrocephalus in the brain and syringomyelia in the spinal cord.

3.5.1 Meningitis and Subarachnoid Haemorrhage

Bacterial and fungal infections of the subarachnoid space result in an outpouring of polymorphonuclear leucocytes and protein from the blood into the CSF (Brown and Gray 2008; Weller 1998). Inflammatory cells remain mostly confined to the subarachnoid space and do not, in general, invade the underlying brain or spinal cord tissue. The pia mater, subpial collagen and the tightly packed astrocyte processes, which form the glia limitans on the surface of the brain and spinal cord, appear to act as a barrier to the entry of infection and inflammatory cells into the CNS. Often the only reaction at the surface of the brain is proliferation of microglia. In tuberculous meningitis, however, caseating granulomata not only involve the leptomeninges

but also extend into the surface of the brain or involve cranial nerve roots; there is invasion of the CSF by lymphocytes and high protein levels may be attained in the CSF (Brown and Gray 2008). One of the major complications of both pyogenic and tuberculous meningitis is inflammation in the walls of leptomeningeal arteries, thrombosis of their lumina and infarction of the underlying CNS tissue (Brown and Gray 2008). In the long term, bacterial meningitis may result in fibrosis of the leptomeninges, interfering with drainage of cerebrospinal fluid and resulting in hydrocephalus and syringomyelia.

In viral infections and in autoimmune disease, such as Guillain-Barré syndrome, there is a rise in the level of protein and the presence of lymphocytes in the CSF, indicating a breakdown in the blood-CSF barrier. The major complications of these conditions are not so much in the CSF but result from the involvement of brain tissue (encephalitis) or involvement of cranial and spinal nerve roots (autoimmune neuritis) (Weller 1998).

Subarachnoid haemorrhage results from rupture of a saccular aneurysm or an arteriovenous malformation or may follow an episode of trauma (Ferrer et al. 2008). Fresh arterial blood floods into the subarachnoid space and may spread widely over the surface of the brain and spinal cord and fill the cisterns at the base of the brain. Frequently there is extension of the haemorrhage into the brain itself resulting in a fatal intracerebral haemorrhage. If the patient survives the initial episode, the arteries that are surrounded by blood in the subarachnoid space may go into spasm resulting in cerebral infarction. The long-term effects of the subarachnoid haemorrhage may be fibrosis of the leptomeninges, disturbance of CSF drainage and hydrocephalus (Ferrer et al. 2008).

Both primary and metastatic tumours can invade the cerebrospinal fluid, and the main effect of this invasion is damage to cranial and spinal nerves and extension of tumour cells into the surface of the brain or spinal cord. Tumours in the ventricles, aqueduct or subarachnoid space may also block the drainage of CSF, resulting in hydrocephalus (Weller 1998).

3.5.2 Obstruction of CSF Flow and Drainage

Interference with the flow and drainage of CSF within the ventricular system of the brain or in the subarachnoid spaces overlying the brain and spinal cord may result in hydrocephalus or syringomyelia. There are many causes of hydrocephalus affecting the brain, occurring at any time from infancy to old age (Harding and Copp 2008). Congenital malformations, primary and metastatic tumours in the brain and fibrosis or tumours in the subarachnoid space may all interfere with the flow of CSF from ventricles to the subarachnoid space and its elimination via arachnoid granulations and lymphatic drainage pathways. The resulting dilatation of the ventricular system is associated with a number of pathological changes in periventricular tissue, particularly around the lateral ventricles. In the acute stages of hydrocephalus, the ependyma becomes stretched and flattened and may rupture, allowing CSF to infuse freely into the periventricular white matter and resulting in interstitial oedema (Weller 1998) (Fig. 3.9a–c). This stage may be followed by destruction and gliosis of white matter and severe dilatation of the ventricles (Fig. 3.9d). In human infants that develop hydrocephalus before the sutures of the skull bones have fused, ventricular dilatation, head enlargement and severe attenuation of the cerebral mantle may ensue (Harding and Copp 2008). Damage to nerve fibres in periventricular white matter in hydrocephalus is difficult to detect as it occurs over a protracted time period. It is only in the acute stages of hydrocephalus, when the tissue is oedematous, that axonal degeneration is obvious (Weller and Shulman 1972). As the interstitial oedema of the acute stages of hydrocephalus subsides, the periventricular white matter becomes gliotic.

Compared with white matter, the grey matter of the cerebral cortex and the basal ganglia are relatively well preserved in hydrocephalus (Fig. 3.9b, c). This may be due to a number of factors including the restricted nature of the extracellular space in grey matter, which prevents the entry of fluid (Weller and Wisniewski 1969)

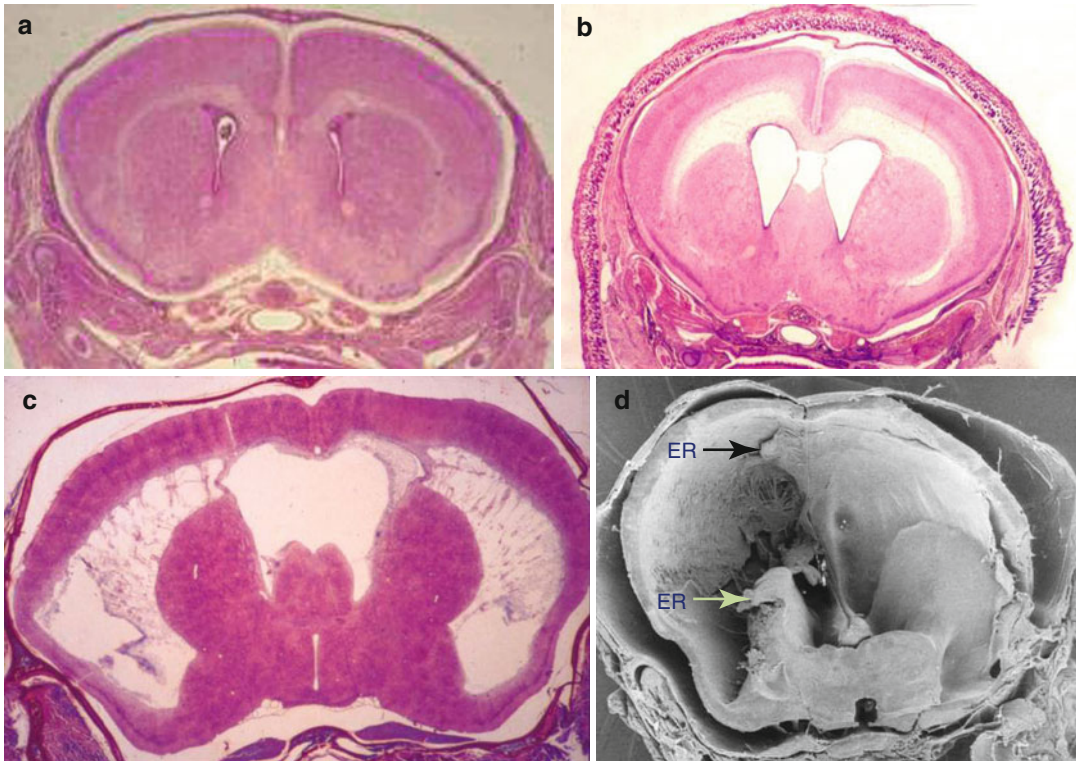


Fig. 3.9 Coronal sections of mouse brains showing progressive hydrocephalus with interstitial oedema and destruction of the white matter. (a) Normal mouse brain with small lateral ventricles. Haematoxylin and eosin $\times 8$. (b) Early stages of hydrocephalus with dilatation of the lateral ventricles and severe interstitial oedema of the white matter. Haematoxylin and eosin $\times 8$. (c) Severe destruction of the oedematous white matter in hydroceph-

alus but with relatively good preservation of the central grey matter and cerebral cortex. Phosphotungstic acid haematoxylin (PTAH) $\times 8$. (d) Scanning electron micrograph of a severely hydrocephalic mouse brain showing extensive dilatation of the lateral ventricles and rupture of the ependyma (ER) $\times 6$ (Reproduced with permission (a–c) from Weller (1998))

and the more efficient perivascular drainage of interstitial fluid from grey matter compared with white matter (see Sect. 3.6.2)

3.6 Syringomyelia

Syringomyelia can be defined as an elongated fluid-filled cavity in the central regions of the spinal cord. Syrinx, a shepherd's (pan) pipe, describes the shape of the syringomyelic cyst, often tapered at the upper and lower ends. The cervical region of the spinal cord is most frequently involved, and four types of syringomyelia have been described (Fernandez et al. 2009):

Type I syringomyelia is associated with obstruction of the foramen magnum with a Chiari type 1 malformation or another obstructive lesion, such as fibrosis or tumour.

Type II syringomyelia is without obstruction of the foramen magnum and is so-called idiopathic.

Type III syringomyelia is associated with other diseases of the spinal cord such as spinal tumours, traumatic lesions of the cord and spinal arachnoiditis.

Type IV is hydromyelia usually associated with hydrocephalus. Hydromyelia is when the central canal is dilated and may be lined by normal ependyma; in the later stages, the ependyma is

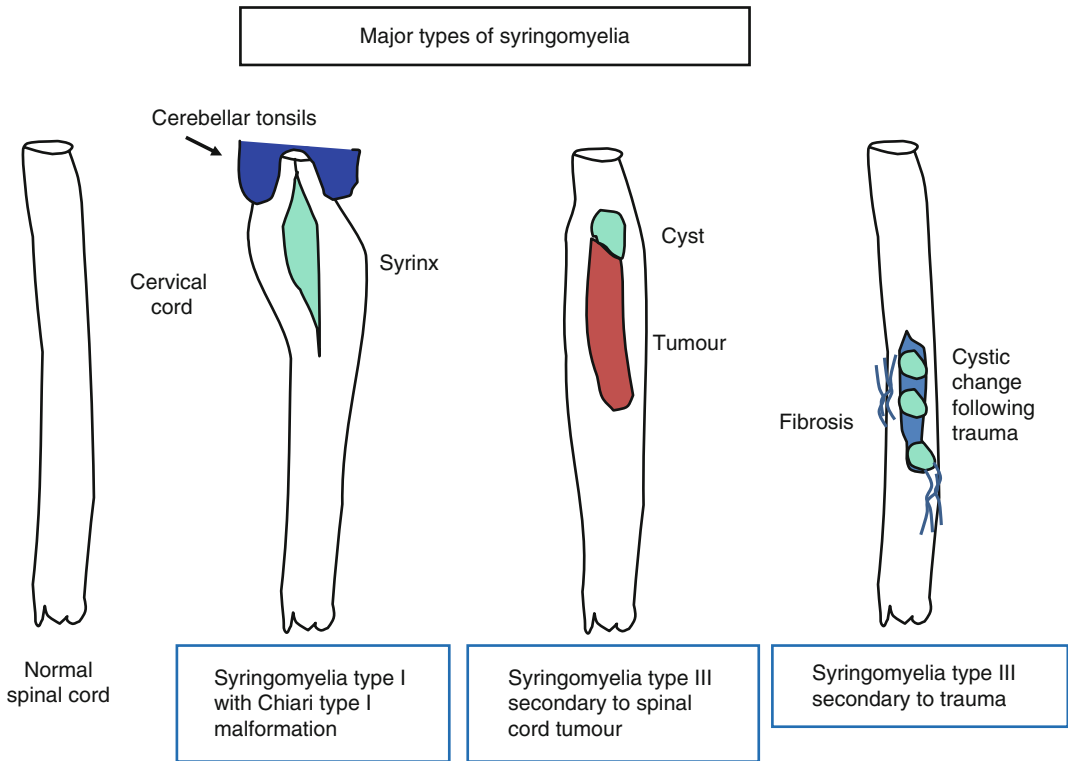


Fig. 3.10 Diagram to illustrate the major types of syringomyelia

replaced by glial tissue. Dilatation may be focal and more pronounced in the lumbar spinal cord. Hydromyelia may be an isolated finding and asymptomatic, or it may be part of a more complex syndrome (Harding and Copp 2008).

3.6.1 Aetiology of Syringomyelia

Figure 3.10 summarises the aetiology of the main types of syringomyelia.

Most cases of syringomyelia and almost 90 % of cases of type 1 syringomyelia are associated with Chiari malformations. Conversely, some 40–75 % of Chiari type 1 malformations have associated syringomyelia (Fernandez et al. 2009). Of the four types of Chiari malformation, type 1 has been defined radiographically as cerebellar tonsillar herniation, or ectopia of 5 mm or greater below the foramen magnum (Sekula et al. 2011; Ellison et al. 2004) (Figs. 3.11 and 3.12).

Maldevelopment of the skull results in reduced length of the occipital portion of the clivus, whereas the sphenoid portion is often normal. Platybasia and abnormalities of the occipital condyles and atlas are also seen. As a result of the malformations, the volume of the posterior fossa is effectively reduced, whereas the volume of the cerebellum is normal.

Cerebellar tonsillar herniation in the Chiari type 1 malformation appears to be the result of a normal cerebellar mass in a small posterior fossa and is thus secondary to the bony abnormality (Goel 2001). Syringomyelia in this case is a tertiary event and is thought to be due to disturbance of CSF flow through the foramen magnum (Heiss et al. 1999; Wetjen et al. 2008) (see Sect. 5.1.2). Other types of Chiari malformation may be associated with further abnormalities of the skull or brain, and in Chiari type 2 malformation, there is an associated myelomeningocele and hydrocephalus (Harding and Copp 2008).

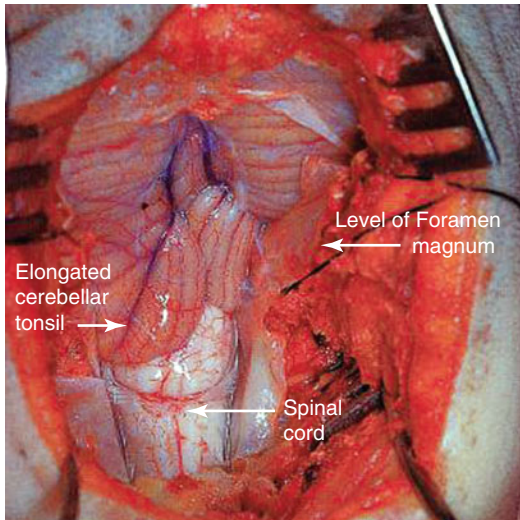


Fig. 3.11 A view of Chiari type 1 malformation at surgery. The posterior aspect of the cerebellum and spinal cord has been exposed by removing the bone of the foramen magnum. Elongated cerebellar tonsils extend through the foramen magnum posterior to the spinal cord (Reproduced with permission from Ellison et al. (2004))

Patients with a posterior fossa arachnoid cyst may develop acquired Chiari malformation and syringomyelia due to displacement of the cerebellar tonsils through the foramen magnum (Galarza et al. 2010).

Although the majority of cases of syringomyelia appear to be due to cranio-cervical malformations that are present at birth, the average age of presentation is approximately 35 years (Fernandez et al. 2009).

3.6.2 Pathology of Syringomyelia

Exposure of the syringomyelic spinal cord at surgery or at post-mortem usually results in collapse of the cavity. The full extent of a syrinx is, therefore, more adequately visualised by MRI. At post-mortem examination, the spinal cord in cross-section reveals a cystic space in the centre of the cord that is often asymmetrical and extending laterally towards one or other dorsal root entry zone (Fig. 3.13a). Microscopically, the syrinx may be totally separate from the

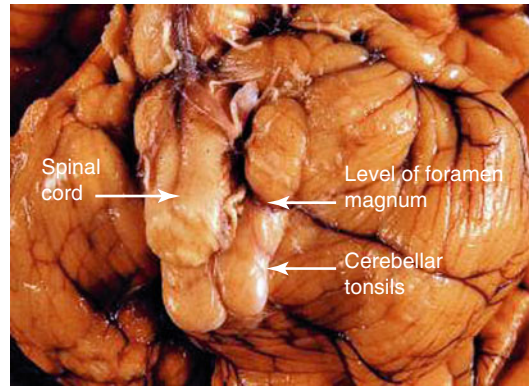


Fig. 3.12 Chiari type 1 malformation in a post-mortem brain. A fixed post-mortem brain at the level of the foramen magnum, viewed from the front. The spinal cord has been cut away to reveal the elongated cerebellar tonsils on its dorsal aspect (Reproduced with permission from Ellison et al. (2004))

central canal or may be partly lined by ependyma. A syrinx of long-standing is often lined by a layer of dense gliotic scar tissue (Fig. 3.13b) (Harding and Copp 2008). Acute syringomyelia induced experimentally (Williams and Weller 1973) shows disruption of the ependyma of the spinal cord, interstitial oedema of the cord tissue surrounding the syrinx and associated nerve fibre damage and reactive astrocytosis (Fig. 3.14). This suggests that fluid may be forced into the tissue around the syrinx as in hydrocephalus (Sect. 3.4.2). Similar tissue oedema may be seen in syringomyelia in humans and other species (Harding and Copp 2008).

At the level of the syrinx, ascending sensory tracts are often damaged, including those in the dorsal columns and the spinothalamic tracts. Locally, anterior horn motor neurons may be damaged. Remotely, above and below the syrinx, long tracts may show changes due to the damage at the level of the syrinx (Harding and Copp 2008).

In type III syringomyelia, there is a cavity in the cord associated with tumour, trauma or arachnoiditis. Oedema fluid derived from a spinal tumour appears to be a precursor of a tumour-associated syringomyelia (Baggenstos et al. 2007) in which the syrinx may be irregular in shape and lined by tumour. Following spinal cord

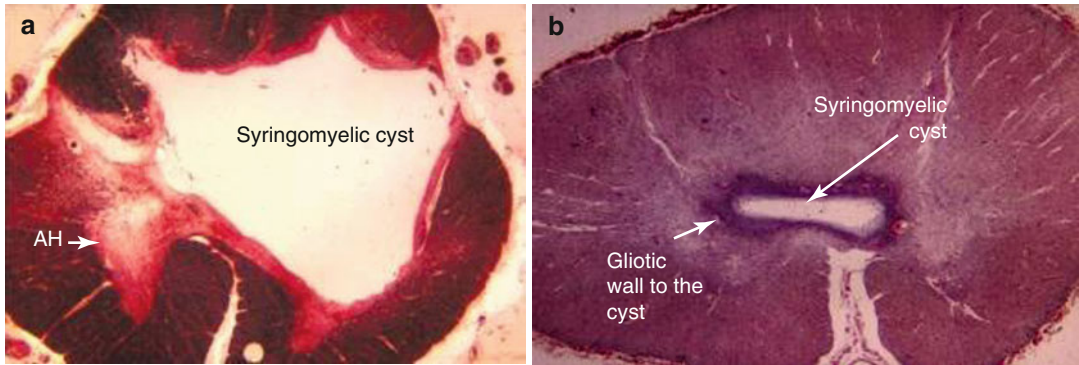


Fig. 3.13 Transverse sections of spinal cords with syringomyelia. (a) A large asymmetrical syringomyelic cyst extends towards one dorsal root entry zone. Anterior horn of grey matter (AH) on the opposite side

of the cord. Weigert-Pal stain $\times 4$. (b) Although this long-standing syringomyelic cyst in the spinal cord is small, it is surrounded by a thick layer of purple-stained gliosis (arrow). Phosphotungstic acid haematoxylin (PTAH) $\times 6$

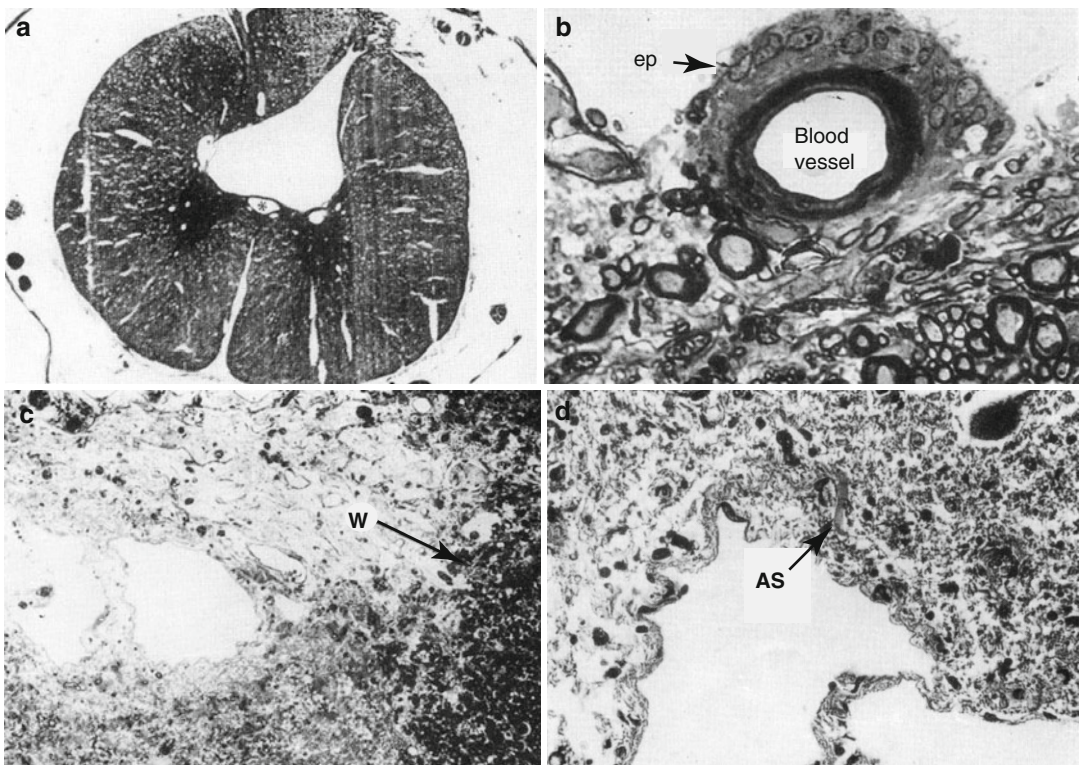


Fig. 3.14 Experimental syringomyelia. (a) Transverse section of the spinal cord showing a syringomyelic cyst extending towards one dorsal root entry zone. Haematoxylin and eosin $\times 8$. (b) Histology of the wall of the syrinx showing disrupted ependyma (ep) partly surrounding a blood vessel. Toluidine blue-stained resin section $\times 720$. (c) Interstitial oedema in the acute stage of

syringomyelia; a damaged nerve fibre is present at the edge of the oedematous region (W). Toluidine blue-stained resin section $\times 120$. (d) The oedematous wall of the cyst shows reactive astrocytosis (AS). Haematoxylin and eosin $\times 120$ (Reproduced with permission from Williams and Weller (1973))

injury, a syringomyelic cavity may be associated with arachnoiditis and tethering of the spinal cord or may be due to myelomalacia resulting from direct damage or ischemia of the cord linked to the trauma (Falci et al. 2009).

3.6.3 Dynamics of CSF Movement at the Foramen Magnum

Recent data on the dynamics of CSF flow at the foramen magnum are mainly derived from phase-contrast MRI (Ambarki et al. 2007; Battal et al. 2011). The model presented is that of a rigid skull containing three incompressible elements, namely brain, CSF and blood (Ambarki et al. 2007). CSF has a viscosity close to that of water and is distributed in three spaces that communicate with each other, the cerebral ventricles and the cranial and spinal subarachnoid spaces. Both the brain and spinal cord float in the CSF, and the surface of the CNS is crossed by a vascular network of arteries and veins. The overall intracranial volume remains constant, and the Monro-Kellie doctrine describes the blood, brain and CSF as incompressible. If the volume of one of the intracranial components increases, static mechanisms force one or both of the other components out of the cranial cavity, to maintain a constant intracranial volume. Pulsations of intracranial arteries result in a cyclical expansion of cerebral blood volume, which is transferred as pulsations in the CSF (Ambarki et al. 2007). Maintenance of intracranial volume is by expulsion of CSF from the cranial to the spinal subarachnoid space, which itself is expandable due to distensibility of the spinal dural sac, which acts as a mediator of compliance. CSF oscillates through the foramen magnum in response to pulsatile cerebral blood flow. This results in a coupling between changes in blood volume and CSF volume (Ambarki et al. 2007). Disturbance of the normal free flow of CSF through the foramen magnum appears to be a major factor responsible for the formation of a syrinx in the cervical spinal cord (Heiss et al. 1999; Wetjen et al. 2008). However, failure of absorption or drainage of extracellular fluid may also play a role, either

in the pathogenesis of a syringomyelic cavity or in maintaining the volume of fluid within it (Koyanagi and Houkin 2010).

3.7 Disorders of Interstitial Fluid and Its Drainage

Maintaining a constant external environment for neurons within the central nervous system depends upon homeostasis of the interstitial fluid, itself achieved through the control of nutrients, metabolites and other soluble materials in the extracellular compartment of the CNS. Entry of fluid and solutes into the interstitial fluid is controlled by the blood–brain barrier (Abbott 2004), and their elimination is along perivascular pathways in the narrow basement membranes in the walls of capillaries and arteries (see Sect. 3.3.2). Drainage of antigens by this route from the brain and spinal cord may play a role in immunological protection of the central nervous system and in neuroimmunological disease (Weller et al. 2009b, 2010). Equally important are the neurodegenerative diseases, such as Alzheimer’s disease, in the category of *protein-elimination failure arteriopathies (PEFA)* that are associated with failure of drainage of interstitial fluid and solutes from the CNS (Weller et al. 2008, 2009b; Carare 2013).

3.7.1 Cerebral Amyloid Angiopathy and Alzheimer’s Disease

Alzheimer’s disease is characterised, pathologically, by the accumulation of neurofibrillary tangles within neurons and deposition of insoluble amyloid- β ($A\beta$) in brain parenchyma and in artery walls, as cerebral amyloid angiopathy. Some 5 % of cases of Alzheimer’s disease are familial disorders of $A\beta$ production, caused by defects in the amyloid precursor protein and presenilin genes (Bertram and Tanzi 2011). In the majority of cases of Alzheimer’s disease, however, age is the major risk factor and failure of elimination of $A\beta$ from the brain with age appears to be a major causative factor in the disease. Several mechanisms

for the elimination of A β from the brain have been identified; they include the enzyme neprilysin in brain parenchyma and vessel walls, absorption of A β into the blood and drainage of soluble A β out of the brain along perivascular pathways (Weller et al. 2009c, 2011). As cerebral arteries age, elasticity in the walls is reduced and elimination of A β along perivascular pathways appears to be less efficient (Schley et al. 2006; Weller et al. 2009a). Failure of elimination of A β results in the deposition of A β as insoluble plaques (Duyckaerts and Dickson 2011), a rise in soluble A β in brain tissue (Lue et al. 1999; McLean et al. 1999) and loss of homeostasis of the neuronal environment, leading to the cognitive decline we see in Alzheimer's disease. Although it is not the only factor in the aetiology of Alzheimer's disease, failure of perivascular drainage of soluble A β appears to play an important role.

Deposition of amyloid is mainly in the cortex and to a lesser extent in the basal ganglia, but the white matter is also affected in Alzheimer's disease. Leukoaraiosis is the accumulation of fluid in the subcortical white matter that is detectable by CT and MRI in a proportion of patients with Alzheimer's disease. The blood supply for subcortical white matter is from leptomeningeal arteries on the surface of the brain; long thin arteries penetrate the cortex to supply the underlying white matter. Accumulation of fluid in the subcortical white matter in leukoaraiosis is associated with severe cerebral amyloid angiopathy of leptomeningeal arteries (Roher et al. 2003); it appears that deposition of A β in artery walls interferes with the drainage of fluid from the subcortical white matter.

3.7.2 Interrelationships Between Cerebrospinal Fluid and Interstitial Fluid

CSF fills the ventricles and cerebral and spinal subarachnoid spaces, functioning as a buoyancy fluid for the brain and spinal cord. Interstitial fluid plays a role in maintenance of homeostasis within the parenchyma of the brain and spinal cord. Although largely separate in their functions

and drainage systems, there are areas of interface between CSF and interstitial fluid. On the one hand, a small proportion of interstitial fluid leaks into the CSF during drainage along the artery walls (Szentistvanyi et al. 1984), and on the other hand, tracers, such as horseradish peroxidase, injected into the subarachnoid space, diffuse along perivascular spaces into the CNS (Rennels et al. 1985). Despite the connections between the two fluids, failure of drainage of one is not compensated by increased drainage of the other. In acute hydrocephalus, for example, CSF enters periventricular white matter resulting in interstitial oedema. As outlined in Sect. 3.4.2 and Fig. 3.9, interstitial oedema affects the white matter, but grey matter areas such as the basal ganglia and cortex are largely spared in hydrocephalus. This suggests that drainage of interstitial fluid along artery walls from grey matter is maintained in hydrocephalus, whereas such a drainage system in the white matter is overloaded and cannot cope with the infusion of CSF. It is still unclear why CSF, accumulating within the ventricles of the brain in hydrocephalus and in the spinal cord in syringomyelia, does not drain along perivascular pathways in the surrounding brain or spinal cord tissue. It is possible that perivascular drainage of interstitial fluid is limited and is unable to cope with the excess volume of CSF when drainage of the latter is impaired. Similarly, the failure of elimination of A β by perivascular drainage from grey matter is not compensated by elimination of fluid and A β into the CSF. In fact, the level of A β is reduced in the CSF in Alzheimer's disease (Mawuenyega et al. 2010).

Conclusions

Balanced production and elimination of CSF plays a significant role in maintaining physical stability of the brain and spinal cord. Similarly, the balance between production and elimination of interstitial fluid ensures the stable tissue environment for neurological activity. Disturbances in the elimination of CSF and interstitial fluid result in retention of fluid and solutes in the CNS. CSF and interstitial fluid are largely separate in their production and elimination, and although there is an

interface between the two fluids systems, neither system appears to compensate fully for deficiencies in the other. Facilitating drainage of CSF would have major effects in the treatment of hydrocephalus and syringomyelia, whereas facilitating the elimination of interstitial fluid and the soluble metabolites that it contains would have a major effect on the treatment of neurodegenerative diseases. On the other hand, increasing the capacity to drain extracellular fluid along perivascular pathways may reduce the fluid in hydrocephalic ventricles and syringomyelic cysts, and increasing the drainage of interstitial fluid into CSF would facilitate the elimination of soluble metabolites from the brain in cerebral amyloid angiopathy and Alzheimer's disease.

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