Research into the Physiology of Cerebrospinal Fluid Reaches a New Horizon: Intimate Exchange between Cerebrospinal Fluid and Interstitial Fluid May Contribute to Maintenance of Homeostasis in the Central Nervous System

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Abstract

Cerebrospinal fluid (CSF) plays an essential role in maintaining the homeostasis of the central nervous system. The functions of CSF include: (1) buoyancy of the brain, spinal cord, and nerves; (2) volume adjustment in the cranial cavity; (3) nutrient transport; (4) protein or peptide transport; (5) brain volume regulation through osmoregulation; (6) buffering effect against external forces; (7) signal transduction; (8) drug transport; (9) immune system control; (10) elimination of metabolites and unnecessary substances; and finally (11) cooling of heat generated by neural activity. For CSF to fully mediate these functions, fluid-like movement in the ventricles and subarachnoid space is necessary. Furthermore, the relationship between the behaviors of CSF and interstitial fluid in the brain and spinal cord is important. In this review, we will present classical studies on CSF circulation from its discovery over 2,000 years ago, and will subsequently introduce functions that were recently discovered such as CSF production and absorption, water molecule movement in the interstitial space, exchange between interstitial fluid and CSF, and drainage of CSF and interstitial fluid into both the venous and the lymphatic systems. Finally, we will summarize future challenges in research. This review includes articles published up to February 2016.

Key words: cerebrospinal fluid, interstitial fluid, Virchow-Robin space, lymphatic drainage, aquaporin

History of CSF Discovery

Edwin Smith’s surgical papyrus is a medical document from around the 17th century BC and is well known for its description of cerebrospinal fluid (CSF). It describes 48 cases, and the sixth case refers to a patient with a head injury due to a fight. This particular case contains a description of a comminuted skull fracture followed by an explanation of fluid outflow from a tear in the membrane (dura mater) that covers the occipital region of the brain. This portrayal of fluid flowing out from the occipital region is considered to be the first description of CSF. Later, great Greek scholars such as Hippocrates and Herophilus studied the structure of the brain, although direct descriptions of CSF are not found. Furthermore, although great scholars such as Herophilus, Galen, da Vinci, Vesalius, Varolius, Vieuxsens, Ruysch, Pacchioni, Monro, Sylvius, and Luschka presented anatomical findings of the ventricles and subarachnoid space, the existence of CSF was not known for some time. This is postulated to be because attention was not focused on the presence of fluid that fills the ventricles and subarachnoid space and because CSF had most likely leaked out along with blood when cervical decapitation was performed during autopsy or dissection.1) For detailed descriptions of these historical accounts of CSF, starting with Edwin Smith’s surgical papyrus, refer to the textbook by Deisenhammer.2)

Subsequently, Cotugno,3) Swedenborg,4) and vonHaller5) described CSF in a systematic manner (Fig. 1). Cotugno, an Italian anatomist from Naples, observed the presence of water (“liquor cotunnii”) around the ventricles and the spinal cord by conducting 20 autopsies. Another notable observation he made

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Fig. 1  a: Albrecht von Haller (1708–1777) is a Swiss anatomist and physiologist. His book, Primae lineae physiologiae in usum praelectionum academicarum. Gottingae: A. Vandenhoec (1747), is shown. Von Haller, who was given credit for the discovery of cerebrospinal fluid (CSF) by Domenico Cotugno, stated interesting anatomical findings including the observation that the consistency of CSF increases after death (Public domain). b: Domenico Felice Antonio Cotugno (1736–1822) is a Neapolitan anatomist. His book, De ischiade nervosa commentarius. Viennae: Apud Rudolphum Gräffer (1770), is shown. Cotugno reported that liquid is present and air bubbles are absent at the meninges when it is incised and opened carefully. Therefore, Cotugno postulated that the presence of CSF at the spinal cord and brain surface may have been overlooked with the conventional cervical decapitation method. c: Emanuel Swedenborg (1688–1772) is an anatomist with a degree in mining engineering. Swedenborg described CSF using terms such as “spirituous lymph” and “highly gifted juice.” His book, The Cerebrum and Its Parts. London: James Speirs (1882), is shown (Public domain).
was that the brain decreases in size and the relative volume of water increases with increasing age. These anatomical findings were summarized in “De Ischiade Nervosa Commentarius,” which was published in Latin in 1764 in Naples and in English in 1775 in London. Many researchers consider the discovery of CSF to be the work of Cotugno. However, it should be noted that Cotugno himself gave credit to von Haller, who we introduce next, for the discovery of CSF. Von Haller was a Swiss physiologist, who presented a revolutionary article in 1747 that described that CSF is secreted within the ventricles and that CSF is absorbed by the veins.

Swedenborg, who had a unique career, graduated from the University of Uppsala and received a degree in mining engineering. After working in the coal mines, he pursued the field of anatomy in Germany, France, and Italy from 1736 to 1740, although the precise years are unknown. Swedenborg drafted his work from this time period between 1741 and 1744; however, because he was a mining engineer, he was not able to meet a medical publisher, and his manuscript was abandoned for 150 years until its discovery in Stockholm. In 1882, it was finally published as “The Brain: Considered Anatomically, Physiologically and Philosophically” (translated and edited by RL Tafel) in London. Since the first academic description of CSF by these scientists, many researchers have studied the physiology of CSF within the central nervous system. The first appearance of the term “cerebrospinal fluid” in published literature is “Le liquid cérébro-spinal” in a French document written by Magendie in 1842 (Fig. 2). This term was used to describe fluid in the ventricles and subarachnoid

Fig. 2 The front cover (left) and part of page 8 (right) of “liquide céphalo-rachidien ou cérébro-spinal” described by François Jean Magendie owned by Kyoto University Library are shown. The foramen of Magendie that exists at the exit of the fourth ventricle is named after this scientist, who is well known for demonstrating the connection between the ventricular system and subarachnoid space. However, he is also famous for using the term “Le liquid cérébro-spinal” for the first time (red underlined portion in right figure). Photos reprinted with the permission of Kyoto University Library.
space and has been translated into various languages as “cerebrospinal fluid,” which has subsequently become established as a medical term.

Short summary
1. Edwin Smith’s surgical papyrus is the first description of fluid surrounding the brain that is thought to be CSF.
2. von Haller first described the existence of CSF systematically.
3. The term “cerebrospinal fluid” first appears in a document written by Magendie.

CSF Is Also Produced by Structures Other than the Choroid Plexus

The discovery of the choroid plexus by Galen and Vesalius naturally led to investigations of the choroid plexus as the production site of CSF, because choroid plexus protrusion is observed mostly at the ventricles, and some protrudes from the fourth ventricle into the subarachnoid space at the foramen of Luschka. Willis demonstrated that this choroid plexus displays a glandular structure, and Davson et al. concluded that this structure is ideal for CSF production. Later, Dandy et al. demonstrated in dogs that ventricular dilatation does not occur when the foramen of Monro is blocked and when the choroid plexus is excised from the lateral ventricle, but dilatation is observed on the side in which the choroid plexus is preserved, demonstrating that the choroid plexus is the site of CSF production. However, Hassin et al. contradicted this experiment conducted by Dandy et al. and stated from an early stage that CSF is produced by structures other than the choroid plexus. It is also important to note that Hassin considered that an intimate exchange between CSF and interstitial fluid occurs and that this plays an essential role in maintaining the homeostasis of the central nervous system (Footnote 1).

Next, we will introduce the mechanism of CSF production in the choroid plexus. de Rougemont et al. and Ames et al. measured the electrolytes in the fluid secreted by the choroid plexus and compared these values with the serum electrolyte concentration to examine the production of CSF. Investigations of the microstructure of the choroid plexus led to a variety of conclusions such as CSF is passively produced via hydrostatic pressure, CSF production is dependent on gradients of osmotic and hydrostatic pressures, and CSF is actively produced independent of hydrostatic pressure or colloid osmotic pressure. There is a well-known study by Welch regarding the amount of CSF production in the choroid plexus in which the author measured the hematocrit in the artery that drains into the choroid plexus and in the vein that drains out from the choroid plexus in an animal experiment with the goal of measuring the amount of CSF production from choroid plexus blood flow volume. Eventually, for measuring the amount of CSF production, methods such as extracorporeal perfusion of the choroid plexus and ventriculocisternal perfusion developed by the Pappenheimer group that can measure CSF production and absorption at the cerebrospinal cavity became widespread as standard techniques. In recent years, it has become feasible to observe the state of the choroid plexus, which changes morphologically along with the heartbeat, by inserting a micro-video probe into the lateral ventricle, and this method has been attracting attention as a novel research technique.

Milhorat, famous for his studies on the choroid plexus, had frequently questioned the view that the choroid plexus is the sole place in which CSF is produced based on the choroid plexus excision experiments he carried out in animals. Furthermore, when examining the overall amount of CSF produced in the ventricles and subarachnoid space, 58.5% of CSF is produced in the extra-ventricular CSF space in dogs, and 33% of CSF is produced at non-choroid plexus structures in rabbits. This led to the recognition that a considerable amount of CSF is produced outside the choroid plexus, and the focus on CSF production eventually shifted to non-choroid plexus sites. Hammock et al. reported that CSF production and composition do not change when the choroid plexus is excised from humans and monkeys, and Tamburini et al. reported an insufficient decrease in CSF production with endoscopic bilateral choroid plexus cauterization. Milhorat, who was already skeptical that the choroid plexus is the sole site of CSF production, conducted a bilateral plexectomy in a 5-year-old child and found that CSF formation did not change after 5 years. Of course, removal of the choroid plexus is incomplete with plexectomy of the lateral ventricles alone because the

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choroid plexus in the third and fourth ventricles still remains. However, it has been shown clinically that eliminating the majority of choroid plexus function does not cure hydrocephalus; thus, this procedure is not established as a standard therapeutic method.\(^{39}\) The over-production of CSF has been detected in hyperplasia of the choroid plexus and in some choroid plexus papillomas, and it is therefore necessary to specify that, without a doubt, excessive CSF production certainly takes place at the choroid plexus.\(^{42,43}\)

We will now focus on the lateral and third ventricles where the majority of the choroid plexus is present. If CSF produced by the choroid plexus is not absorbed within the ventricles, then all CSF produced anatomically should flow out from the Sylvian aqueduct. To test this hypothesis, Orešković et al. placed a cannula in the Sylvian aqueduct of cats to observe CSF outflow.\(^{44}\) The authors monitored potential CSF outflow from the cannula inserted into the Sylvian aqueduct for a long period of time, but not a single drop of CSF emerged from the cannula.\(^{44}\)

They consequently concluded that a balance of CSF production and absorption is maintained in the lateral and third ventricles.\(^{44}\) While this article by Orešković et al. is important, it does not provide the mechanism for the onset of obstructive hydrocephalus that clinicians frequently experience, indicating that their conclusion is still debatable.

We will now introduce several articles that explored non-choroid plexus structures as sites of CSF production. Some articles sought out the brain itself as the site of CSF production,\(^{45,46}\) whereas others claimed CSF production from the cerebral superficial subarachnoid space,\(^{37}\) the perivascular system,\(^{47}\) or the pial artery.\(^{48}\) Moreover, a study suggested its production by the spinal cord,\(^{49}\) and another has shown the presence of ependymal fluid secretion from the ependyma of the spinal cord central canal.\(^{50}\)

Based on these reports, it is difficult at the present time to claim the choroid plexus as the sole source of CSF production. In addition, the ventriculo-cisternal perfusion method that spread due to the report by Pappenheimer et al. which was consequently utilized in studies investigating CSF production\(^{46}\) has been questioned in cat experiments by Maraković et al.\(^{51}\) as there are limitations in performing invasive procedures in animals to conduct CSF studies. Moreover, this method is invasive in humans, indicating the difficulty with its application in humans. In the future, studies using different methods are desired.

**Short summary**

1. The classical concept in which the choroid plexus is the sole production site of CSF has changed due to recent studies that have demonstrated the existence of other non-choroid plexus sites that produce CSF.

2. The ventriculo-cisternal perfusion method that became widespread due to the report by Pappenheimer et al. is being questioned at the present time for its interpretation.

3. In obstructive hydrocephalus, the ventricles dilate above the obstruction site. However, if the balance between CSF production and absorption is maintained within the ventricles, then obstructive hydrocephalus does not explain the mechanism of ventricle dilatation.

**CSF Is Also Absorbed by Structures Other than Arachnoid Granulation Or villi**

In the rather unique article by Milhorat et al., CSF absorption by the choroid plexus, which is normally considered to be the CSF production site, was suggested in eight patients with hydrocephalus.\(^{52}\) However, Wislocki et al. experimentally disproved CSF absorption by the choroid plexus.\(^{53}\) and additional experiments regarding CSF absorption by the choroid plexus were therefore not conducted.

Key et al. published an extremely famous article in 1875 showing that CSF is absorbed by the arachnoid granulation or villi (Figs. 3, 4).\(^{54}\) Many classic textbooks cited this particular article, and for a long time thereafter it was believed that the arachnoid granulation or villi absorbs CSF.\(^{55-59}\) Certainly, the unique shape of the arachnoid villus in which it protrudes into the superior sagittal sinus from the subarachnoid space facilitates its interpretation as a pathway where CSF in the cerebral superficial subarachnoid space is absorbed by the venous system.\(^{60}\) However, there have been objections against the work by Key et al. because the pressure in which colored gelatin with soluble Berlin blue was injected into the subarachnoid space of a cadaver was high at 60 mmHg, and changes in arachnoid villus morphology may have occurred because the dye was injected in a non-physiological condition.\(^{51}\) Later, using radioisotopes (RIs) in an animal experiment, Davson et al. explained the circulation of CSF from the lateral ventricle to the arachnoid granulation or villi.\(^{62}\) With regard to CSF absorption from the arachnoid villi, this process has been demonstrated through an association between CSF pressure and venous sinus pressure\(^{63}\) and through light microscopic and electron microscopic observations.\(^{47,60,64-67}\) However, there are reports regarding the arachnoid granulation or villus, which protrudes into the lateral lacunae of the superior sagittal sinus, suggesting that open channels of communication are present between the CSF and blood through the arachnoid villi;\(^{68}\) that
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CSF communication occurs through its extracellular space, that CSF passes through the arachnoid villi via a one-way valve mechanism, and that the arachnoid villi are covered by endothelium and do not allow free fluid passage, indicating that a histological consensus has yet to be attained. It is important to note here that the human arachnoid villi are more developed compared to the rat arachnoid granulation or villus and that interspecies differences should be taken into consideration when interpreting the experimental results.

We will now shift our focus to the histological investigations that were conducted to study the human arachnoid villi. An interesting observation from studies in humans that investigated arachnoid granulation modifications that occur along with development is that although some researchers oppose this idea, the arachnoid granulation does not exist during prenatal and neonatal periods. If this was true, it is necessary to ascertain a CSF absorption route other than the arachnoid granulation that exists around the venous sinus during the fetal to neonatal stages. Aside from the venous system absorption described later, lymphatic drainage is considered to function earlier than the arachnoid granulation.

With regard to absorption from structures other than the arachnoid villi or granulation, there is indirect evidence from magnetic resonance imaging (MRI) that during childhood CSF is absorbed from capillaries due to hydrostatic pressure. On an experimental level, Bowsher administered radioactive feline serum protein into the CSF space and found that CSF migrates not only via the arachnoid granulation, but also to the pia mater capillaries in the brain and spinal cord.

Regarding CSF absorption at sites other than the areas around the venous sinuses, it has been reported that the compositions of aqueous humor and CSF closely resemble each other and that the perineural olfactory sheath is an important site of CSF outflow. Some have also reported that the areas around the optic nerve and retro-orbital tissue are involved in the absorption of CSF. It is interesting that the article by Key et al. that drew attention for describing CSF absorption by the arachnoid villi also describes the absorption of CSF from these retro-orbital tissues. In addition, Manzo et al. demonstrated in rabbit experiments that CSF is absorbed by the inner ear.

We will now discuss the absorption of CSF by the spinal canal. There are reports that discussed CSF absorption by the spinal canal and by the spinal nerve root. There are also reports that stated the presence of the arachnoid villi or granulation in the vicinity of the spinal nerve root and suggested that CSF is absorbed here. Moreover, fluid movement in the perivascular space (Virchow-Robin space) of the spinal cord has been demonstrated. Pollay stated that the spinal arachnoid granulation plays an auxiliary role when the intracranial arachnoid granulation becomes non-functional, and Weed reported that CSF absorption from the cranial subarachnoid space is faster than that from the spinal subarachnoid space. The above reports primarily explored the migration of CSF into the venous blood.

If the arachnoid villi, which are located at the convexity in the parietal region as a continuation...
of arachnoid tissue, have minimal involvement in CSF absorption, then it would be understood as a simple anatomical structure that is suspended in the brain in the perpendicular direction. The role of the arachnoid villi in CSF absorption may be minor, although there is an important article by Kida et al. who stated that the arachnoid villi are responsible for CSF absorption in a state of increased intracranial pressure. In addition, the discovery of red blood cells in the arachnoid granulation channels after subarachnoid hemorrhage confirms a role for these channels in CSF outflow in adults. Thus, the association between CSF absorption and the arachnoid villi cannot be completely rejected.

Next, we will shift our focus to the association between CSF and the lymphatic system. The
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Article by Key et al., which proved absorption by the arachnoid granulation or villi and CSF migration to retro-orbital tissues, also appears here, as it clearly demonstrated the migration of dye injected into the subarachnoid space to the cervical lymph node.\(^{105}\) Schwabbe injected Berlin blue into the dog subarachnoid space and found that the lymphatic system is an important pathway that absorbs CSF.\(^{99}\) Love et al. reported that the lymph flow increases and the protein concentration in the lymph decreases when artificial CSF is injected into the cisterna magna.\(^{100}\) and Hasuo et al. reported that the lymph flow increases when the intracranial pressure rises,\(^{101}\) indicating an indirect association between lymph and CSF absorption. Bradbury et al. injected \(^{125}\)I- or \(^{131}\)I-albumin into the ventricles and caudate nucleus and found that there are drainage pathways into the cervical lymphatic vessels from the Virchow-Robin space and perivascular spaces through the subarachnoid space and also from the olfactory lobe through the submucous space of the nasal cavity.\(^{102–104}\) McComb et al. used \(^{125}\)I-albumin in cats to show that CSF drains into the lymphatic system both under normal pressure and augmented intracranial pressure conditions.\(^{105}\) Furthermore, Mortensen and Sullivan visually portrayed in a dog experiment that a contrast agent in the CSF migrates to the cervical lymphatic vessels.\(^{100}\) Mathieu et al. reported non-invasive in vivo hyperspectral imaging to identify the CSF lymphatic drainage system.\(^{107}\) Later, many reports proved the migration of CSF into the lymphatic system through experiments using dye, contrast agents, and RI. A pathway in which CSF re-appears in the lymphatic system is unlikely once it migrates from the arachnoid granulation or villi to the venous system. For this reason, a pathway that has been attracting attention in recent years is one in which CSF reaches the nasal mucosa from the cribiform plate through tissue around the olfactory nerve and subsequently migrates to the cervical lymph node.\(^{108}\) Recently, Johnston et al. injected microfil into the cisterna magna of sheep, pigs, rabbits, rats, mice, and human cadavers and demonstrated that the microfil migrates to the olfactory bulb and cribiform plate in all these mammals.\(^{109}\) Moreover, Di Chiro et al., who studied CSF behavior by administering an RI tracer into the CSF space,\(^{110}\) injected gadolinium contrast agent into the cisterna magna of dogs and found on MRI that the contrast agent aggregates in the nasal mucosa.\(^{111}\) Furthermore, an animal experiment, albeit a paradoxical one, has demonstrated that the prelymphatic space expands and cerebral edema develops when the cervical lymphatic vessels are ligated in cats and rabbits.\(^{112}\) Using an analytical modeling approach, Fard et al. showed that CSF is primarily absorbed by the lymphatic system and that impairment in the lymphatic system induces high-pressure hydrocephalus, emphasizing the importance of the lymphatic system as an absorption route of CSF.\(^{113}\) In addition, a study mentioned the presence of a link between the spinal cord subarachnoid space and the lymphatic system.\(^{114}\) Although CSF migration has been investigated carefully in other cranial nerves, it appears that except for the olfactory nerve, these nerves have minimal involvement.\(^{76}\)

CSF movement in the subarachnoid space and ventricles, which are the CSF reservoirs, has been considered to follow a pathway in which CSF produced by the choroid plexus descends the ventricular system of the brain and drains into the subarachnoid space via the fourth ventricle exit, ultimately reaching the arachnoid granulation or villi for absorption. However, recent research progress has illuminated different views. Greitz modified the traditional interpretation of radio-nuclide cisternography and negated the bulk flow theory, which states that CSF ultimately reaches the arachnoid villi for absorption.\(^{28,115}\) He furthermore concluded that CSF is mixed through pulsatile flow, is diluted with newly secreted CSF from the ventricular system, and is ultimately absorbed by the blood vessels. Recently published MRI analyses of CSF movement also refuted the unidirectionality of CSF and demonstrated a repetition of stirring and spreading or oscillating within reservoirs such as the ventricles and subarachnoid space.\(^{116–127}\)

In other words, several different views regarding the absorption of CSF were published. These included: the opinion that lymphatic drainage is the primary pathway for CSF absorption;\(^{128}\) an explanation in a review by Pollay that both the arachnoid granulation or villi and lymphatic system are involved in CSF absorption with a comparable balance;\(^{76}\) the observation that 40–48% of the CSF in the cranial compartment drains into the extracranial lymphatics according to experiments in sheep conducted by Boulton et al.;\(^{129}\) an explanation that the arachnoid granulation or villi play an essential role in CSF absorption and that the lymphatic system is an accessory pathway that supplements the arachnoid granulation or villi according to a review by Weed;\(^{130}\) and a view by Courtice et al. that very little CSF drains into the lymphatic system in experimental rabbits.\(^{130}\) However, Grzybowski et al. proved that fluid passage is observed when harvested human arachnoid villi are perfused and subsequently examined morphologically with electron microscopy,\(^{64}\) and furthermore, Welch et al. conducted a perfusion experiment of monkey arachnoid villi and concluded

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that substances smaller than erythrocytes can pass through the arachnoid villi. Thus, the results from these experiments do not completely disprove CSF absorption by the arachnoid villi. In animal experiments, it appears that the ratio of arachnoid granulation or villi to lymphatic routes for CSF absorption differs depending on the experimental method and species used, and a consensus has yet to be reached.

The next question is: is the nasal mucosa the only route in which CSF reaches the cervical lymph node from the cribriform plate via the nasal mucosa. Although the nasal mucosa pathway is a well-known route in which CSF drains into the lymphatic system, recently, the presence of the lymphatic system was discovered in the dura mater and has been attracting interest. In 2015, while the Kipnis group was exploring pathways in which T cells circulate within the central nervous system, they discovered an area where immune cells aggregated around the venous sinus in the dura mater of mice, and conducted an analysis and provided an explanation using markers such as lymphatic endothelial markers. They subsequently named these luminal structures “meningeal lymphatic vessels” and demonstrated that these vessels connect to the cervical lymphatic system. Interestingly, they also noted that a similar tissue is found around the venous sinus of the dura mater in humans and that additional studies are necessary. The existence of lymphatic drainage has been postulated for some time, and an article by Kida et al. in 1993 described that the “CSF drains directly from the subarachnoid space into nasal lymphatics in the rat” and presented a figure that depicts “dural lymphatics” together with the olfactory pathway, which is worth noting (in Fig. 5: “Anatomy, histology and immunological significance”). Surprisingly, according to a report from Bucchieri et al., the presence of lymphatics in human dura mater had already been described by Mascagni (1787) in “Vasorum lymphaticorum corporis humani historia et ichnographia.” However, because the dura mater arises to direct and guide the skull, some may consider it no wonder if the lymphatic system exists in the dura mater. Louveau et al. injected fluorescent tracer dye into the ventricles and demonstrated its appearance in the meningeal lymphatic vessels. Likewise, in 2015, Aspelund et al. discovered a similar structure in mice with findings that dural lymphatic vessels are found extensively at the base of the skull and penetrate the base of the skull along with the cranial nerves, and that tracers administered into the brain parenchyma exit into the dural lymphatic vessels. Thus, it is suggested that CSF reaches the meningeal lymphatic vessels through some sort of pathway; however, the precise mechanism of this pathway is yet unknown. Perhaps, because meningeal lymphatic vessels exist near the venous sinus, an anastomosis of the venous and lymphatic systems mediates this pathway. Or, perhaps CSF drainage into the lymphatic system is present around the nerve foramina at the base of the skull, similar to the cribriform plate. Although it is a fact that lymphatic vessels are absent in the brain parenchyma, additional studies regarding meningeal lymphatic vessels and the drainage of CSF and interstitial fluid are anticipated.
Short summary
1. Key et al. indicated the arachnoid granulation or villi and retro-orbital tissues as pathways for CSF absorption and also showed that dye administered into the subarachnoid space reaches the cervical lymph node.
2. Various locations within the central nervous system such as the arachnoid granulation or villi, periphery of some cranial nerves including the olfactory nerve, spinal nerve root, and capillaries of the brain parenchyma are postulated as routes for CSF absorption.
3. CSF that exits from the subarachnoid space to the dura mater and epidural space is known to travel to the systemic circulation via the venous sinus or to the cervical lymphatic system through the nasal mucosa or meningeal lymphatic vessels (Fig. 5).
4. The route in which CSF migrates from the subarachnoid space to the meningeal lymphatic vessel is yet unknown, and further elucidation is awaited.

Exchange between Interstitial Fluid and CSF

Until now, we have summarized previous works related to CSF production and absorption that are historically important. But, does CSF, which fills the ventricles in the deep brain and the brain surface, and interstitial fluid in the brain parenchyma ever exchange substances? And do CSF in the ventricles and CSF in the subarachnoid space maintain a completely independent existence? If the subarachnoid space and ventricles exist as a reservoir of CSF, pathways in which CSF moves in and out from this reservoir are necessary. Several studies have derived answers to these questions. Weller et al. demonstrated a clear pathway in which CSF secreted by the ventricles and subarachnoid space and interstitial fluid secreted by the brain parenchyma, spread through diffusion and further with bulk flow, and eventually reach the cervical lymph nodes. Bradbury and Abbott stated that interstitial fluid, which is secreted into the extracellular space through the blood-brain barrier, mixes with CSF and maintains the balance between CSF production and absorption. It has also been reported that interstitial fluid production and bulk flow in the brain are profoundly involved in brain volume regulation. Morphologically, the existence of the Virchow-Robin space has gained interest, and the term “Virchow-Robin space” has been used synonymously with perivascular space, periarterial space, and paravascular space, although these terms are also used distinctly at times. In this review, we will use the terms “Virchow-Robin space” or “Virchow-Robin space and perivascular spaces” (Footnote 2).

The renowned German anatomist Rudolf Virchow (1821–1902), known for discovering the Virchow-Robin space, made his greatest contribution in the dissection of the lymphatic system. In particular, he noted the relationship between cancer and lymph nodes. It should also be acknowledged that he was the first to use the terms lymphoma and lymphosarcoma. Furthermore, it is interesting whether it is coincidental that the Virchow-Robin space, named after Virchow, acts as an interstitial fluid drainage route in the brain and that CSF moving in the Virchow-Robin space is eventually connected to the cervical lymph node.
spaces.\textsuperscript{190} and Zhang et al. demonstrated with electron microscopy that there is a continuity from the human pia mater to the Virchow-Robin space and perivascular spaces.\textsuperscript{149} Furthermore, although it has been shown with MRI in humans that the Virchow-Robin space and perivascular spaces connect with the ventricular wall, which is situated deep in the brain,\textsuperscript{171} it is understood by many researchers that these spaces enter the cortex from the cerebral superficial subarachnoid space together with the artery.\textsuperscript{156,172,173} and that a cul-de-sac structure is observed at a certain point after entry.\textsuperscript{172} The substance that forms the periphery of the Virchow-Robin space is the glial membrane (glia limitans), which covers the brain parenchyma.\textsuperscript{175} The basement membrane of the glia joins the outer vascular membrane at the deep Virchow-Robin space, and this is where the cul-de-sac structure exists.\textsuperscript{176} The pial sheath is present on the outside of the vascular wall and migrates to the brain surface to cover the pial cells. This migration occurs at the point where the blood vessels enter the Virchow-Robin space, and the outer layer of the Virchow-Robin space ends here.\textsuperscript{177} Fenestration forms in the pial sheath around the blood vessels, and substance transport takes place at this location.\textsuperscript{149} It has been demonstrated in the Virchow-Robin space that horseradish peroxidase administered into the cerebral superficial subarachnoid space is taken up by the brain parenchyma and is subsequently cleared within 24 hours.\textsuperscript{178} A separate human study has also shown that metrizamide administered into the subarachnoid space migrates to the parenchyma of the cerebrum and cerebellum.\textsuperscript{179} These reports indicate that CSF not only circulates in the subarachnoid space and Virchow-Robin space, but also freely enters and exits the brain parenchyma. Yang et al. administered tracer into CSF and demonstrated the presence of free fluid communication between perivascular CSF and interstitial fluid.\textsuperscript{180} Furthermore, it has been demonstrated histologically that water movement occurs not only in the Virchow-Robin space, but also between the subarachnoid space and brain parenchyma via the pia mater.\textsuperscript{181} Recently, fluid motion in the Virchow-Robin space and perivascular spaces has gained vast interest, and this has led to studies that utilize mathematical models.\textsuperscript{182} This fluid motion in the Virchow-Robin space has also been attracting attention as a pathway for \(\beta\)-amyloid elimination.\textsuperscript{153,183–189} In 1968, Földi et al. claimed that the perivascular space functions as a lymphatic drainage system in the brain.\textsuperscript{190} In addition, impairment in peri-arterial drainage is considered to be the mechanism of onset of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), and is known to be strongly associated with the onset of immunological diseases as well as age-related changes in the brain.\textsuperscript{151,186,187} Moreover, arterial pulsation is known to be profoundly involved in substance movement within the Virchow-Robin space and perivascular spaces.\textsuperscript{191} The migration of \(\beta\)-amyloid that has drained from the brain parenchyma into the subarachnoid space is known to change with age, and it has been reported that \(\beta\)-amyloid deposits are observed at the Virchow-Robin space and perivascular spaces due to age-related weakening of arterial pulsation in the perivascular space.\textsuperscript{187} Furthermore, the intimate relationship between glia and the vascular network as well as the elimination of substances through the Virchow-Robin space is called the “glymphatic system” or “garbage truck of the brain” and a review concerning the decrease in the function of this system due to age and neurodegenerative, neurovascular, and neuroinflammatory diseases has been published.\textsuperscript{192–194}

There are no tight junctions at the pia mater, which forms the outside of the brain parenchyma, and it has been shown with electron microscopy that water molecules freely migrate through this area.\textsuperscript{186} Regarding the behavior of fluid in the extracellular space of the brain parenchyma, there are several theories including bulk flow in which interstitial fluid motion occurs in a unidirectional manner through the intercellular space\textsuperscript{41,196,197} as well as diffusion.\textsuperscript{196–200} Furthermore, studies that used tracers such as \(\beta\)-water showed the presence of rapid capillary absorption of CSF after its migration to the extracellular space.\textsuperscript{155,185} A pathway in which interstitial fluid in the brain parenchyma travels to the cervical lymph node through the Virchow-Robin space and perivascular spaces has been explained using tools such as dye, contrast agents, \textsuperscript{157}\(\beta\)-albumin, and \(\beta\)-tritiated diisopropyl-fluorophosphate.\textsuperscript{196,201–207} Xie et al. presented an interesting report in which \(\beta\)-amyloid in interstitial fluid clears through the Virchow-Robin space and perivascular spaces and increases during sleep.\textsuperscript{208} Furthermore, there is an article that reported the morphology and function of the Virchow-Robin space and perivascular spaces in association with increasing age of animals, and it is interesting that the authors linked such morphology and function with the elimination of \(\beta\)-amyloid that increases with age.\textsuperscript{209} In addition, Bulat et al. showed that CSF is secreted through capillary filtration and absorbed by adjacent microvessels.\textsuperscript{210} They also demonstrated that ventricular dilatation does not occur even when the cerebral aqueduct of animals is blocked and that the balance between CSF production and absorption in the ventricles is maintained. On the other hand, a tracer study that showed CSF migration from the subarachnoid space to the brain parenchyma via the Virchow-Robin space and perivascular spaces demonstrated the differences in the time required to migrate to the brain parenchyma based on differences

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This study also demonstrated that once CSF reaches this point, it can freely enter and exit the extracellular space from the ependyma and subarachnoid space, and also that there is a pathway in which CSF drains from the brain parenchyma into the lymphatic system. Furthermore, it is also interesting that cerebrovascular pulsation induces fluid movement in the Virchow-Robin space and perivascular spaces and plays an important role in interstitial fluid exchange. A similar study has also explored the association between fluid movement and the arteries in the Virchow-Robin space and perivascular spaces of the spinal cord. CSF that saturates the tissues of the central nervous system frequently exchanges substances with interstitial fluid and is subsequently eliminated into reservoirs such as the subarachnoid space and ventricles. Thus, intimate exchange between CSF and interstitial fluid is considered to be essential for maintaining the homeostasis of the brain.

These works contrast with the traditional textbook or review concepts of CSF production and absorption, and recent reviews describe new findings related to this topic.

**Short summary**

1. The subarachnoid space and ventricles exist as a reservoir of CSF and are known to extensively exchange water and substances with the surrounding tissue.
2. CSF enters the brain parenchyma, mixes with interstitial fluid that is produced there, and is eliminated into reservoirs such as the subarachnoid space and ventricles from the brain parenchyma as CSF again (Fig. 6).
3. The exchange between CSF and interstitial fluid is bidirectional (Fig. 6).

Fig. 6 A schematic diagram of cerebrospinal fluid (CSF) and interstitial fluid exchange among the ventricle, subarachnoid space reservoir, and brain parenchyma is shown. Glia, which covers the neurovascular unit, is located at the border of the area in which water enters and exits the brain and spinal cord, and water is exchanged at the aquaporin channel of astrocyte foot processes or at other sites through the endothelium via diffusion or vesicular transport. Water movement at the ependymal layer, pia mater, and Virchow-Robin space is bidirectional. The right cerebral hemisphere has a mixing of interstitial fluid secreted within the brain parenchyma and CSF that enters the brain parenchyma, and subsequent drainage from the brain parenchyma into the CSF reservoir (subarachnoid space and ventricles). The left cerebral hemisphere shows that CSF penetrates from the ventricles and subarachnoid space into the brain parenchyma.
4. The Virchow-Robin space is an important exit route from the slightly deep area of the brain parenchyma to the subarachnoid space for interstitial fluid and CSF (Fig. 6).

5. CSF and interstitial fluid play an important role in the exchange of substances in the brain parenchyma and are therefore essential for maintaining the homeostasis of the brain.

**Water Exchange through the Aqua Pore in the Cell Membrane**

Agre, a researcher of human erythrocytes, focused on a certain unique protein that exists on the cell membrane of erythrocytes, overexpressed this protein in oocytes of African clawed frogs (Xenopus laevis), and found that water permeability is markedly enhanced. 

Agre named this protein, a pore that is present on the cell membrane and that plays an important role in passing water, “aquaporin” (AQP). It has been believed for a long time that a special structure is necessary for water to pass through the lipid bilayer of the cell membrane, and with the discovery and elucidation of AQP studies on the movement of water molecules have accelerated dramatically. In 2003, Agre received the Nobel Prize in Chemistry for this work. Fig. 7 shows the structure of AQP. At the narrowest portion of the AQP pore, asparagine/proline/alanine (NPA) motifs facilitate water molecules to pass through by breaking the hydrogen bond between water molecules that come in contact with each other (Fig. 8). At least 14 AQPs have been discovered to date. Some AQPs (AQP-3, AQP-7, AQP-9) are known to pass not only water, but also other molecules such as glycerol. Among the AQP family members, AQP-1 is known to be highly expressed in the choroid plexus, and AQP is therefore considered to be involved in CSF production and absorption. AQP-4 is widely distributed in the brain including the astrocyte foot processes, glia limitans, and ependymal and subependymal astrocytes, and many researchers therefore have selected AQP-4 as the target topic of research. AQP-4 is present at an important location in which interstitial fluid and CSF exchange occurs, and the presence of AQP is therefore necessary for water exchange to occur between the interstitial fluid and CSF cavity. Although interstitial fluid movement is non-specific and slow, water movement through AQP exhibits directionality and selectivity and is faster compared to interstitial fluid movement. Thus, AQP-4 plays a key role at the glia and ependymal layer where interstitial fluid and CSF contact each other and facilitates water exchange with some degree of selectivity that occurs faster than in the brain parenchyma. Recently, it has become feasible to visualize the location of AQP-4 with positron emission tomography, and this has been a major advancement for studies that aim to ascertain the movement of water that enters and exits the brain parenchyma. AQP-4 controls cell volume by regulating chloride and calcium and is also involved in potassium clearance after neural activity because it coexists with potassium channel, indicating that AQP-4 exhibits other neuro-physiological effects other than a physical role of allowing water permeability. Indeed, AQP-4 is responsible for removing metabolites produced by neural activity through water permeability, thereby greatly contributing to the functional maintenance of the brain.

Let us shift our focus to AQP studies conducted in various disease states. Peritumoral edema around gliomas is known to upregulate AQP-1, and there have been studies that endeavored to design treatments for...
peritumoral edema by upregulating AQP-1 via genetic modification or directly inhibiting AQP-1. AQP-4 knockout mice were created by Ma et al. in 1997. Subsequently, studies using AQP-4 knockout mice in various diseases became popular. There is also an article that investigated the relationship between cerebral blood flow and AQP and showed that the regional cerebral blood flow increases when AQP-4 is inhibited. In addition, the protective effect of progesterone may be related to the down-regulation of AQP-4 expression in hypoxic ischemic brain damage. Furthermore, it is also interesting that a review discussed the association between cerebral blood flow and AQP and showed that the regional cerebral blood flow increases when AQP-4 is inhibited. In addition, the protective effect of progesterone may be related to the down-regulation of AQP-4 expression in hypoxic ischemic brain damage. Furthermore, it is also interesting that a review discussed the association between cerebral blood flow and AQP and showed that the regional cerebral blood flow increases when AQP-4 is inhibited. In addition, the protective effect of progesterone may be related to the down-regulation of AQP-4 expression in hypoxic ischemic brain damage.

Recently, based on these contradictory study results on AQP, it has become viewed in general that AQP does not play an important role under physiologically normal conditions.

**Short summary**

1. AQP molecules present on the cell membrane play an important role in the passage of water through the cell membrane.
2. AQP-1 is present in the choroid plexus, and AQP-4 is distributed widely in the brain in areas such as the astrocyte foot processes, glia limitans, and ependymal and subependymal astrocytes. These AQPs play a key role in the water permeability of CSF and interstitial fluid.
3. The function of AQP differs between physiologically normal and abnormal conditions.
4. The development of diagnostic and therapeutic methods targeting AQP has been initiated.

**Future Directions**

1. It is necessary to focus once again on the ventricles, and this pertains to classical anatomical observations. The interesting shape of the ventricular system is visually clear and poses a scientific conundrum. The question arises: why is this unique ventricular structure, which shares common features with other mammals, built in this particular shape and size? With this particular shape, CSF and interstitial fluid communicate to exchange fluids. Tanyocytes and microglia form bridges between the ependymal surface and the pial membrane, establishing an intimate relationship between neurons and endothelial cells. The solid lines in Fig. 9 indicate almost the same distance from each ventricular surface to the most adjacent subarachnoid space throughout the brain. Thus, the exchange of CSF and interstitial fluid is clearly important. Of particular importance is the existence of the distal portion of the Sylvian fissure, which is the large subarachnoid space underneath...
the frontal and temporal lobes. Without this fissure, the distance between the third ventricular wall and the nearby subarachnoid space (Fig. 9, dashed line) would be much longer than that between the other ventricular walls and subarachnoid spaces. As shown in Fig. 9, morphological observation shows that the Sylvian fissure extends deep between the frontal and temporal lobes. However, white matter is mostly present between the convexity of the subarachnoid space and the lateral ventricular wall, whereas the basal ganglia are interposed between the Sylvian fissure and the third ventricular wall. Generally, water moves more rapidly in the white matter than the gray matter. Thus, from the viewpoint of water movement, the subarachnoid space such as the Sylvian fissure is better positioned to more deeply enter the brain parenchyma than the subarachnoid space of the convexities. Therefore, from the point of view of CSF and interstitial fluid, investigation of the rate of water movement in both the white and gray matter is a research issue for the future.

Next, we discuss the shape of the rounded anterior horns of the lateral ventricle that extend into the frontal lobe. The body of the lateral ventricle curves upward from the posterior half of the frontal lobe to the parietal and occipital lobes in a manner that lifts these lobes. Furthermore, the ventricles take a form that slightly raises the temporal lobe from the trigone to the temporal horn. It is important to anatomically re-examine (1) why the ventricles display such a shape so that they are in a floating state within the brain regardless of the body position and (2) whether or not the ventricles are positioned nearly equidistant from the subarachnoid space because such form is advantageous for substance and fluid exchange in the deep white matter.

2. It is obviously necessary to consider the differences in experimental methods and in species when examining the results from animal studies. For example, with regards to CSF absorption, it is thought that the human arachnoid granulation or villi are more developed than the rat arachnoid granulation, and in contrast, human leptomeningeal anastomosis is less developed compared to other species. Taking these into consideration, it is presumable that the ratios of drainage of CSF into the venous system and lymphatic system are different among species. Thus, analyses of water molecule movements with MRI and CSF movement with non-invasive methods such as positron emission tomography targeting AQP or β-amyloid are desired, especially in humans.

3. The successful discovery of the meningeal lymphatic vessel in 2015 is a major accomplishment. However, the pathway in which CSF in the subarachnoid space reaches this meningeal lymphatic vessel is unknown, and further analysis including its mechanism is anticipated in the future.

4. AQP plays a key role in water permeability, and is important in the interstitial fluid-CSF exchange. However, a consensus regarding its role in physiologically normal conditions and in physiologically abnormal conditions is desired in the future.

5. With regard to the movement of interstitial fluid and CSF, which have gained interest as elimination...
routes for heat generated by neural activity and metabolites of neural activity, the promotion of studies focus not only on CSF exit from the brain, but also on entrance of nutrients into the brain parenchyma and the subsequent signal transduction, is desired.

**Conclusion**

Liquid that covers the brain was observed over 2000 years ago, and von Haller was the first to systematically describe its existence. Moreover, the widely accepted medical term “cerebrospinal fluid” was first used by Magendie. CSF is produced not only by the choroid plexus, but also by many other non-choroid plexus structures, and is absorbed not only by the arachnoid granulation or villi, but also by many other non-arachnoid granulation or villus structures. Glia, which covers the neurovascular unit, is located at the border of the area where water enters and exits the brain and spinal cord, and water exchange occurs through the endothelium via diffusion or vesicular transport at AQP channels on astrocyte foot processes, or at other sites. Extensive exchange of CSF and interstitial fluid occurs between CSF reservoirs (ventricles and subarachnoid space) and the brain parenchyma, and this exchange occurs in a bidirectional manner. The homeostasis of the central nervous system is maintained through CSF and interstitial fluid exchange, which facilitates processes such as adjustment of cerebrospinal volume, nutrient and drug transport, signal transduction, metabolite elimination, and dissipation of heat generated by neural activity. CSF eliminated from the subarachnoid space is known to move out via a pathway from the arachnoid granulation or villi to the venous system, and via a pathway from the meningeal lymphatic vessels within the dura mater and where the cranial nerve exits the dura mater to the lymphatic system. Concerning studies on CSF physiology, from anatomical examinations to histological assessments and from studies in ventriculo-cisternal perfusion (Pappenheimer et al.\(^\text{29}\)) to dynamic assessment of water with M\(R\)F, numerous new research results such as the discovery of water channels, notably AQP, as well as the discovery of a lymphatic drainage path that works along with the venous drainage path have emerged. Thus, we are diving into new territory regarding studies on the homeostasis of the central nervous system, primarily of CSF.

**Conflicts of Interest Disclosure**

The authors declare no conflicts of interest.

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**References**

1) Di leva A, Yaşargil MG: Liquor cotunnii: the history of cerebrospinal fluid in Domenico Cotugno’s work. Neurosurgery 63: 352–358; discussion 358, 2008
2) Deisenhammer F: The history of cerebrospinal fluid, in Deisenhammer F, Sellebjerg F, Teunissen CE, Tumani H (eds): Cerebrospinal Fluid in Clinical Neurology. Cham, Springer International Publishing, 2015, pp 3–16
3) Cotugno D: De ischiade nervosa commentarius. Viennae, Apud Rudolphum Gräffier, 1770
4) Swedenborg E: The Cerebrum and its Parts, Vol 1. London, Swedenborg Library Academy of the New Church, 1882
5) von Haller A: Primae lineae physiologiae in usum praelectionum academicarum. Göttinten, Vandenhoeck, 1747
6) Viets HR: Domenico Cotugno: his description of the cerebrospinal fluid, with a translation of part of his De Ischiade Nervosa Commentarius (1764) and a bibliography of his important works. Bulletin of the Institute of the History of Medicine—The Johns Hopkins University 3: 701–713, 1935
7) Haymaker W, Schiller F: The Founders of Neurology: One Hundred and Thirty-three Biographical Sketches Prepared for the Fourth International Neurological Congress in Paris by Eighty-four Authors. Springfield, C.C. Thomas, 1970
8) Hajdu SI: A note from history: discovery of the cerebrospinal fluid. Ann Clin Lab Sci 33: 334–336, 2003
9) Magendie F: Recherches physiologiques et cliniques sur le liquide céphalo-rachidien ou cérébro-spinal. Paris, Méquignon-Marvis fils, 1842
10) Hildebrand R: Soemmerring’s work on the nervous system: a view on brain structure and function from the late eighteenth century. Anat Embryol 210: 337–342, 2005
11) Galen C: On the brain (Book IX), in De anatomica administrationibu, Reprint. New York, Oxford University Press, 1956, pp 226–237
12) Willis T: Cerebri anatome: cui accessit nervorum descriptio et usus. London, Londini, typis Jo. Flesher, impensis Jo. Martyn & Ja. Allestry apud insignis Campanae in Coemeterio D. Pauli, 1664
13) Davson H, Welch K, Segal MB: Physiology and Pathophysiology of the Cerebrospinal Fluid. Edinburgh, Churchill Livingstone, 1987
14) Dandy WE, Blackfan KD: Internal hydrocephalus: experimental, clinical and pathological study. Am J Dis Child 8: 406–482, 1914
15) Dandy WE, Blackfan KD: An experimental and clinical study of internal hydrocephalus. JAMA 61: 2216–2217, 1913
16) Hassin GB, Oldberg E, Tinsley M: Changes in the brain in plexectomized dogs: with comments on the cerebrospinal fluid. Arch Neuropsych 38: 1224–1239, 1937

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The Cerebrum and its Parts. Viennae, 2008

Deisenhammer F, sellebjerg F, teunissen ce, tumani H (eds): Cerebrospinal Fluid in Clinical Neurology. Cham, Springer International Publishing, 2015, pp 3–16
17) Hassin GB: So called circulation of the cerebrospinal fluid; chairman’s address. JAMA 101: 821–823, 1933
18) Hassin GB: Notes on the nature and origin of the cerebrospinal fluid. Journal of Nervous & Mental Disease 59: 113–121, 1924
19) Hassin GB: Circulation of cerebrospinal fluid. Journal of Nervous & Mental Disease 79: 465, 1934
20) de Rougemont, Ames A 3rd, Nesbett FB, Hofmann HF: Fluid formed by choroid plexus; a technique for its collection and a comparison of its electrolyte composition with serum and cisternal fluids. J Neurophysiol 23: 485–495, 1960
21) Ames A 3rd, Sakanoue M, Endo S: Na, K, Ca, Mg, and Cl concentrations in choroid plexus fluid and cisternal fluid compared with plasma ultrafiltrate. J Neurophysiol 27: 672–681, 1964
22) Pollay M, Stevens FA, Roberts PA: Alteration in choroid-plexus blood flow and cerebrospinal-fluid formation by increased ventricular pressure, in Wood J (ed): Neurobiology of Cerebrospinal Fluid 2. New York, Plenum Press, 1983, pp 687–695
23) Maraković J, Orešković D, Rados M, Vukić M, Jurjević I, Chudy D, Klarica M: Effect of osmolarity on CSF volume during ventriculo-aqueductal and ventriculo-cisternal perfusions in cats. Neuroni Sci Lett 484: 93–97, 2010
24) O’Connell JE: Cerebrospinal fluid mechanics. Proc R Soc Med 63: 507–518, 1970
25) Welch K: Secretion of cerebrospinal fluid by choroid plexus of the rabbit. Am J Physiol 205: 617–624, 1963
26) Pollay M, Stevens A, Estrada E, Kaplan R: Extracorporeal perfusion of choroid plexus. J Appl Physiol 32: 612–617, 1972
27) Pollay M: Formation of cerebrospinal fluid. Relation of studies of isolated choroid plexus to the standing gradient hypothesis. J Neurosurg 42: 665–673, 1975
28) Heisey SR, Held D, Pappenheimer JR: Bulk flow and diffusion in the cerebrospinal fluid system of the goat. Am J Physiol 203: 775–781, 1962
29) Pappenheimer JR, Heisey SR, Jordan EF, Downer deC: Perfusion of the cerebral ventricular system in unanesthetized goats. Am J Physiol 203: 763–774, 1962
30) Sato O, Bering EA Jr, Yagi M, Tsugane R, Hara M, Amano Y, Asai T: Bulk flow in the cerebrospinal fluid system of the dog. Acta Neurol Scand 51: 1–11, 1975
31) Lorenzo AV, Page LK, Watters GV: Relationship between cerebrospinal fluid formation, absorption and pressure in human hydrocephalus. Brain 93: 679–692, 1970
32) Zheng W, Chodobski A: The Blood-Cerebrospinal Fluid Barrier. Boca Raton, CRC Press, 2005
33) Milhorat TH: Structure and function of the choroid plexus and other sites of cerebrospinal fluid formation. Int Rev Cytol 47: 225–288, 1976
34) Milhorat TH: Choroid plexus and cerebrospinal fluid production. Science 166: 1514–1516, 1969
35) Milhorat TH, Hammock MK, Fenstermacher JD, Levin VA: Cerebrospinal fluid production by the choroid plexus and brain. Science 173: 330–332, 1971
36) Pollay M, Curl F: Secretion of cerebrospinal fluid by the ventricular ependyma of the rabbit. Am J Physiol 213: 1031–1038, 1967
37) Bering EA Jr, Sato O: Hydrocephalus: changes in formation and absorption of cerebrospinal fluid within the cerebral ventricles. J Neurosurg 20: 1050–1063, 1963
38) Hammock MK, Milhorat TH: Recent studies on the formation of cerebrospinal fluid. Dev Med Child Neurol Suppl 15: 27–34, 1973
39) Tamburrini G, Caldarelli M, Di Rocco F, Massimi L, D’Angelo L, Pasano T, Di Rocco C: The role of endoscopic choroid plexus coagulation in the surgical management of bilateral choroid plexuses hyperplasia. Childs Nerv Syst 22: 605–608, 2006
40) Milhorat TH, Hammock MK, Chien T, Davis DA: Normal rate of cerebrospinal fluid formation five years after bilateral choroid plexectomy. Case report. J Neurosurg 44: 735–739, 1976
41) Milhorat TH: Failure of choroid plexectomy as treatment for hydrocephalus. Surg Gynecol Obstet 139: 505–508, 1974
42) Anesi R, Hayashi Y, Hiroshima S, Mitsui N, Orimoto R, Uemori G, Saito M, Sato M, Wada H, Hododuka A, Kamada K: Hydrocephalus due to diffuse villous hyperplasia of the choroid plexus. Neurol Med Chir (Tokyo) 51: 437–441, 2011
43) Safaee M, Clark AJ, Bloch O, Oh MC, Singh A, Augste Kl, Gupta N, McDermott MW, Aghī MK, Berger MS, Parsa AT: Surgical outcomes in choroid plexus papillomas: an institutional experience. J Neurooncol 113: 117–125, 2013
44) Orešković D, Klarica M, Vukić M: The formation and circulation of cerebrospinal fluid inside the cat brain ventricles: a fact or an illusion? Neurosci Lett 327: 103–106, 2002
45) Weed LH: The development of the cerebrospinal spaces in pig and in man. Contrib Embryol Carnegie Inst 5: 1–116, 1917
46) Bering EA: Cerebrospinal fluid production and its relationship to cerebral metabolism and cerebral blood flow. Am J Physiol 197: 825–828, 1959
47) Weed LH: Studies on cerebro-spinal fluid. No. IV: the dual source of cerebro-spinal fluid. J Med Res 31: 93–117, 1914
48) Hassin GB: The morphology of the pail blood vessels and its bearing on the formation and absorption of the cerebrospinal fluid. J Neuropathol Exp Neurol 7: 432–438, 1948
49) Sato O, Asai T, Amano Y, Hara M, Tsugane R, Yagi M: Formation of cerebrospinal fluid in spinal subarachnoid space. Nature 233: 129–130, 1971
50) Sonnenberg H, Solomon S, Frazier DT: Sodium and chloride movement into the central canal of cat spinal cord. Proc Soc Exp Biol Med 124: 1316–1320, 1967
51) Maraković J, Orešković D, Jurjević I, Rados M, Chudy D, Klarica M: Potential error in ventriculocisternal perfusion method for determination of cerebrospinal fluid formation rate in cats. Coll Antropol 35(Suppl 1): 73–77, 2011

Neur Med Chir (Tokyo) 56, July, 2016
Physiology of CSF in the Central Nervous System

52) Milhorat TH, Mosher MB, Hammock MK, Murphy CF: Evidence for choroid-plexus absorption in hydrocephalus. N Engl J Med 283: 286–289, 1970

53) Wislocki GB, Putnam TJ: Absorption from the ventricles in experimentally produced internal hydrocephalus. Am J Anat 29: 313–320, 1921

54) Key A, Retzius G: Studien in der Anatomie des Nervensystems und des Bindegewebes. Stockholm, Norstedt & Söner, 1875

55) Marburg O: Hydrocephalus: Its Symptomatology, Pathology, Pathogenesis and Treatment. New York, Oskar Piest, 1940

56) Millen JW, Woollam DHM: The Anatomy of the Cerebrospinal Fluid. London, Oxford University Press, 1962

57) Shapiro K, Marmarou A, Portnoy H: Hydrocephalus. New York, Raven Press, 1984

58) Turner L: The structure and relationships of arachnoid granulations, in Wolstenholme GEW, O'Connor CM (eds): Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption. Chichester, John Wiley & Sons Ltd., 1958, pp 32–54

59) Selverstone B: Studies of the formation and absorption of the cerebrospinal fluid using radioactive isotopes: a critical evaluation of data and conclusions, in Wolstenholme GEW, O'Connor CM (eds): Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption. Chichester, John Wiley & Sons Ltd., 1958, pp 147–167

60) Kida S, Yamashima T, Kubota T, Ito H, Yamamoto S: A light and electron microscopic and immunohistochemical study of human arachnoid villi. J Neurosurg 69: 429–435, 1988

61) Weed LH: Studies on cerebro-spinal fluid. No. II: the theories of drainage of cerebro-spinal fluid with an analysis of the methods of investigation. J Med Res 31: 21–40, 1914

62) Davson H, Homer FR, Hollingsworth JR: The mechanism of drainage of the cerebrospinal fluid. Brain 96: 329–336, 1973

63) Shulman K, Yarnell P, Ransohoff J: Dural sinus pressure. In normal and hydrocephalic dogs. Arch Neurol 10: 575–580, 1964

64) Grzybowski DM, Holman DW, Katz SE, Lubow M: In vitro model of cerebrospinal fluid outflow through human arachnoid granulations. Invest Ophthamol Vis Sci 47: 3664–3672, 2006

65) Welch K, Friedman V: The relation between the structure of arachnoid villi and their functions. Surgical Forum 10: 767–769, 1960

66) Yamashima T: Ultrastructural study of the final cerebrospinal fluid pathway in human arachnoid villi. Brain Res 384: 68–76, 1986

67) Tripathi BJ, Tripathi RC: Vacuolar transcellular channels as a drainage pathway for cerebrospinal fluid. J Physiol (Lond) 239: 195–206, 1974

68) Shabo AL, Maxwell DS: Electron microscopic observations on the fate of particulate matter in the cerebrospinal fluid. J Neurosurg 29: 464–474, 1968

69) Levine JE, Povlishock JT, Becker DP: The morphological correlates of primate cerebrospinal fluid absorption. Brain Res 241: 31–41, 1982

70) Alksne JF, Lovings ET: The role of the arachnoid villus in the removal of red blood cells from the subarachnoid space. An electron microscope study in the dog. J Neurosurg 36: 192–200, 1972

71) Weller RO, Kida S, Zhang ET: Pathways of fluid drainage from the brain—morphological aspects and immunological significance in rat and man. Brain Pathol 2: 277–284, 1992

72) Gomez DG, Ehmann JE, Gordon Potts D, Pavese AM, Gilianan A: The arachnoid granulations of the newborn human: an ultrastructural study. Int J Dev Neurosci 1: 139–147, 1983

73) Osaka K, Handa H, Matsumoto S, Yasuda M: Development of the cerebrospinal fluid pathway in the normal and abnormal human embryos. Childs Brain 6: 26–38, 1980

74) Oi S, Di Rocco C: Proposal of “evolution theory in cerebrospinal fluid dynamics” and minor pathway hydrocephalus in developing immature brain. Childs Nerv Syst 22: 662–669, 2006

75) Papaiconomou C, Bozanovic-Sosic R, Zakharov A, Johnston M: Does neonatal cerebrospinal fluid absorption occur via arachnoid projections or extracranial lymphatics? Am J Physiol Regul Integr Comp Physiol 283: R869–R876, 2002

76) Pollay M: The function and structure of the cerebrospinal fluid outflow system. Cerebrospinal Fluid Res 7: 9, 2010

77) Bateman GA, Napier BD: External hydrocephalus in infants: six cases with MR venogram and flow quantification correlation. Childs Nerv Syst 27: 2087–2096, 2011

78) Bowshier D: Pathways of absorption of protein from the cerebrospinal fluid: an autoradiographic study in the cat. Anat Rec 128: 23–39, 1957

79) Bito LZ, Davson H, Fenstermacher JD: The ocular and cerebrospinal fluids, Proceedings of a Fogarty International Center Symposium, Bethesda, Md. 3–6 May 1976, Vol 25, Supplement 1. London, Academic Press, 1977

80) Foltz E, Blanks J, Morton ME: Experimental transcerebral fistula. Perineural olfactory CSF flow in the normal, hydrocephalic, and postoperative hydrocephalic dog shown by radionuclide ventriculography. J Neurosurg 61: 355–364, 1984

81) Arnold W, Ritter R, Wagner WH: Quantitative studies on the drainage of the cerebrospinal fluid into the lymphatic system. Acta Otolaryngol 76: 156–161, 1973

82) Tripathi RC: The functional morphology of the outflow systems of ocular and cerebrospinal fluids. Exp Eye Res 25 Suppl: 65–116, 1977

83) Erlich SS, McComb JG, Hyman S, Weiss MH: Ultrastructure of the orbital pathway for cerebrospinal fluid drainage in rabbits. J Neurosurg 70: 926–931, 1989

84) Field EJ, Brierley JB: The retro-orbital tissues as a site of outflow of cerebrospinal fluid. Proc R Soc Med 42: 447–450, 1949

Neurol Med Chir (Tokyo) 56, July, 2016
volunteers and patients with normal pressure hydrocephalus. *Neurol Med Chir (Tokyo)* 55: 657–662, 2015

117) Matsumae M, Hirayama A, Atsumi H, Yatsushiro S, Kuroda K: Velocity and pressure gradients of cerebrospinal fluid assessed with magnetic resonance imaging. *J Neurosurg* 120: 218–227, 2014

118) Yatsushiro S, Hirayama A, Matsumae M, Kuroda K: Visualization of pulsatile CSF motion separated by membrane-like structure based on four-dimensional phase-contrast (4D-PC) velocity mapping, *Conf Proc IEEE Eng Med Biol Soc* 2013: 6470–6473, 2013

119) Stadlbauer A, Salomonowitz E, Brenneis C, Ungersböck K, van der Riet W, Buchfelder M, Ganslandt O: Magnetic resonance velocity mapping of 3D cerebrospinal fluid flow dynamics in hydrocephalus: preliminary results. *Eur Radiol* 22: 232–242, 2012

120) Howden L, Giddings D, Power H, Aroussi A, Vloerberghs M, Garnett M, Walker D: Three-dimensional cerebrospinal fluid flow within the human ventricular system. *Comput Methods Biomech Biomed Engin* 11: 123–133, 2008

121) Bradley WG Jr: Magnetic resonance imaging in the evaluation of cerebrospinal fluid flow abnormalities. *Magn Reson Q* 8: 169–196, 1992

122) Bradley WG Jr, Scalzo D, Queralt J, Nitz WN, Atkinson DJ, Wong P: Normal-pressure hydrocephalus: evaluation with cerebrospinal fluid flow measurements at MR imaging. *Radiology* 198: 523–529, 1996

123) Greitz D: Cerebrospinal fluid circulation and associated intracranial dynamics. A radiologic investigation using MR imaging and radionuclide cisternography. *Acta Radiol Suppl* 386: 1–23, 1993

124) Naidich TP, Altman NR, Gonzalez-Arias SM: Phase contrast cine magnetic resonance imaging: normal cerebrospinal fluid oscillation and applications to hydrocephalus. *Neurosurg Clin N Am* 4: 677–705, 1993

125) Greitz D, Franck A, Nordell B: On the pulsatile nature of intracranial and spinal CSF-circulation demonstrated by MR imaging. *Acta Radiol* 34: 321–328, 1993

126) Hirayama A, Matsumae M, Yatsushiro S, Abdulla A, Atsumi H, Kuroda K: Visualization of pulsatile csf motion around membrane-like structures with both 4D velocity mapping and time-SLIP technique. *Magn Reson Med Sci* 14: 263–273, 2015

127) Yamada S: Cerebrospinal fluid physiology: visualization of cerebrospinal fluid dynamics using the magnetic resonance imaging Time-Spatial Inversion Pulse method. *Croat Med J* 55: 337–346, 2014

128) Kidö, Pantazis A, Weller RO: CSF drains directly from the subarachnoid space into nasal lymphatics in the rat. Anatomy, histology and immunological significance. *Neuropathol Appl Neurobiol* 19: 480–488, 1993

129) Boulton M, Flessner M, Armstrong D, Hay J, Johnston M: Determination of volumetric cerebrospinal fluid absorption into extracranial lymphatics in sheep. *Am J Physiol* 274: R88–R96, 1998

130) Courtice FC, Simmonds WJ: The removal of protein from the subarachnoid space. *Aust J Exp Biol Med Sci* 29: 255–263, 1951

131) Welch K, Pollay M: Perfusion of particles through arachnoid villi of the monkey. *Am J Physiol* 201: 651–654, 1961

132) Loukas M, Bellary SS, Kuklinski M, Ferruaola J, Yadav A, Shoja MM, Shaffer K, Tubbs RS: The lymphatic system: a historical perspective. *Clin Anat* 24: 807–816, 2011

133) Clouse ME: History, in Clouse ME, Wallace S (eds): *Lymphatic Imaging Lymphography, Computed Tomography and Scintigraphy*, ed 2. Baltimore, Williams & Wilkins, 1985, pp 1–14

134) Harrison DA, Clouse ME: Normal anatomy, in Clouse ME, Wallace S (eds): *Lymphatic Imaging Lymphography, Computed Tomography and Scintigraphy*, ed 2. Baltimore, Williams & Wilkins, 1985, pp 15–94

135) Louveau A, Smirnov I, Keyes TJ, Eccles JD, Rouhani SJ, Peske JD, Derecki NC, Castle D, Mandell JW, Lee KS, Harris TH, Kipnis J: Structural and functional features of central nervous system lymphatic vessels. *Nature* 523: 337–341, 2015

136) Bucchi F, Farina F, Zumo G, Cappello F: Lymphatic vessels of the dura mater: a new discovery? *J Anat* 227: 702–703, 2015

137) Mascagni P: *Vasorum lymphaticorum corporis humani historia et ichnographia*. Siena, Pazzini Carli, 1787

138) Aspeldund A, Antila S, Proulx ST, Karlsson TV, Karaman S, Detmar M, Wiig H, Alitalo K: A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules. *J Exp Med* 212: 991–999, 2015

139) Weller RO, Galea I, Carare RO, Minagar A: Pathophysiology of the lymphatic drainage of the central nervous system: implications for pathogenesis and therapy of multiple sclerosis. *Pathophysiology* 17: 295–306, 2010

140) Bradbury M: Physiopathology of the blood-brain barrier, in Levi G, Battistin L, Lajtha A (eds): *Transport Phenomena in the Nervous System*. New York, Plenum Press, 1976, pp 507–516

141) Abbott NJ: Evidence for bulk flow of brain interstitial fluid: significance for physiology and pathology. *Neurochem Int* 45: 545–552, 2004

142) Cserr HF: Role of secretion and bulk flow of brain interstitial fluid in brain volume regulation. *Ann N Y Acad Sci* 529: 9–20, 1988

143) Virchow R: Ueber die Erweiterung kleinerer Gefäße. *Arch Pathol Anat Physiol Klin Med* 3: 427–462, 1851

144) Robin C: Recherches sur quelques particularités de la structure des capillaires de l’encéphale. *J Physiol Homme* 2: 537–548, 1859

145) Bechmann I, Priller J, Kovac A, Böntert M, Wehner T, Klett FF, Bohsung J, Stuschke M, Dirnagl U, Nitsch R: Immune surveillance of mouse brain
perivascular spaces by blood-borne macrophages. *Eur J Neurosci* 14: 1651–1658, 2001

146) Bilston LE, Fletcher DF, Brodbelt AR, Stoodley MA: Arterial pulsation-driven cerebrospinal fluid flow in the perivascular space: a computational model. *Comput Methods Biomech Biomed Engin* 6: 235–241, 2003

147) Ichimura T, Fraser PA, Cserr HF: Distribution of extracellular tracers in perivascular spaces of the rat brain. *Brain Res* 545: 103–113, 1991

148) Schley D, Carare-Rnadi R, Please CP, Perry VH, Weller RO: Mechanisms to explain the reverse perivascular transport of solutes out of the brain. *J Theor Biol* 238: 962–974, 2006

149) Zhang ET, Inman CB, Weller RO: Interrelationships of the pia mater and the perivascular (Virchow-Robin) spaces in the human cerebrum. *J Anat* 170: 111–123, 1990

150) Hladky SB, Barrand MA: Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence. *Fluids Barriers CNS* 11: 26, 2014

151) Carare RO, Hawkes CA, Weller RO: Affermant and efferent immunological pathways of the brain. Anatomy, function and failure. *Brain Behav Immun* 36: 9–14, 2014

152) Iliff JJ, Wang M, Zeppenfeld DM, Venkataraman a, Plogg BA, Liao y, Deane r, Nedergaard M: Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. *J Neurosci* 33: 18190–18199, 2013

153) Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, Benveniste H, Vates GE, Deane R, Goldman SA, Nagelhus EA, Nedergaard M: A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid β. *Sci Transl Med* 4: 147ra111, 2012

154) Rennels ML, Gregory TF, Blaumanis OR, Fujimoto K, Grady PA: Evidence for a ‘paravascular’ fluid circulation in the mammalian central nervous system, provided by the rapid distribution of tracer protein throughout the brain from the subarachnoid space. *Brain Res* 326: 47–63, 1985

155) Bulat M, Lupret V, Orekhovič D, Klarica M: Transventricular and transpial absorption of cerebrospinal fluid into cerebral microvessels. *Coll Antropol* 32(Suppl 1): 43–50, 2008

156) Zhang ET, Richards HK, Kida S, Weller RO: Directional and compartmentalised drainage of interstitial fluid and cerebrospinal fluid from the rat brain. *Acta Neuropathol* 83: 233–239, 1992

157) Brightman MW: The distribution within the brain of ferritin injected into cerebrospinal fluid compartments. I. Ependymal distribution. *J Cell Biol* 26: 99–123, 1965

158) Brightman MW: The intracerebral movement of proteins injected into blood and cerebrospinal fluid of mice. *Prog Brain Res* 29: 19–40, 1968

159) Bulat M: Dynamics and statics of the cerebrospinal fluid: the classical and a new hypothesis, in Avezaat CJ, van Eijndhoven JHM, Maas AIR, Tans JT (eds): *Intracranial Pressure VIII*. Springer Berlin Heidelberg, 1993, pp 726–730

160) Weller RO, Kida S, Harding BN: Aetiology and pathology of hydrocephalus, in Schurr PH, Polkey CE (eds): *Hydrocephalus*. Oxford, Oxford University Press, 1993, pp 48–99

161) Bedussi B, van Lier MG, Bartstra JW, de Vos J, Siebes M, VanBavel E, Bakker EN: Clearance from the mouse brain by convection of interstitial fluid towards the ventricular system. *Fluids and Barriers CNS* 12: 23, 2015

162) Crone C: The blood-brain barrier as a tight epithelium: where is information lacking? *Ann N Y Acad Sci* 481: 174–185, 1986

163) Brightman MW, Palay SL: The fine structure of ependyma in the brain of the rat. *J Cell Biol* 19: 415–439, 1963

164) Brightman MW: The distribution within the brain of ferritin injected into cerebrospinal fluid compartments. II. Parenchymal distribution. *Am J Anat* 117: 193–219, 1965

165) Sahar A, Hochwald GM, Ransohoff J: Alternate pathway for cerebrospinal fluid absorption in animals with experimental obstructive hydrocephalus. *Exp Neurol* 25: 200–206, 1969

166) Naidich TP, Epstein F, Lin JP, Kricheff II, Hochwald GM: Evaluation of pediatric hydrocephalus by computed tomography. *Radiology* 119: 337–345, 1976

167) Weller RO, Mitchell J: Cerebrospinal fluid edema and its sequelae in hydrocephalus. *Adv Neurol* 28: 111–123, 1980

168) Drayer BP, Rosenbaum AE, Higman HB: Cerebrospinal fluid imaging using serial metrizamide CT cisternography. *Neuroradiology* 13: 7–17, 1977

169) Bering EA Jr: Water exchange of central nervous system and cerebrospinal fluid. *J Neurosurg* 9: 275–287, 1952

170) Williams MA, McAllister JP, Walker ML, Kranz DA, Bergsneider M, Del Bigio MR, Fleming L, Frim DM, Gwinn K, Kestle Jr, Luciano MG, Madsen Jr, Oster-Granite ML, Spinella G: Priorities for aneurysm pathology of hydrocephalus, *eds*): *The Cerebrospinal Fluid*. Kluwer Academic Publishers, 1989, pp 15–43

Neurol Med Chir (Tokyo) 56, July, 2016
174) Woollam DH, Millen JW: The perivascular spaces of the mammalian central nervous system and their relation to the perineuronal and subarachnoid spaces. *J Anat* 89: 193–200, 1955

175) Krahn V: The pia mater at the site of the entry of blood vessels into the central nervous system. *Anat Embryol* 164: 257–263, 1982

176) Ge S, Song L, Pachter JS: Where is the blood-brain barrier... really? *J Neurosci Res* 79: 421–427, 2005

177) Krisch B, Leonhardt H, Oksche A: Compartments and perivascular arrangement of the meninges covering the cerebral cortex of the rat. *Cell Tissue Res* 238: 459–474, 1984

178) Turner PT, Harris AB: Ultrastructure of exogenous peroxidase in cerebral cortex. *Brain Res* 74: 305–326, 1974

179) Drayer BP, Rosenbaum AE: Metrizamide brain penetration. *Acta Radiol Suppl* 355: 280–293, 1977

180) Yang L, Kress BT, Weber HJ, Thiagarajan M, Wang B, Deane R, Benveniste H, Iliff JJ, Nedergaard M: Evaluating glymphatic pathway function utilizing clinically relevant intrathecal infusion of CSF tracer. *J Transl Med* 11: 107, 2013

181) Hutchings M, Weller RO: Anatomical relationships of the pia mater to cerebral blood vessels in man. *J Neurosurg* 65: 316–325, 1986

182) Wang P, Olbricht WL: Fluid mechanics in the perivascular space. *J Theor Biol* 274: 52–57, 2011

183) Weller RO, Subash M, Preston SD, Mazanti I, Carare RO: Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer’s disease. *Brain Pathol* 18: 253–266, 2008

184) Preston SD, Steart PV, Wilkinson A, Nicoll JA, Weller RO: Capillary and arterial cerebral amyloid angiopathy in Alzheimer’s disease: defining the perivascular route for the elimination of amyloid beta from the human brain. *Neuropathol Appl Neurobiol* 29: 106–117, 2003

185) Carare RO, Bernardes-Silva M, Newman TA, Page AM, Nicoll JA, Perry VH, Weller RO: Solute transport in the human brain: from the brain parenchyma along basement membranes of capillaries and arteries: significance for cerebral amyloid angiopathy and neuroinimmunology. *Neuropathol Appl Neurobiol* 34: 131–144, 2008

186) Carare RO, Hawkes CA, Jeffrey M, Kalaria RN, Weller RO: Review: cerebral amyloid angiopathy, prion angiopathy, CADASIL and the spectrum of protein elimination failure angiopathies (PEFA) in neurodegenerative disease with a focus on therapy. *Neuropathol Appl Neurobiol* 39: 593–611, 2013

187) Hawkes CA, Härtig W, Kacza J, Schliebs R, Weller RO, Nicoll JA, Carare RO: Perivascular drainage of solutes is impaired in the ageing mouse brain and in the presence of cerebral amyloid angiopathy. *Acta Neuropathol* 121: 431–443, 2011

188) Suzuki Y, Nakamura Y, Yamada K, Igarashi H, Kasuga K, Yokoyama Y, Ikeuchi T, Nishizawa M, Kwee IL, Nakada T: Reduced CSF water influx in Alzheimer’s disease supporting the β-amyloid clearance hypothesis. *PLoS One* 10: e0123708, 2015

189) Carare RO, Teeling JL, Hawkes CA, Püntener U, Weller RO, Nicoll JA, Perry VH: Immune complex formation impairs the elimination of solutes from the brain: implications for immunotherapy in Alzheimer’s disease. *Acta Neuropathol Commun* 1: 48, 2013

190) Földi M, Csillik B, Zoltán OT: Lymphatic drainage of the brain. *Experimentia* 24: 1283–1287, 1968

191) Hadaczek P, Yamashita Y, Mirek H, Tamas L, Bohn MC, Noble C, Park JW, Bankiewicz K: The “perivascular pump” driven by arterial pulsation is a powerful mechanism for the distribution of therapeutic molecules within the brain. *Mol Ther* 14: 69–78, 2006

192) Simon MJ, Iliff JJ: Regulation of cerebrospinal fluid (CSF) flow in neurodegenerative, neurovascular and neuroinflammatory disease. *Biochim Biophys Acta* 1862: 442–451, 2016

193) Kiviniemi V, Wang X, Korhonen V, Keinänen T, Tuovinen T, Autio J, LeVann P, Keilholz S, Zang YF, Hennig J, Nedergaard M: Ultra-fast magnetic resonance encephalography of physiological brain activity—glymphatic pulsation mechanisms? *J Cereb Blood Flow Metab* 2015 [Epub ahead of print]

194) Nedergaard M: Neuroscience. Garbage truck of the brain. *Science* 340: 1529–1530, 2013

195) Alcolado R, Weller RO, Parrish EP, Garrod D: The cranial arachnoid and pia mater in man: anatomical and ultrastructural observations. *Neuropathol Appl Neurobiol* 14: 1–17, 1988

196) Cserr HF, Ostrach LH: Bulk flow of interstitial fluid after intracranial injection of blue dextran 2000. *Exp Neurol* 45: 50–60, 1974

197) Cserr HF: Bulk flow of cerebral extracellular fluid as a possible mechanism of CSF-brain exchange, in Cserr HF, Fenstermacher JD, Fencl V (eds): *Fluid Environment of the Brain*. New York, Academic Press Inc., 1975, pp 215–224

198) Fenstermacher J, Kaye T: Drug “diffusion” within the brain. *Ann N Y Acad Sci* 531: 29–39, 1988

199) Patlak CS, Fenstermacher JD: Measurements of dog blood-brain transfer constants by ventriculocisternal perfusion. *Am J Physiol* 229: 877–884, 1975

200) Syková E, Nicholson C: Diffusion in brain extracellular space. *Physiol Rev* 88: 1277–1340, 2008

201) Kozma M, Zoltán OT, Csillik B: Die anatomischen Grundlagen des prälymphatischen systems im Gehirn. *Cells Tissues Organs* 81: 409–420, 1972

202) Oehmichen W, Gencic M: Experimental studies on kinetics and functions of mononuclear phagocytes of the central nervous system. *Acta Neuropathol Suppl* Suppl 6: 285–290, 1975

203) Cserr HF: Convection of brain interstitial fluid and its drainage into deep cervical lymph. *Wiss Z Karl Marx Univ Leipzig Math Naturwiss R* 36: 127–130, 1987
204) Cserr HF, Knopf PM: Cervical lymphatics, the blood-brain barrier and the immunoreactivity of the brain: a new view. *Immunol Today* 13: 507–512, 1992

205) Cserr HF: Relationship between cerebrospinal fluid and interstitial fluid of brain. *Fed Proc* 33: 2075–2078, 1974

206) Chikly B: Is human CSF reabsorbed by lymph? Lymph drainage therapy (LDT) and manual drainage of the central nervous system. *The Academy of Osteopathy Journal* 8: 28–34, 1998

207) Fenstermacher JD, Patlak CS: The exchange of material between cerebrospinal fluid and brain, in Cserr HF, Fenstermacher JD, Fencel V (eds): *Fluid Environment of the Brain*. New York, Academic Press Inc., 1975, pp 201–214

208) Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiagarajan M, O'Donnell J, Christensen DJ, Nicholson C, Illiff JJ, Takano T, Deane R, Nedergaard M: Sleep drives metabolite clearance from the adult brain. *Science* 342: 373–377, 2013

209) Kress BT, Illiff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, Xie L, Kang H, Xu Q, Liew JA, Plog BA, Ding F, Deane R, Nedergaard M: Impairment of paravascular clearance pathways in the aging brain. *Ann Neurol* 76: 845–861, 2014

210) Bulat M, Klarica M: Recent insights into a new hydrodynamics of the cerebrospinal fluid. *Brain Res Rev* 65: 99–112, 2011

211) Martin BA, Reymond P, Novy J, Balédent O, Bulat M, Klarica M: Recent insights into a new cerebrospinal fluid pathway, in Cserr HF, Fenstermacher JD, Fencel V (eds): *Fluid Environment of the Brain*. New York, Academic Press Inc., 1975, pp 201–214

212) Davson H: *Physiology of the Cerebrospinal Fluid*. London, Churchill, 1967

213) Cushing H: Studies on the cerebro-spinal fluid: I. Introduction. *J Med Res* 31: 1–19, 1914

214) Bowsher D: *Cerebrospinal Fluid Dynamics in Health and Disease*. Springfield, C.C. Thomas, 1960

215) Davson H: Formation and drainage of the cerebrospinal fluid. *Am J Physiol Heart Circ Physiol* 302: H1492–H1509, 2012

216) Davson H: *The Cerebrospinal Fluid: Production, Circulation and Absorption*. London, churhill, 1967

217) Craven J: Cerebrospinal fluid and its circulation. *Anaesth Intens Care Med* 11: 355–356, 2010

218) Clarke E, O’Malley CD: The ventricular system and cerebrospinal fluid, in *The Human Brain and Spinal Cord: A Historical Study Illustrated by Writings from Antiquity to the Twentieth Century*. San Francisco, Norman Publishing, 1996, pp 708–755

219) Hammock MK, Milhorat TH, Davis DA: Isotope cisternography and ventriculography in the diagnosis of hydrocephalus. *Dev Med Child Neurol* 16: 58–71, 1974

220) Han CY, Backous DD: Basic principles of cerebrospinal fluid metabolism and intracranial pressure homeostasis. *Otolaryngol Clin North Am* 38: 569–576, 2005

221) Herndon RM, Brumback R: *The Cerebrospinal Fluid*. Boston, Kluwer Academic Publishers, 1989

222) Kappers JA: Structural and functional changes in the telencephalic choroid plexus during human ontogenesis, in Wolstenholme GEW, O’Connor CM (eds): *Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption*. Chichester, John Wiley & Sons Ltd., 1958, pp 3–31

223) Wislocki GB, Ladman AJ: The fine structure of the mammalian choroid plexus, in Wolstenholme GEW, O’Connor CM (eds): *Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption*. Chichester, John Wiley & Sons Ltd., 1958, pp 55–79

224) Cooper ERA: Nerves of the meninges and choroid plexuses, in Wolstenholme GEW, O’Connor CM (eds): *Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption*. Chichester, John Wiley & Sons Ltd., 1958, pp 80–96

225) Wooliam DHM, Millen JW: Observations on the production and circulation of the cerebrospinal fluid, in Wolstenholme GEW, O’Connor CM (eds): *Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption*. Chichester, John Wiley & Sons Ltd., 1958, pp 124–146

226) Davson H: Some aspects of the relationship between the cerebrospinal fluid and the central nervous system, in Wolstenholme GEW, O’Connor CM (eds): *Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption*. Chichester, John Wiley & Sons Ltd., 1958, pp 189–208

227) Herlin L: The existence of a barrier between the cerebrospinal fluid and the boundary of the brain; Including experimental investigations on rabbits, using bilirubinaemia, in Wolstenholme GEW, O’Connor CM (eds): *Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption*. Chichester, John Wiley & Sons Ltd., 1958, pp 209–229

228) Zülch KJ: Neuropathological observations on the cerebrospinal fluid pathway, in Wolstenholme GEW, O’Connor CM (eds): *Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption*. Chichester, John Wiley & Sons Ltd., 1958, pp 230–245

229) Dott NM, Gillingham JF: Mechanical aspects of the cerebrospinal fluid circulation—physiological, pathological, surgical, in Wolstenholme GEW, O’Connor CM (eds): *Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption*. Chichester, John Wiley & Sons Ltd., 1958, pp 246–264

230) Johnson KM: Clinicopathological aspects of the cerebrospinal fluid circulation, in Wolstenholme GEW, O’Connor CM (eds): *Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption*. Chichester, John Wiley & Sons Ltd., 1958, pp 265–281

*Neurol Med Chir (Tokyo)* 56, July, 2016
Bowsher D: A possible mechanism of hydrocephalus: the osmotic regulation of cerebrospinal fluid volume. in Wolstenholme GEW, O'Connor CM (eds): Ciba Foundation Symposium—The Cerebrospinal Fluid: Production, Circulation and Absorption. Chichester, John Wiley & Sons Ltd., 1958, pp 282–301

Potts G: Hydrocephalus. J Neuroradiol 8: 195–206, 1981

Brinker T, Stopa E, Morrison J, Klinge P: A new look at cerebrospinal fluid circulation. Fluids Barriers CNS 11: 10, 2014

Orešković D, Klarica M: The formation of cerebrospinal fluid: nearly a hundred years of interpretations and misinterpretations. Brain Res Rev 64: 241–262, 2010

Johanson CE, Duncan JA 3rd, Klinge PM, Brinker T, Stopa EG, Silverberg GD: Multiplicity of cerebrospinal fluid functions: new challenges in health and disease. Cerebrospinal Fluid Res 5: 10, 2008

Raybaud C, MR assessment of pediatric hydrocephalus: a road map. Childs Nerv Syst 32: 19–41, 2016

Johanson C: Choroid plexus—cerebrospinal fluid circulatory dynamics: impact on brain growth, metabolism, and repair, in Conn PM (ed): Neuroscience in Medicine. Totowa, Humana Press, 2008, pp 173–200

Irani DN: Cerebrospinal Fluid in Clinical Practice. Elsevier Health Sciences, 2008

Johnston I, Teo C: Disorders of CSF hydrodynamics. Childs Nerv Syst 16: 776–799, 2000

Johnston CE: Ventricles and cerebrospinal fluid, Chapter 10, in Conn PM (ed): Neuroscience in Medicine. Philadelphia, Lippincott, 1995, pp 171–196

Koh L, Zakharov A, Johnston M: Integration of the subarachnoid space and lymphatics: is it time to embrace a new concept of cerebrospinal fluid absorption? Cerebrospinal Fluid Res 2: 6, 2005

Liddelow SA: Fluids and barriers of the CNS: a historical viewpoint. Fluids Barriers CNS 8: 2, 2011

Sato O, Takei F, Yamada S: Hydrocephalus: is impaired cerebrospinal fluid circulation only one problem involved? Childs Nerv Syst 10: 151–155, 1994

Sakka L, Coll G, Chazal J: Anatomy and physiology of cerebrospinal fluid. Eur Ann Otorhinolaryngol Head Neck Dis 128: 309–316, 2011

Tuman H: Anatomy of CSF-related spaces and barriers between blood, CSF, and brain, in Deisenhammer F, Sellebjerg F, Teunissen CE, Tuman H (eds): Cerebrospinal Fluid in Clinical Neurology. Cham, Springer International Publishing, 2015, pp 17–24

Tuman H: Physiology and constituents of CSF, in Deisenhammer F, Sellebjerg F, Teunissen CE, Tuman H (eds): Cerebrospinal Fluid in Clinical Neurology. Cham, Springer International Publishing, 2015, pp 25–34

Chikly B, Quaghebeur J: Reassessing cerebrospinal fluid (CSF) hydrodynamics: a literature review presenting a novel hypothesis for CSF physiology. J Bodyw Mov Ther 17: 344–354, 2013

Spector R, Robert Snodgrass S, Johanson CE: A balanced view of the cerebrospinal fluid composition and functions: focus on adult humans. Exp Neurol 273: 57–68, 2015

Preston GM, Agre P: Isolation of the cDNA for erythrocyte integral membrane protein of 28 kilodaltons: member of an ancient channel family. Proc Natl Acad Sci USA 88: 11110–11114, 1991

Agre P, Preston GM, Smith BL, Jung JS, Raina S, Moon C, Guggino WB, Nielsen S: Aquaporin CHIP: the archetypal molecular water channel. Am J Physiol 265: F463–F476, 1993

Nielsen S, Kwon TH, Frokiaer J, Agre P: Regulation and dysregulation of aquaporins in water balance disorders. J Intern Med 261: 53–64, 2007

Murata K, Mitsuoka K, Hirai T, Walz T, Agre P, Heymann JB, Engel A, Fujiyoshi Y: Structural determinants of water permeation through aquaporin-1. Nature 407: 599–605, 2000

Kozono D, Yasui M, King LS, Agre P: Aquaporin water channels: atomic structure molecular dynamics meet clinical medicine. J Clin Invest 109: 1395–1399, 2002

de Groot BL, Grumbhüler H: The dynamics and energetics of water permeation and proton exclusion in aquaporins. Curr Opin Struct Biol 15: 176–183, 2005

Badaut J, Lasbennes F, Magistretti PJ, Regli L: Aquaporins in brain: distribution, physiology, and pathophysiology. J Cereb Blood Flow Metab 22: 367–378, 2002

Ishibashi K: Aquaporin superfamily with unusual npa boxes: S-aquaporins (superfamily, sip-like and subcellular-aquaporins). Cell Mol Biol (Noisy-le-grand) 52: 20–27, 2006

Day RE, Kitchen P, Owen DS, Bland C, Marshall L, Conner AC, Bill RM, Conner MT: Human aquaporins: regulators of transcellular water flow. Biochim Biophys Acta 1840: 1492–1506, 2014

Tait MJ, Saadoun S, Bell BA, Papadopoulos MC: Water movements in the brain: role of aquaporins. Trends Neurosci 31: 37–43, 2008

Yang M, Gao F, Liu H, Yu WH, He GQ, Zhuo F, Qiu GP, Sun SQ: Immunolocalization of aquaporins in rat brain. Anat Histol Embryol 40: 299–306, 2011

Yamamoto N, Yoneda K, Asai K, Sobue K, Tada T, Fujita Y, Katsuya H, Fujita M, Aihara N, Mase M, Yamada K, Miura Y, Kato T: Alterations in the expression of the AQP family in cultured rat astrocytes during hypoxia and reoxygenation. Brain Res Mol Brain Res 90: 26–38, 2001

Chai RC, Jiang JH, Wong AY, Jiang F, Gao K, Vatcher G, Hoi Yu AC: AQP5 is differentially regulated in astrocytes during metabolic and traumatic injuries. Glia 61: 1746–1765, 2013
262) Praetorius J, Nielsen S: Distribution of sodium transporters and aquaporin-1 in the human choroid plexus. *Am J Physiol, Cell Physiol* 291: C59–C67, 2006

263) Speake T, Freeman LJ, Brown PD: Expression of aquaporin 1 and aquaporin 4 water channels in rat choroid plexus. *Biochim Biophys Acta* 1609: 80–86, 2003

264) Akdemir G, Kaymaz F, Gursoy-Ozdemir Y, Akalan N, Akdemir ES: The time course changes in expression of aquaporin 4 and aquaporin 1 following global cerebral ischemic edema in rat. *Surg Neurol Int* 7: 4, 2016

265) Hasegawa H, Ma T, Skach W, Matthay MA, Verkman AS: Molecular cloning of a mercurial-insensitive water channel expressed in selected water-transporting tissues. *J Biol Chem* 269: 5497–5500, 1994

266) Ishibashi K, Kuwahara M, Sasaki S: Molecular biology of aquaporins, in *Reviews of Physiology Biochemistry and Pharmacology*, Vol 141. Berlin, Springer-Verlag, 2000, pp 1–32

267) Sobue K, Yamamoto N, Yoneda K, Fujita K, Miura Y, Asai K, Tsuda T, Katsuya H, Kato T: Molecular cloning of two bovine aquaporin-4 cDNA isoforms and their expression in brain endothelial cells. *Biochim Biophys Acta* 1489: 393–398, 1999

268) Venero JL, Vizuete ML, Machado A, Cano J: Aquaporins in the central nervous system. *Prog Neurobiol* 63: 321–336, 2001

269) Nielsen S, Nagelhus EA, Amiry-Moghaddam M, Bourque C, Agre P, Ottersen OP: Specialized membrane domains for water transport in glial cells: high-resolution immunogold cytochemistry of aquaporin-4 in rat brain. *J Neurosci* 17: 171–180, 1997

270) Di Benedetto B, Malik VA, Begum S, Jablonowski L, Gómez-González GB, Neumann ID, Rupprecht R: Fluoxetine requires the endfeet protein aquaporin-4 to enhance plasticity of astrocyte processes. *Front Cell Neurosci* 10: 8, 2016

271) Ibata K, Takimoto S, Morisaku T, Miyawaki A, Yasui M: Analysis of aquaporin-mediated diffusional water permeability by coherent anti-stokes Raman scattering microscopy. *Biophys J* 101: 2277–2283, 2011

272) Igarashi H, Tsujita M, Kwee IL, Nakada T: Water influx into cerebrospinal fluid is primarily controlled by aquaporin-4, not by aquaporin-1: 17O JJVcPe influx into cerebrospinal fluid is primarily controlled by aquaporin-4, not by aquaporin-1: 17O JJVcPe *MRI study in knockout mice. Neuroreport* 25: 39–43, 2014

273) Rash JE, Yasumura T, Hudson CS, Agre P, Nielsen S: Direct immunogold labeling of aquaporin-4 in square arrays of astrocyte and ependymocyte plasma membranes in rat brain and spinal cord. *Proc Natl Acad Sci USA* 95: 11981–11986, 1998

274) Agre P: The aquaporin water channels. *Proc Am Thorac Soc* 3: 5–13, 2006

275) Suzuki Y, Nakamura Y, Yamada K, Huber VJ, Tsujita M, Nakada T: Aquaporin-4 positive emision tomography imaging of the human brain: first report. *J Neuroimaging* 23: 219–223, 2013

276) Benfenati V, Ferroni S: Water transport between CNS compartments: functional and molecular interactions between aquaporins and ion channels. *Neuroscience* 168: 926–940, 2010

277) Guadagno E, Moukhles H: Laminit-induced aggregation of the inwardly rectifying potassium channel, Kir4.1, and the water-permeable channel, AQP4, via a dystroglycan-containing complex in astrocytes. *Glia* 47: 138–149, 2004

278) Verkman AS, Binder DK, Bloch O, Auguste K, Papadopoulos MC: Three distinct roles of aquaporin-4 in brain function revealed by knockout mice. *Biochim Biophys Acta* 1758: 1085–1093, 2006

279) Yukutake Y, Yasui M: Regulation of water permeability through aquaporin-4. *Neuroscience* 168: 885–891, 2010

280) Papadopoulos MC, Verkman AS: Aquaporin water channels in the nervous system. *Nat Rev Neurosci* 14: 265–277, 2013

281) MacAulay N, Zeuthen T: Water transport between CNS compartments: contributions of aquaporins and cotransporters. *Neuroscience* 168: 941–956, 2010

282) Owler BK, Pitham T, Wang D: Aquaporins: relevance to cerebrospinal fluid physiology and therapeutic potential in hydrocephalus. *Cerebrospinal Fluid Res* 7: 15, 2010

283) Oshio K, Binder DK, Liang Y, Bollen A, Feuerstein B, Berger MS, Manley GT: Expression of the aquaporin-1 water channel in human glial tumors. *Neurosurgery* 56: 375–381; discussion 375–381, 2005

284) Oshio K, Binder DK, Bollen A, Verkman AS, Berger MS, Manley GT: Aquaporin-1 expression in human glial tumors suggests a potential novel therapeutic target for tumor-associated edema. *Acta Neurochir Suppl* 86: 499–502, 2003

285) Ma T, Yang B, Gillespie A, Carlson EJ, Epstein CJ, Verkman AS: Generation and phenotype of a transgenic knockout mouse lacking the mercurial-insensitive water channel aquaporin-4. *J Clin Invest* 100: 957–962, 1997

286) Verkman AS: Knock-out models reveal new aquaporin functions. *Handb Exp Pharmacol* 359–381, 2009

287) Badaut J, Fukuda AM, Jullienne A, Petry KG: Aquaporin and brain diseases. *Biochim Biophys Acta* 1840: 1554–1565, 2014

288) Hirt L, Fukuda AM, Ambadipudi K, Rashid F, Binder D, Verkman A, Ashwal S, Obenaus A, Badaut J: Improved long-term outcome after transient cerebral ischemia in aquaporin-4 knockout mice. *J Cereb Blood Flow Metab* 2016 [Epub ahead of print]

289) Igarashi H, Tsujita M, Suzuki Y, Kwee IL, Nakada T: Inhibition of aquaporin-4 significantly increases regional cerebral blood flow. *Neuroreport* 24: 324–328, 2013

290) Li X, Bai R, Zhang J, Wang X: Effect of progesterone intervention on the dynamic changes of AQP-4 in hypoxic-ischaemic brain damage. *Int J Clin Exp Med* 8: 18831–18836, 2015

Neurol Med Chir (Tokyo) 56, July, 2016
Physiology of CSF in the Central Nervous System

291) Nakada T: Virchow-Robin space and aquaporin-4: new insights on an old friend. *Croet Med J* 55: 328–336, 2014

292) Zador Z, Stiver S, Wang V, Manley GT: Role of aquaporin-4 in cerebral edema and stroke. *Handb Exp Pharmacol* 159–170, 2009

293) Patil RV, Xu S, van Hoek AN, Rusinko A, Feng Z, May J, Hellberg M, Sharif NA, Wax MB, Irgoyen M, Carr G, Brittain T, Brown P, Colbert D, Kumari S, Varamakaraj K, Mitra AK: Rapid identification of novel inhibitors of the human aquaporin-1 water channel. *Chem Biol Drug Des* 2015 [Epub ahead of print]

294) Hokari M, Yoskoseki A, Arakawa M, Saji E, Yanagawa K, Yanagimura F, Toyoshima Y, Okamoto K, Ueki S, Hatase T, Ohashi K, Fukuchi T, Akazawa K, Yamada M, Kakita A, Takahashi H, Nishizawa M, Kawachi I: Clinicopathological features in anterior visual pathway in neuromyelitis optica. *Ann Neurol* 2016 [Epub ahead of print]

295) Kim W, Lee JE, Kim SH, Huh SY, Hyun JW, Jeong IH, Park MS, Cho JY, Lee SH, Lee KS, Kim HJ: Cerebral cortex involvement in neuromyelitis optica spectrum disorder. *J Clin Neurol* 2016 [Epub ahead of print]

296) Kariya Y, Kariya Y, Saito T, Nishiyama S, Honda T, Tanaka K, Yoshida M, Fujihara K, Hashimoto Y: Increased cerebrospinal fluid osteopontin levels and its involvement in macrophage infiltration in neuromyelitis optica. *BBA Clin* 3: 126–134, 2015

297) Pandit L: Neuromyelitis optica spectrum disorders: an update. *Ann Indian Acad Neurol* 18: S11–S15, 2015

298) Pereira WL, Roiche EM, Kallaur AP, Kaimen-Maciel DR: Epidemiological, clinical, and immunological characteristics of neuromyelitis optica: a review. *J Neurol Sci* 355: 7–17, 2015

299) Bloch O, Auguste Ki, Manley GT, Verkman AS: Accelerated progression of kaolin-induced hydrocephalus in aquaporin-4-deficient mice. *J Cereb Blood Flow Metab* 26: 1527–1537, 2006

300) Manley GT, Fujimura M, Ma T, Noshita N, Filiz F, Bollen AW, Chan P, Verkman AS: Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. *Nat Med* 6: 159–163, 2000

301) Saadoun S, Tait MJ, Reza A, Davies DC, Bell BA, Verkman AS, Papadopoulos MC: AQP4 gene deletion in mice does not alter blood-brain barrier integrity or brain morphology. *Neuroscience* 161: 764–772, 2009

302) Li X, Kong H, Wu W, Xiao M, Sun X, Hu G: Aquaporin-4 maintains ependymal integrity in adult mice. *Neuroscience* 162: 67–77, 2009

303) Kuriyama N, Yamada K, Sakai K, Tokuda T, Akazawa K, Tomii Y, Tamura A, Kondo M, Watanabe I, Ozaki E, Matsui D, Nakagawa M, Mizuno T, Watanabe Y: Ventricular Temperatures in Idiopathic Normal Pressure Hydrocephalus (iNPH) Measured with DWI-based MR Thermometry. *Magn Reson Med* 14: 305–312, 2015

304) Iliiff JJ, Goldman SA, Nedergaard M: Implications of the discovery of brain lymphatic pathways. *Lancet Neurol* 14: 977–979, 2015

305) Ohno N, Miyati T, Mase M, Osawa T, Kan H, Kasai H, Hara M, Shibamoto Y, Hayashi N, Gabata T, Matsui O: Idiopathic normal-pressure hydrocephalus: temporal changes in ADC during cardiac cycle. *Radiology* 261: 560–565, 2011

306) Mase M, Yamada K, Banno T, Miyachi T, Ohara S, Matsumoto T: Quantitative analysis of CSF flow dynamics using MRI in normal pressure hydrocephalus. *Acta Neurochir Suppl* 71: 350–353, 1998

307) Miyati T, Mase M, Banno T, Kasuga T, Yamada K, Fujita H, Koshida K, Sanada S, Onoguchi M: Frequency analyses of CSF flow on cine MRI in normal pressure hydrocephalus. *Eur Radiol* 13: 1019–1024, 2003

308) Le Bihan D, Moonen CT, van Zijl PC, Pekar J, DesPres D: Measuring random microscopic motion of water in tissues with MR imaging: a cat brain study. *J Comput Assist Tomogr* 15: 19–25, 1991

309) Zelenina M: Regulation of brain aquaporins. *Neurochem Int* 57: 468–498, 2010

310) Sato O: [Reconsideration of research into cerebrospinal fluid], in Arai H, Ishikawa M, Mori E (eds): *iNPH: Idiopathic Normal Pressure Hydrocephalus*. Kyoto, Kinpodo, 2014, pp 8–18 (Japanese)

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