The New Concepts of Cerebrospinal Fluid Physiology

9

Jiawei Wang and Ningli Wang

9.1 The History of Cerebrospinal Fluid

The description of cerebrospinal fluid first appeared in the 17th century BC [1]. An antique dealer named Edwin Smith bought a surgical papyrus which described the watery fluid around the brain. In 1747, Albrecht von Haller, a Swiss anatomist and physiologist, first described the existence of CSF systematically [2]. Subsequently, Cotugno, an Italian anatomist from Naples, observed the presence of water ("liquor cotunnii") around the ventricles and the spinal cord by conducting 20 autopsies [3]. Also, he found that the brain gets smaller in size and the volume of watery fluid around the ventricles and the spinal cord increases with age increase. His notable observations were published in Latin in 1764 in Naples and in English in 1775 in London. The term cerebrospinal fluid in published literature is "le liquid cérébrospinal" in a French document by Magendie in 1842 [4].

9.2 The Classical Concept of CSF Physiology

In 1875, Key published a very famous paper in which he demonstrated the CSF is absorbed by the arachnoid granulation or villi [5]. A long period of time after that, it is widely accepted that the CSF is absorbed by the arachnoid granulation or villi. Key's article has been cited by many classic textbooks. In 1913, Dandy published his extremely famous experiment in JAMA. He blocked the foramen of Monro of dogs, then excised the choroid plexus from the lateral ventricle, and preserved the choroid plexus from the contralateral lateral ventricle. The result of the experiment shows that ventricular dilatation does not occur in the choroid plexus excised side but occurs in the choroid plexus preserved side [6]. This experimental result demonstrated that the CSF is produced by choroid plexus. In 1926, Cushing, the American pioneering brain surgeon, introduced the concept of the "third circulation" which asserts CSF is produced by the choroid plexus and circulates unidirectional from the ventricles to the subarachnoid space to be absorbed by the arachnoid villi [7].

9.3 The New Concept of CSF Physiology

During 100 years, after Dany demonstrated that the choroid plexus is the site of CSF production, many scientists found that the CSF is also produced by structures other than the choroid plexus. Some articles sought out the brain itself as the site of CSF production [8], whereas others claimed CSF production from the cerebral superficial subarachnoid space [9], the perivascular system [10], or the pial artery [11]. Moreover, a study suggested its production by the spinal cord [12], and another has shown the presence of ependymal fluid secretion from the ependyma of the spinal cord central canal [13]. The hypothesis of Oreskovic and Klarica is the mostly accepted now. It asserts that the CSF is formed everywhere and resorbed everywhere in the brain [14]. Also it introduced the term of Virchow-Robin space (VRS), also known as the pericapillary space, in which the CSF was produced and resorbed.

In 1992, Agre discovered that red blood cells contain a membrane protein of high water permeability [15]. This protein, later called aquaporin-1 (AQP-1), turned out to be a member of a large family of water channel proteins that allow bidirectional transport of water across the phospholipid

J. Wang
Department of Neurology and Medical Research Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China

N. Wang (✉)
Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing, China

Beijing Ophthalmology & Visual Sciences Key Laboratory, Beijing, China
e-mail: wningli@vip.163.com

N. Wang (ed.), *Intraocular and Intracranial Pressure Gradient in Glaucoma*,
Advances in Visual Science and Eye Diseases 1, https://doi.org/10.1007/978-981-13-2137-5_9

bilayer of the plasma membrane. In 2014, Nakada demonstrated that it was AQP-4 that regulated water influx into CSF [16]. In this experiment, he chose wild-type AQP-1 knockout and AQP-4 knockout mice. This experiment investigates water flux into CSF in wild-type AQP-1 knockout and AQP-4 knockout mice utilizing ^{17}O-labeled water and JJ vicuna coupling proton exchange (JJVCPE) MRI. This experiment supports the hypothesis that water movement within the Virchow-Robin space is critical for CSF volume. The result clearly demonstrated that water influx into CSF is regulated by AQP-4, known to be responsible for water homeostasis of the pericapillary space [17], and not by AQP-1 found in the choroid plexus. At the same time, this experiment strongly supports the Oreskovic and Klarica hypothesis.

The "third circulation," also known as the bulk flow theory of CSF introduced by Cushing in 1926, was recently replaced by the "cardiac cycle-dependent systolic-diastolic to-and-fro cranio-spinal CSF movements" [18]. This new concepts of CSF movement are based on three main factors. The first one is physiological oscillations of arterial and venous blood during cranio-spinal blood circulation. The second one is respiratory activity, and body activity and posture is the last one. The CSF movement hypothesis is now widely accepted benefits from the advancements in neuroimaging [19].

9.4 The Function of CSF

The CSF is very important for the brain to survive and function. The function of CSF includes five parts [20]:

1. Buoyancy: the CSF can provide partial buoyancy for the brain helping to prevent the brain from being impaired by its own weight. The actual mass of the human brain is about 1400 g. However, the net weight of the brain suspended in the CSF is about 25 g. The brain therefore exists in neutral buoyancy, which allows the brain to maintain its density without being impaired by its own weight, which would cut off blood supply and kill neurons in the lower sections without CSF.
2. Protection: when head hit occurs, the CSF may cushion the brain within the skull.
3. Chemical stability: the CSF exchanges components with interstitial fluid to maintain the chemical stability.
4. Prevention of brain ischemia: the CSF can act as a means to compensate for the changes in blood volume within the skull during the cardiac cycle.
5. Clearing waste: the CSF could take away the waste products from the brain.

9.5 Intracranial Hypertension

The normal intracranial pressure ranges from 5 to 15 mmHg (in the supine position) in adults. The signs of intracranial hypertension involve headache (diffuse and persistent, most severe in the morning), nausea and vomiting (typically in the morning−paroxysmal dry heaves), as well as papilledema. The common cause of intracranial hypertension includes (a) idiopathic intracranial hypertension, (b) intracranial mass lesion, (c) traumatic brain injury, (d) ischemic stroke, (e) nontraumatic intracranial hemorrhage, (f) intracranial infection, (g) hydrocephalus, (h) impaired venous outflow from the brain, (i) hypoxemia/hypercarbia (causes cerebral vasodilation), and (j) drugs and metabolic [21]. The classic radiologic findings of intracranial hypertension include empty sella, downward brain herniation, dilation of the optic nerve sheaths, flattening of the posterior globe, optic nerve head protrusion, and venous stenosis at the distal portion of the transverse sinuses.

9.6 Intracranial Hypotension

Intracranial hypotension refers to the intracranial pressure lower than 60 mmH_2O, and the clinical manifestations involve orthostatic headache, posterior neck pain, nausea, vomiting, photophobia, tinnitus, decreased level of consciousness, and coma. The CSF leakage through a dural defect is the main cause of this. The causes of CSF leakage vary from the secondary causes such as lumbar puncture, cranial or spinal surgery, head or spine trauma to the primary causes like actual or underlying dural defect, and connective disorders (meningeal diverticula, Frank holes, Marfan syndrome, etc.). The classic radiologic findings of intracranial hypotension include pachymeningeal enhancement, venous engorgement, dural thickening, pituitary fossa enlargement, and herniation of the hindbrain.

References

1. Deisenhammer F, Sellebjerg F, Teunissen CE, Tumani H (eds). Cerebrospinal fluid in clinical neurology, 2015; pp 3–6.
2. Matsumae M, Sato O, Hirayama A, et al. 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[J]. Neurol Med Chir. 2016;56(7):416–41.
3. Di Ieva A, Yasargil MG. Liquor cotunnii: the history of cerebrospinal fluid in Domenico Cotugno's work[J]. Neurosurgery. 2008;63(2):352–8.
4. Magendie F. Recherches physiologiques et cliniques sur le liquide céphalo-rachidien ou cérébro-spinal[M]. Méquignon-Marvis fils. 1842.

5. Key A, Retzius G. Studien in der Anatomie des Nervensystemes[J]. Arch Mikrosk Anat. 1873;9(1):308–86.
6. Dandy WE, Blackfan KD. An experimental and clinical study of internal hydrocephalus[J]. J Am Med Assoc. 1913;61(25):2216–7.
7. Cushing H. Studies in intracranial physiology & surgery: the third circulation, the hypophysics, the gliomas [M]. H. Milford, Oxford University Press, 1926.
8. Bering EA. Cerebrospinal fluid production and its relationship to cerebral metabolism and cerebral blood flow[J]. American Journal of Physiology—Legacy Content. 1959;197(4):825–8.
9. Bering EA Jr, Sato O. Hydrocephalus: Changes in Formation and Absorption of Cerebrospinal Fluid Within the Cerebral Ventricles*[J]. J Neurosurg. 1963;20(12):1050–63.
10. Weed LH. Studies on cerebro-spinal fluid. No. IV: the dual source of cerebro-spinal fluid[J]. J Med Res. 1914;31(1):93.
11. Hassin GB. The morphology of the pial blood vessels and its bearing on the formation and absorption of the cerebrospinal fluid[J]. J Neuropathol Exp Neurol. 1948;7(4):432–8.
12. Sato O, Asai T, Amano Y, et al. Formation of cerebrospinal fluid in spinal subarachnoid space[J]. Nature. 1971;233:129–30.
13. Sonnenberg H, Solomon S, Frazier DT. Sodium and chloride movement into the central canal of cat spinal cord[J]. Exp Biol Med. 1967;124(4):1316–20.
14. Orešković D, Klarica M. The formation of cerebrospinal fluid: nearly a hundred years of interpretations and misinterpretations[J]. Brain Res Rev. 2010;64(2):241–62.
15. Preston GM, Agre P. Appearance of water channels in Xenopus oocytes expressing red cell CHIP28 protein[J]. Science. 1992;256(5055):385.
16. Igarashi H, Tsujita M, Kwee IL, et al. Water influx into cerebrospinal fluid is primarily controlled by aquaporin-4, not by aquaporin-1: 17O JJVCPE MRI study in knockout mice[J]. Neuroreport. 2014;25(1):39–43.
17. Brinker T, Stopa E, Morrison J, et al. A new look at cerebrospinal fluid circulation[J]. Fluids and Barriers of the CNS. 2014;11(1):1.
18. Orešković D, Klarica M. A new look at cerebrospinal fluid movement[J]. Fluids and Barriers of the CNS. 2014;11(1):1.
19. Yamada S, Kelly E. Cerebrospinal fluid dynamics and the pathophysiology of hydrocephalus: new concepts[C]. Semin Ultrasound, CT and MRI. WB Saunders. 2016;37(2): 84–91.
20. Hladky SB, Barrand MA. Mechanisms of fluid movement into, through and out of the brain: evaluation of the evidence[J]. Fluids and Barriers of the CNS. 2014;11(1):1.
21. Rangel-Castillo L, Gopinath S, Robertson CS. Management of intracranial hypertension[J]. Neurol Clin. 2008;26(2):521–41.