The history of cerebrospinal fluid: from Classical Antiquity to the late modern period

M. A. Tola Arribas
Department of Neurology. Hospital Universitario Río Hortega, Valladolid, Spain.

ABSTRACT

Introduction. The study of cerebrospinal fluid (CSF) is essential in neurological clinical practice. We review the main historical contributions to the description of the ventricular system and the discovery of CSF in the light of the available evidence.

Development. Although the first accounts of a fluid filling the skull come from ancient Egypt and the classical Greek physicians Hippocrates and Galen, the first detailed study of CSF was conducted by Cotugno in the 18th century. Prior tu Cotugno, Vesalius rejected the classical theory of a gaseous humour and, in the 16th century, described the aqueous humour and the cerebral ventricles, inaugurating the modern era of neuroanatomy. From the Renaissance to the beginning of the late modern period, the anatomical description of the ventricular system was completed and the physiological basis of CSF flow dynamics was introduced. In the 19th century, Quincke was the first to use a needle for lumbar puncture, while Magendie proposed the name "cerebrospinal fluid."

Conclusions. The study of CSF is closely linked to the history of the neuroanatomy of the ventricular system and the meninges. Understanding of the CSF developed in parallel with the main advances in this field.

KEYWORDS

Anatomy, cerebrospinal fluid, history, lumbar puncture, physiology, ventricular system

Introduction

The analysis of cerebrospinal fluid (CSF) is a fundamental part of modern clinical practice. Although the first references to a fluid flowing inside the cranial cavity date from ancient Egypt, classical Greece, and the Roman Empire, the discovery of CSF is considerably more recent. The knowledge of CSF and of its composition, characteristics, and extraction constitutes the pinnacle of the descriptions made by classical and Renaissance neuroanatomists of the anatomy of the ventricular system. We review the main achievements in this field of neuroscience from Antiquity to the present day.

Development

Descriptions of CSF in Antiquity

The first written reference to the existence of a fluid flowing inside the skull dates from ancient Egypt. In 1862, Edwin Smith (1822-1906), an American collector of antiquities, bought a 4.68-long papyrus from a seller in Luxor. The papyrus describes 48 clinical cases, most of which correspond to patients with brain, spinal, and peripheral nervous system injuries. The cases provide data on the clinical examination, diagnosis, prognosis, and treatment of different types of lesions. The origin of the Edwin Smith Surgical Papyrus is uncertain. It is written in hieratic script, which suggests that it dates

Corresponding author: Dr Miguel Ángel Tola Arribas
E-mail: mtola.nrl@gmail.com

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Figure 1. Fragment of the Edwin Smith Papyrus (The New York Academy of Medicine Library). Public domain image

to Dynasties XVI-XVII in ancient Egypt (17th century BC).[1] Certain linguistic anachronisms suggests that the papyrus may be even older; it is believed to be a copy of another text dating from the Old Kingdom, between 3000 and 2500 BC. It has been speculated that the author of the original manuscript was Imhotep, chancellor to the pharaoh Djoser (2700-2650 BC), although other scribes of the time may have participated.

James Henry Breasted published a translation and detailed study of the papyrus in 1930.[2] As is the case with the Ebers Papyrus, the Edwin Smith Papyrus suffered a series of historical vicissitudes. After a brief period at the New-York Historical Society, to which it was donated by Edwin Smith's daughter, the papyrus is now held at the New York Academy of Medicine (Figure 1).

Case 6 addresses the "instructions concerning a gaping wound in his head, penetrating to the bone, smashing his skull, [and] rending open the brain of his skull." It also describes "the membrane enveloping his brain, so that it breaks open his fluid in the interior of his head." As in every case of the papyrus, a prognosis is established: "An ailment not to be treated" (Figure 2).[2]

No further references to the CSF or the ventricular system are found until classical Greece. Despite it being forbidden to dissect human corpses, Hippocrates of Kos (460-375 BC) confirmed the presence of a fluid inside the cavities of the brain and was the first to recognise and attempt to treat hydrocephalus, which he considered to constitute an accumulation of extra-axial fluid, rather than an increase in ventricle size. The *Hippocratic corpus*, dating from the 5th century BC, makes reference to the meninges, stating that one is thick whereas the other is thin, and explains that the brain is divided in two halves separated by a membrane. It also describes *nẖ*, "fluid" is evidently the same as *nẖ* (Pyr. 1965 a) and (Pyr. 686b). The determinative of the latter example is the human mouth spitting or drooling. Very important in this connection is the form "water" (Pyr. 25c). Compare also the noun (Pyr. 1965 a). Elsewhere this word occurs five times in our papyrus (XIII 19; XIV 15, where *m* is an error for *w*; XIV 16; XVII 9; X 20), written with *š* instead of *ẖ*, the interchange so often observable in the Pyramid Texts, and another evidence of the great age of our treatise. It is explained in a gloss (XIV 15–16; consult commentary) as meaning to "issue, stream forth, flow out." As a noun it means "exudation," "fluid," and the like. The noun is found designating some fluid secretion (in *Mutter und Kind*, 1, 2: 3, 1 *et passim*) which is adjured to "run out" (1, 2–3 or 3, 4). Cf. Oefele, *Zeitschrift*, 39 (1901), pp. 149 ff. The reference in our passage is possibly to the soft or viscous consistency of the brain itself. Dr. Luckhardt remarks that this description "most certainly refers to the cerebrospinal fluid by which the brain is surrounded." "his head" is abbreviated to the determinative. It is impossible to determine whether the surgeon means "head" (*tp* or *ḏ'ḏ'*) or "skull" (*ḏnn·t*).

Figure 2. Breasted's 1930 translation and comments on case 6 of the Edwin Smith Papyrus. Public domain text

the pathological process by which the brain "attract[s] water from elsewhere inside the body." In any case, the main achievement of Hippocrates and his school was the separation of illness from religion and ethics.[3]

Aristotle (384-322 BC) identified the heart as the organ of intelligence. According to the author, the brain was in charge of "tempering the heat and seething of the heart." His works contain several erroneous neuroanatomical concepts. In *History of animals*, however, he mentions the membranes enveloping the brain and ventricles that may be seen in nearly all animals.[4]

Herophilus of Chalcedon (335-280 BC), a Greek physician of the school of Alexandria, is considered by medical historians to be the first anatomist. Herophilus was deeply interested in neuroanatomy; in violation of the law, he performed numerous public dissections of human corpses and even vivisections of criminals sentenced to death. He described the distribution of brain blood vessels and, particularly, the confluence of sinuses, known since then as the torcular Herophili. He also described the fourth ventricle and the meninges, and was the first to mention the choroid plexus. As a member of the school of Hippocrates, Herophilus regarded the brain as the seat of thought and soul.[1,3] Most of his works have been lost.

Several centuries later, Galen of Pergamon (130-200 AC) was without a doubt the most influential physician in the Roman Empire. Galen began his studies in Pergamon (modern Turkey), where he was born, and completed them in Alexandria, where he had the opportunity to read Herophilus' works. His extensive work was partly destroyed in a fire in the Temple of Peace during one of his long stays in Rome, where he was physician to the Emperor. He was considered a scientific authority and his works were acknowledged until the 16th century. He developed the theory of the three forms of *pneuma* (or spirit): the *pneuma physicon* (natural spirit), seated in the liver, *pneuma zoticon* (or vital spirit), located in the chest, and *pneuma psychicon* (animal spirit), inherent to the brain and responsible for the rational soul.[5] This theory was accepted for over a thousand years due to its compatibility with the Christian doctrine of the Trinity. Human dissection was forbidden in Alexandria; therefore, Galen first described the ventricular system in animals, which explains many of his errors in the field. Galen described two covers, one hard and thick and the other soft, with the latter penetrating the ventricular cavities, forming the choroid plexuses. He also described two extensions to these "covers", referring to the falx cerebri and the tentorium cerebelli. Regarding the function of the ventricles, Galen believed that the lateral ventricles were responsible for imagination, the third ventricle for cognition, and the fourth ventricle for memory.[3] Galen described a "gaseous humour" in the ventricular system that "provides energy to the whole body."[6,7]

Knowledge of the ventricular system and the meninges: the role of neuroanatomists

No significant advances were made in the anatomical or physiological description of the CSF or the ventricular system during the Middle Ages. The Renaissance, however, saw the reintroduction of human dissection as a method of study and research, ushering in a new era for anatomical study.

Leonardo da Vinci (1452-1519) was a precursor to this movement. His numerous works reflect a genuine interest in human anatomy. Da Vinci planned to write a treatise on anatomy, although none of his observations came to light until the late 19th century. In an example of his outstanding creativity, he produced wax casts of the ventricular system, which he used as models for his drawings of the human brain. He would inject melted wax into the ventricular system through the fourth ventricle, then remove the brain tissue when it hardened to expose the three-dimensional model of the ventricular system.[8] An examination of the rete mirabile in these casts indicates that they were created using the brain of an ox rather than a human brain.

The first detailed anatomical description of the ventricles was made by Andreas Vesalius (1514-1564), author of *De humani corporis fabrica*, one of the most influential works on human anatomy. Book 7 of the collection is dedicated to the central nervous system and the sensory organs.[9] In 1543, Vesalius noted that the ventricles were filled with an aqueous fluid rather than with a gaseous humour, which led to the decline of Galen's theory of the three forms of *pneuma*. Several years later, Constanzo Varolio (1543-1575), a physician from Vesalius' school of anatomy in Padua and Bologna, confirmed Vesalius' findings, paving the way for a paradigm shift from a philosophical approach to more precise description of human anatomy.[10] The "spirits" were history.

Since Galen, the descriptions of the brain's "membranes" focused on the pia mater and the dura mater. The first description of the arachnoid mater is attributed to the Dutch anatomist Gerard Blasius (1627-1682).[11]

Some years later, the neuroanatomists Raymond Vieussens (1635-1715) and Frederik Ruysch (1638-1731) completed Blasius' work.[12,13] In 1705, Antonio Pacchioni (1665-1726) published a treatise where he described the arachnoid granulations now known by the eponym "Pacchionian granulations."[14]

Although Vesalius identified a physical connection between the lateral ventricles and the third ventricle, the first author to provide a detailed description of the interventricular foramina was Alexander Monro, secundus (1733-1817), a Scottish surgeon and anatomist from the University of Edinburgh.[15] These foramina are now known by the eponym "foramina of Monro." The French anatomist Félix Vicq d'Azyr (1748-1794) had previously described the interventricular foramina, although his observations came to light some time later.[16]

Franciscus Sylvius (1614-1672), also known as Franz de le Boë, was a German physician who developed his theories in the Netherlands. He gave a precise description of the aqueduct of Sylvius, which connects the third and fourth ventricles. Franciscus Sylvius also made a detailed analysis of the Sylvian fissure, the main lateral fissure of the brain. Jacques Dubois, frequently known as Jacobus Sylvius (1478-1555) was a French anatomist and a teacher to Vesalius who described an erroneous connection between the midbrain and the cerebellar vermis a century before Franciscus Sylvius did. His work was completely overshadowed by that of Vesalius, one of his students.[17] The "puzzle" of the anatomy of the ventricular system was completed by François Magendie (1783-1855) in Paris and Hubert von Luschka (1820-1875) in Tübingen; these authors described the median and lateral apertures of the fourth ventricle.[18,19]

The study of cerebrospinal fluid

The 17th and 18th centuries saw considerable advances in understanding of CSF.[20] The Italian anatomist Antonio Maria Valsalva (1666-1723) described CSF as "an ounce of a certain liquid in cutting the cord membrane of a dog, a fluid resembling that seen in articulations." In 1664, Thomas Willis (1621-1675), an English physician and professor at the University of Oxford, stated that the fluids of the brain flowed through the pituitary gland, the mammillary bodies, and the cribriform plate, toward the general circulation. Some time later, Richard Lower (1631-1691), a student of Willis', suggested that CSF may enter the venous system directly, with excess CSF draining to the base of the skull and the spinal canal, causing hydrocephalus. Albrecht von Haller (1708-1777) was a Swiss physician and physiologist who in 1757 described CSF as "viscid fluids, coagulable by a heat of about 150 degrees, by alcohol and by strong acids."[3]

Domenico Felice Antonio Cotugno (1736-1822) was no doubt the most prominent figure in the study of CSF of the time. Born in Ruvo di Puglia, in southern Italy, Cotugno was a physician, surgeon, and anatomist and held the Chair of Anatomy in Naples (Figure 3). In 1764, he extracted CSF from the corpses of 20 adult men. Cotugno concluded that the ancient anatomists had failed to find this fluid because they beheaded the corpses before studying them: "by this irrational method of dissecting, all the fluid collecting around the marrow and brain [are] lost, air enters in, and supplies its place." Cotugno also estimated total CSF volume, described its watery appearance, and proposed that the CSF flowed through the ventricular system. He was severely criticised, as many of his observations came from experiments performed with turtles and dogs.[21] Cotugno's greatest mistake was his decision to publish these findings as part of his well-known treatise on sciatica, *De ischiade nervosa commentarius*,[22] which probably led to his observations not receiving the appreciation they merited. In recognition of his work, CSF was known for a long time as *liquor cotunnii*.[23]

We should also mention the contributions made by Emanuel Swedenborg (1688-1772), the well-known Swedish theologist, philosopher, and scientist, and Bishop of Skara. Swedenborg received no medical or anatomical training; he graduated as a mining engineer at Uppsala University. His descriptions of CSF, very similar to those made by Cotugno, were published in a piece of work written between 1741 and 1744 and published in 1887, over a hundred years after his death. As Swedenborg was not a physician, no editor was willing to publish his findings.[24]

Figure 3. A) Domenico Cotugno. B) Heinrich Quincke

François Magendie, a French physician, anatomist, and physiologist, began systematically studying CSF in 1825. He concluded that CSF was a normal component of the brain and performed the first cisterna magna punctures in animals. Magendie coined the terms "liquide céphalo-rachidien" and "liquide cérébro-spinal" (Figure 4).[25] As mentioned previously, Magendie confirmed the existence of a foramen communicating the fourth ventricle with the subarachnoid space, and the continuity of the subarachnoid space around the brain and spinal cord.

Advances in the understanding of cerebrospinal fluid physiology

The first studies into the physiology of the CSF came to light in 1783. Alexander Monro, secundus published his observations on the structure and functioning of the nervous system. Given that the skull is a rigid compartment and the brain is "nearly incompressible", Monro concluded that the amount of blood inside the skull should remain stable in normal and pathological conditions.[15] His theory was confirmed in 1824 when George Kellie (1770-1829), a Scottish physician, observed that the brains of animals dying of exsanguination still

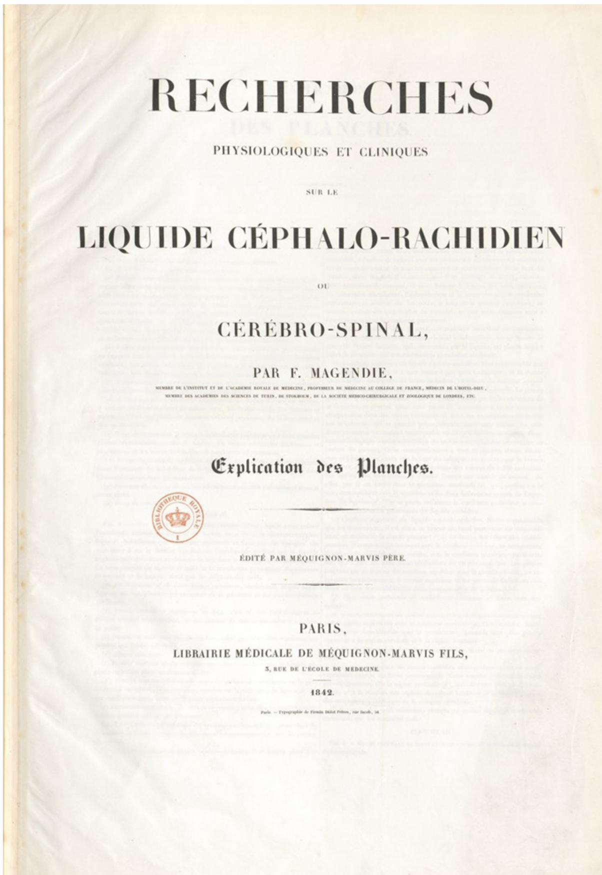
RECHERCHES
PHYSIOLOGIQUES ET CLINIQUES
SUR LE
LIQUIDE CÉPHALO-RACHIDIEN
OU
CÉRÉBRO-SPINAL,
PAR F. MAGENDIE,
Explication des Planches.
ÉDITÉ PAR MÉQUIGNON-MARVIS PÈRE.
PARIS,
LIBRAIRIE MÉDICALE DE MÉQUIGNON-MARVIS FILS,
3, RUE DE L'ÉCOLE DE MÉDECINE.
1842.

Figure 4. Cover of Magendie's treatise on CSF, wherein he coins the term "cerebrospinal fluid". Public domain image

contained blood except in those cases where the integrity of the skull was compromised before death.[26] These observations laid the foundations for the initial Monro-Kellie hypothesis, which postulated that the cranium behaves as a rigid compartment with a fixed interior volume. The English physician George Burrows (1801-1887) introduced some changes to this hypothesis in his 1846 book *On the disorders of the cerebral circulation*, postulating that cerebral blood volume may vary but only to the benefit or the detriment of brain and CSF volumes.[27]

The definitive contribution to this field was made by Swedish anatomists Axel Key (1832-1901) and Gustav Magnus Retzius (1842-1919), from the Karolinska Institute. These authors described in detail the membranes and cavities of the brain and spinal cord, confirmed the presence of the foramina of Luschka and Magendie, and in their famous experiments with dyes demonstrated that CSF passed from the subarachnoid space to the venous sinuses through the pacchionian granulations.[28]

The introduction of the lumbar puncture

James Leonard Corning (1855-1923), an American physician known for his experiments with nerve blockade, was the first to perform lumbar punctures on living human patients.[29] According to some authors, Corning aimed to inject cocaine into the lumbar intervertebral spaces as an analgesic treatment; they question whether the needle reached the subarachnoid space, although some of his patients may have experienced headache due to CSF hypotension.[30]

Lumbar puncture was first used for clinical purposes by the English physician Walter Essex Wynter (1860-1945), the son of the mid-19th century editor of the *British Medical Journal*. Wynter made an incision and then inserted a thin tube into the spinal canal. He published his observations in *The Lancet* under the title "Four cases of tubercular meningitis in which paracentesis of the theca vertebralis was performed for the relief of fluid pressure" in 1891[31,32]; all four patients died.

That same year, the German internist and physiologist Heinrich Irenaeus Quincke (1842-1922) (Figure 3) performed a lumbar puncture using a needle, similarly to the way it is performed today. Quincke was the first to analyse the composition of CSF and measure its pressure with a manometer. He observed that CSF glucose levels were lower in patients with bacterial meningitis.[33] Most medical historians regard Quincke as the father of the lumbar puncture, while others state that this recognition should be shared with Wynter.[32] The scientific community paid little attention to Quincke's presentation of his technique in Wiesbaden in 1891. Some time later, the German neurologist Hans Heinrich Georg Queckenstedt (1876-1918) studied CSF dynamics and discovered fluctuations in CSF pressure during breathing, the Valsalva manoeuvre, and jugular compression.[34] The American military neurosurgeon Byron Stookey (1887-1966) subsequently confirmed Queckenstedt's observations after World War I.

The relevance of lumbar puncture was demonstrated by Paul Fürbringer (1849-1930) in 1895. The German

Table 1. Milestones in the discovery of cerebrospinal fluid and the ventricular system

Year/period	Author(s)	Historical milestones	References
3000-2500 BC	Ancient Egypt (Imhotep?)	First description of CSF in the Edwin Smith Papyrus	1-3
450-280 BC	Hipócrates and Herófilo	First descriptions of the ventricular system. Confirmation of the presence of a fluid inside the skull.	1, 3
130-200	Galeno	Description of the gaseous humour and the pneuma psychicon.	5, 6
1540-1575	Vesalio and Varolio	Completed description of the ventricular system and first description of the dura mater.	9, 10
1650-1725	Blasius, Vieussens, Ruysch, Pacchioni	Description the arachnoid and the arachnoid granulations.	11-14
1733-1875	Monro, Sylvius, Magendie, von Luschka	Description of the interventricular foramina and the median and lateral apertures of the fourth ventricle.	15-19
1764	Cotugno	First detailed analysis of CSF (liquor cotunnii): appearance, volume, and circulation within the ventricular system	21-24
1750-1887	Monro, Kellie, Burrows	First hypotheses on the physiology of CSF and its role in regulating intracranial pressure	15, 26, 27
1842	Magendie	First mention of the term "cerebrospinal fluid" (liquide céphalo-rachidien/cérébro-spinal).	25
1885-1891	Corning, Wynter	First interspinal punctures for therapeutic purposes	29-32
1876	Key, Retzius	Completed understanding of CSF physiology, its circulation in the ventricular system, and its absorption by the arachnoid granulations.	28
1891	Quincke	First lumbar puncture performed with a needle	32, 33
1912	Mestrezat	First monograph on lumbar puncture and CSF composition in different diseases	37

physician described his findings in 85 patients, underscoring the importance of measuring CSF pressure, evaluating the implications of the presence of blood in CSF, and identifying the tubercle bacillus in patients with meningitis.[35,36]

Quantitative studies

The 20th century saw the advent of CSF quantitative analysis; the countless advances this entails are beyond the scope of the present historical review. We should, however, mention William Mestrezat (1883-1928), the author of the first monograph on lumbar puncture and the chemical components of CSF in different diseases: *Le liquide céphalo-rachidien normal et pathologique*.[37] In 1937, Houston Merritt (1902-1979) and Frank Fremont-Smith (1895-1974) published their experience of 20 years at the laboratory of Boston City Hospital and Harvard Medical School, including numerous clinical features of CSF that are still largely valid today.[38]

Many researchers have subsequently made relevant contributions to the understanding of CSF's role in numerous neurological diseases. We should highlight Lange's studies on the colloidal gold reaction in patients with neurosyphilis[39]; the studies by Kabat, Frick, and Scheid-Seydel on immunoglobulins in the CSF[40,41]; and those by Lowenthal, Karcher, and Laterre on oligoclonal bands in multiple sclerosis.[41-44] Tibbling, Link, Tourtellotte, and Reiber are also well known for their formulas estimating serum and CSF protein levels.[45-48] Most of these findings continue to be valid for clinical practice.

Conclusions

Our understanding of CSF has advanced in line with developments in the field of neuroanatomy. Although CSF was described as early as ancient Egyptian times, and in classical texts by Hippocrates and Galen, the widespread practice of decapitating corpses before dissecting them probably prevented physicians from describing CSF until much later. Vesalius and other 16th- and 17th-century neuroanatomists completed our knowledge of the ventricular system. However, it was not until the 18th century that Cotugno made the first detailed descriptions of CSF. In the 19th century, Quincke introduced the technique of lumbar puncture with a needle, and Magendie coined the name of the fluid. Many 20th-century researchers contributed to the study of the composition, physiology, and diagnostic value of CSF in different neurological diseases.

Conflicts of interest

The author has no conflicts of interest to declare. This study has not been presented at any meeting or conference.

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