Cerebrospinal Fluid in Clinical Neurology

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We dedicate this book to our mentors, co-workers, and those interested in cerebrospinal fluid.

Foreword

It is a pleasure to see that CSF analysis continues to march ahead. Professor Florian Deisenhammer is to be congratulated for assembling a strong team, with diverse expertise, to give us a coherent picture of the current state of the art. His spectrum of people extends all the way from the bedside to the bench. They each give an in-depth analysis as well as useful tips about how to get the most information from this important liquid-biopsy of brain fluid.

From the bedside, among other experts, we have Prof. Kaj Blennow who has been a pioneer of CSF analysis in dementia whose work has withstood the test of time and continues to be fundamental for further progress on this ever increasing disease, as we all live longer. There is also useful information from several experts on less common diseases involved in molecular mimicry, or auto-immune syndromes, where again it is found that CSF can provide more useful information rather than only blood tests for the same antibodies, by using the ratio of specific antibody titers which can be normalized to the total antibody ratio. In addition to the traditional acute inflammatory diseases, there are also detailed chapters on chronic noninfectious inflammatory CNS diseases as well as chronic inflammatory diseases of the PNS. On a personal note, I am pleased to see my trusted colleague of many years, Geoff Keir, is still carrying on the basic work for CSF leakage syndromes.

From the bench, the very important pre-analytical role of CSF analysis is given a detailed account which should be heeded by all who are responsible for triage of CSF, since they can have a profound effect on the final results, depending on how samples are to be correctly handled. In addition, the crucial role for the technique of lumbar puncture is addressed.

Although much has been written about diagnostic criteria (not least in MS), nevertheless in terms of basic pathophysiology, CSF offers much more direct evidence than a number of other investigations for the role of immunology in the disease processes under differential consideration. One day we may even understand the exact molecular mechanisms.

This book is to be read by both practicing clinicians as well as those who are entrusted with the most careful analysis of such precious fluid with future promise.

London, UK

Emeritus Prof. Edward J. Thompson,
DSc, MD, PhD, FRCPath, FRCP

Preface

The analysis of cerebrospinal fluid (CSF) is an invaluable diagnostic aid in clinical neurology and can be obtained with relative ease by lumbar puncture. CSF analysis is amenable to various technologies applied in haematology, cytochemistry, clinical chemistry, microbiology and virology. There are not many constituents that are measured during routine diagnostic work-up, nevertheless the combination of these variables gives a wide range of patterns that are often typical for certain neurological diseases. Therefore, it takes a profound knowledge of the particularities of the CSF for analyses and also for reporting. The relative paucity of constituents in the CSF and their low concentration pose a certain methodological challenge; on the other hand it has the advantage of low background activity which makes it better accessible for exploration of new biomarkers. This development has led to discovery of a variety of diagnostic markers expanding the use of CSF in everyday clinical decision making.

In this book we try to give an up-to-date overview as to how the CSF can be applied in clinical neurology. The intention was to create a book of reference for which we invited numerous experts in the field to contribute. The chapters not only focus on technical aspects of CSF analyses but discuss CSF findings in a broader clinical context too.

We do hope you will enjoy reading and find the book helpful not only in your clinical work but also in increasing your knowledge in a wide range of CSF-related topics.

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Acknowledgment by Florian Deisenhammer

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The History of Cerebrospinal Fluid

1

Florian Deisenhammer

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Abstract

There is a long history of the CSF and its anatomical spaces dating back to ancient Egypt when it occurred first in human literature between 3000 and 2500 BC. The development of knowledge of this fluid goes hand in hand with the history of neuroanatomy. Many famous names in medical history turn up in context with the history of CSF such as Hippocrates, Galen of Pergamon, Leonardo da Vinci and François Magendie. Most authors feel that the first full account of the CSF was given by Domenico Cotugno in 1764, and for some time the fluid was referred to as "liquor cotugnii". There is also wide consensus that Heinrich

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Quincke performed the first diagnostic lumbar puncture in 1891 which paved the way for modern CSF diagnostic procedures.

This chapter provides milestones of the history of CSF, the associated neuroanatomy and the diagnostic use.

1.1 Introduction

The history of cerebrospinal fluid (CSF) is not restricted to the fluid itself but must be seen in context with the history of neuroanatomy, neurophysiology and neuropathology. Although a fluid within the skull and vertebral column has been described dating back as early as 2500 BC, the CSF as such has not been discovered before the sixteenth century. Several thoughts on the origin and function have been brought forward, e.g. the CSF replaced or corresponds the ocean as it surrounded all creatures in prehistoric times (Schaltenbrand 1953). For a long time, it was thought that the ventricles contain spirits rather than a fluidic substance, and after the discovery of the fluid, it took roughly two centuries to accept the CSF as a normal constituent in the eighteenth century.

1.2 The Edwin Smith Surgical Papyrus

In 1862 an antique dealer named Edwin Smith bought a papyrus scroll from a local dealer in Luxor, Egypt. This scroll is almost 5 m long and it turned out that it contains one of the most fascinating medical texts from ancient Egypt. It is the oldest known manuscript on traumatic injuries, mostly in the field of neurotrauma. The very scientific approach, omitting magic and spells, makes it outstanding compared to other documents from this age. It dates back to 1500 BC, the time of dynasties 16–17 in ancient Egypt, and it is believed to be a copy of a text written during the period of the old kingdom between 3000 and 2500 BC. Some authors speculated that the author of the original manuscript was Imhotep (Breasted 1930).

The Edwin Smith Papyrus is composed of 48 case reports describing various traumas beginning with the head followed by spinal cord and peripheral nerve injuries. Each case is neatly structured into examination, diagnosis, prognosis and treatment, followed by a gloss, which has been added as an explanation of the original text using terms that were unfamiliar at the time when the Smith Papyrus was written. The document is now displayed at the New York Academy of Medicine (Fig. 1.1).

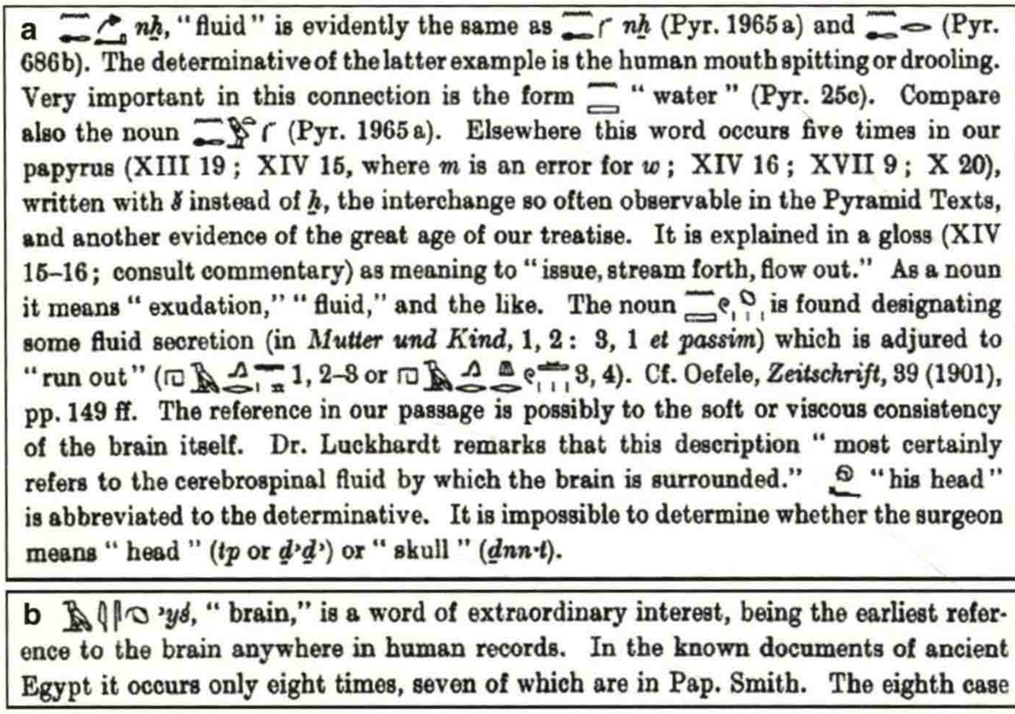
Case number six is of utmost interest with respect to CSF. The patient had "a gaping wound in the head with compound comminuted fracture of the skull and rupture of the meningeal membrane" (Breasted 1930). In this case the meninges were described, but moreover, the word brain (marrow of the skull) occurs the first time in any kind of literature. Apart from the anatomical details, the fluid surrounding the brain, by which the author most likely refers to the cerebrospinal fluid, is

Fig. 1.1 *Bottom* of the second column of the Edwin Smith Papyrus. The hieroglyphs in *blue circles* refer to watery fluid in context with the surface of the brain (Courtesy of The New York Academy of Medicine Library)

also described in this case of brain injury. A number of authors therefore refer to the Smith Papyrus as the first occurrence of the CSF in the medical literature (Clarke and O'Malley 1996; Wilkins 1964) (Fig. 1.2a, b).

1.3 The Greek Physicians and Philosophers

After a long period of lack of documents regarding CSF, it was not before the times of the famous philosophers when further milestones in CSF discovery were achieved by physicians and scientists of ancient Greece (Woollam 1957).


a *nḫ*, "fluid" is evidently the same as *nḫ* (Pyr. 1965 a) and (Pyr. 686 b). 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 *ḫ*, 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*).

b *'yś*, " brain," is a word of extraordinary interest, being the earliest reference to the brain anywhere in human records. In the known documents of ancient Egypt it occurs only eight times, seven of which are in Pap. Smith. The eighth case

Fig. 1.2 (**a**) Self-explaining text from page 172 in Breasted's translation of the Edwin Smith Papyrus (Breasted 1930). (**b**) Text from page 166 in Breasted's translation of the Edwin Smith Papyrus (case six), mentioning the word brain for the first time in medical literature (Breasted 1930) (Public domain)

With Hippocrates CSF-related topics reappeared in the literature. The Corpus Hippocraticum dating back to the fifth century BC, a work of many different authors, describes the brain as an organ attracting water from the rest of the body as a pathological process.

In contrast to Hippocrates, Aristotle thought that the heart was the centre of intelligence and the task of the brain was to alleviate the temperature that came from the heart (Clarke and O'Malley 1996). In *Historia Animalium* he wrote of the membranes around the brain as well as the ventricles which can be found in the "great majority of animals" (Thompson 1910).

Herophilus was specifically interested in the anatomy of the nervous system. As a member of the Hippocratic School, he found the brain to be the centre of thoughts and soul, and the latter he placed to the ventricles. He described the fourth ventricle, the most important one to his mind, as well as the meninges, and his name is still associated with the confluence of sinuses, the torcula Herophili. Also, the choroid plexus appears in his scripts for the first time.

Of note however, there is no direct mentioning of the CSF itself in the ancient Greek literature.

1.4 Claudius Galenus (Galen of Pergamon)

Galen (AD 129–216), a physician and philosopher, was an extremely influential figure in that his work was standard knowledge until the sixteenth century when postmedieval medicine developed and got generally accepted.

Galen developed the famous pneuma (spirits) theory. There were three pneumas, the pneuma zoticon (vital spirit), pneuma physicon (natural spirit) and pneuma psychicon (animal spirit).

The pneuma in general enters the body via respiration into the lungs and through the pulmonary veins as well as the portal veins and reaches the blood where it mingles with the pneuma physicon of the body. The exchange between left and right ventricle of the heart transforms it to the pneuma zoticon, and finally it becomes the pneuma psychicon in the rete mirabile – a vascular network of tiny arteries – at the base of the brain. From there on it enters the anterior horns of the cerebral ventricles and spreads to the rest of the ventricular system. The interesting part is that the pneuma moves along the nerves and by that it operates the muscles (Woollam 1957). The rete mirabile tells us that the anatomical studies were done in oxen, because it does not occur in the human cerebral circulation. Dissection of human bodies was an absolute no-go at that time and in fact for a very long period thereafter. This and the compatibility with Christian trinity were reasons why the pneuma theory held up for more than a millennium.

Before the time of a more fact-based approach, the cerebral ventricles were given various functions; mostly the lateral ventricles were assigned to imagination, the third ventricle to cognition and the fourth ventricle to memory (Sudhoff 1914).

Apart from the flow of pneumas, Galen was ascribed to have discovered a "vaporous humor in the ventricles that provided energy to the entire body" (Conly and Ronald 1983), and also Torack referred to Galen discovering the CSF (Torack 1982). Moreover, he thought that the CSF was produced in the choroid plexus of lateral ventricles and from there passed on to the third and fourth ventricles, an idea that was picked up again only much later in history. Apart from a fluidlike substance in the ventricles, he suggested a fluid between the pia and dura mater. The arachnoid was not mentioned in his books.

This status of knowledge held up through the dark medieval times and was only further developed by the next generation of researchers during the renaissance.

1.5 Leonardo Da Vinci, Andreas Vesalius, Costanzo Varolio (Varolius) and Colleagues

Further advance in the discovery of ventricular and CSF functions started in the renaissance when dissection – particularly human dissection – was reintroduced in medical science. This allowed a more fact-based approach to medical research and started a new epoch in science in general. One milestone was a wax cast of the ventricular system by da Vinci which came, however, probably from an ox's brain as there were signs of the rete mirabile. Da Vinci used these casts for anatomical drawings of the human brain. His findings came to public knowledge only in the nineteenth century (Clark 1935). The first sketches of the ventricles showed a very vague picture of their topographical order which improved clearly after the wax casts were constructed (Fig. 1.3).

Andreas Vesalius became professor of surgery and anatomy in Padova and later taught at Bologna where he performed public dissections at the specifically designed anatomy theatre. He was strongly opposed to Galen's work and put much effort in rewriting human anatomy which ended in his most famous book *De humani corporis fabrica libri septem* (Vesalius 1543). Vesalius initiated a paradigm shift from philosophical approaches to anatomy towards fact-based description of the human body. In order to achieve this goal, he relied on dissection and apparently had access to skilled draughtspersons which led to an unprecedented accurate illustration not only of the ventricles but also of the whole central nervous system. He failed, however, to describe the inter-ventricular foramina explicitly but at least gave credit to a "watery humour" which often was found to fill the ventricles. In his illustration the arachnoid granulations as well as the choroid plexus were depicted in great detail (Singer 1952). Varolius, like Vesalius teaching at the University of Padova, further developed the idea of fluid filling the ventricles rather than spirits, and since then, the pneuma theory was finally left for good (Varolius 1573).

An anatomical fact that was not well covered by the above-mentioned anatomists is the existence of the arachnoid as an important border of the CSF space. The name of the membrane was created by Gerardus Blasius one century later (Blaes 1666). Raymond Vieussens and Frederik Ruysch completed the knowledge by describing its entirety shortly thereafter (Ruysch 1737; Vieussens 1685). Around that time, Antonio Pacchioni precisely described the arachnoid granulations, and he still stands for these structures eponymously (Pacchionus 1705).

1.6 The Next Generation of Neuroanatomists: Monro, Sylvius, Von Luschka and Magendie

It was now time to discover the relationship between the ventricles and the CSF itself. Interestingly, it was Galen who found a physical communication between the lateral and third ventricle which got forgotten for a long time. The first to describe the inter-ventricular foramen in a distinct and accurate way was Alexander Monro secundus, and he also made it clear that there were no other routes of communication between both laterals as well as between the lateral and third ventricles (Monro 1783). Since then these structures are eponymously known as foramina Monro. Monro was a Scottish anatomist at the University of Edinburgh where he succeeded his father Alexander Monro primus. There were of course others who hinted to or gave partial descriptions before mainly referring to the openings, sometimes as anus or vulva (Casserio 1627; Marchetti 1665). A similar precise account of the foramina was provided by Vicq d'Azyr previous to Monro but not published before 1805.