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History of the Concept of Tuberculous Meningitis

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History of neurology · History of tuberculous meningitis · Scottish School of Medicine · Robert Whytt · Philippe Pinel · Jean-Etienne Esquirol · Gaspard Itard · Jean-Louis Brachet

Abstract
More than a century separates the description of *"dropsy of the ventricles of the brain"* by Scottish physicians and Robert Koch's identification of the causal agent of tuberculous meningitis in 1882. This article reviews the writings in Scotland and France that marked the history of the identification of this infectious entity. From John Paisley in 1734 to Robert Whytt in 1738, from Marcellin Chardel in 1799 and L.P. Collinet in 1802 to Isidore Bricheteau in 1814 and Jean-Louis Brachet in 1818, and then Victor Le Diberder in 1837 and Isidore Valleix in 1838, unknown and forgotten physicians outnumber the famous masters in bringing about the progress and knowledge that enabled this frequent and consistently fatal disease in the 19th century to be accurately diagnosed and in most cases cured in the 20th century.

Introduction

Nervous system infections have always existed. Egyptian mummies appear to carry scars of these diseases. Aristotle and Hippocrates described them, referring to a fever associated with headaches and altered states of consciousness [1]. Closer to our times, Thomas Willis (1621–1675), famous for his work on nervous system anatomy, left us with observations that were published 10 years after his death. They described incurable headaches that *"followed abscesses and swellings of the envelopes of the brain, as well as plaques and tubercles of theses membranes."* Death ensued after a state of febrile lethargy. During the autopsies, he noted meningeal inflammation compressing the brain, dilated ventricles, and tuberculomas [2].

A few French authors left observations, but they tended to be approximative and group different conditions together. Hydrocephalus with malformations, recognized at birth from an increased head circumference, was considered together with observations of dilated cerebral ventricles in normal, healthy children before their fatal disease. Examples include the publications of Joseph-Guichard Duverney (1648–1730) in 1704 [3] and those of Jean-Louis Petit (1674–1750) in 1718 [4]. This article relates the progressive knowledge that made it possible to set up the clinical picture of tuberculous meningitis at the end of the 19th century.

The Scottish School Provides the First Descriptions

The first real exhaustive clinical descriptions were the work of the Scottish physicians Andrew Saint-Clair, also spelled Sinclair (?-1728), published after his death in 1737 [5] and John Paisley (?-1740), surgeon in Glasgow [6].

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Regarding a 7-year-old child, Paisley wrote, *"One morning with pain in the left side of his head, attended with unusual drowsiness and lassitude; his pulse not very quick, short cough, an inclination to vomit* […]. *On the eleventh his pulse was exceeding slow and intermitting, his coma so much increased with startings that he could take no kind of aliment and appeared to have no manner of sense; and thus he continued perfectly insensible till next afternoon when he died."* After opening the skull, he noted *"an obstruction in the glands of the dura mater following some inflammation* […]. *In dissecting the brain, I found the ventricles had been much distended and enlarged by the water; the plexus choroeides were hard and scirrhous with a great number of small hydatide (as I supposed) lying along the rows, whose coats were exceeding tender and burst upon the least touch. They remember the lymphaticks delineated in the fifth of Dr Rudley's anatomy of the brain.*"

Robert Whytt (1714–1766), also working in Edinburgh but more well known, analyzed 20 cases in his book, which became a classic: *On the dropsy of the Brain* (1768) [7]. Whytt described the clinical progression of the disease in 3 successive stages, mainly based on pulse rate and regularity. In all cases, the headaches continuously worsened and behavioural difficulties developed. This gradually led to an increasingly deep coma. He underscored the absence of dissociation in cranial sutures along with normal head circumference to distinguish the pathology he was describing from the hydrocephalus observed in newborns and infants who survived: *"the hydrocephalus, or dropsy of the head, is either external or internal. The former has its seat in the cellular substance, between the skin and the pericranium, or between this membrane and the skull. In the internal hydrocephalus, the water is sometimes collected between the cranium and* dura mater*, or between this last and the* pia mater*; but most commonly is found in the ventricles of the brain, immediately below the corpus callosum. And this is not only the most frequent and fatal species of the hydrocephalus but also that with which medical writers seem to have been least acquainted."* Among all of the descriptions he provided, his observation of the pupils made an impression on all those who published cases after his: "*frequently one eyelid loses its motion, and afterwards the other becomes also paralytic. About this time, or rather sooner, the pupil of one or both eyes ceases to contract and remains dilated in the greatest light."*

Whytt gives this summary of his autopsy observations: *"Upon opening the heads of 10 of those patients from whom I have collected the symptoms above mentioned, I found in all of them a clear thin fluid in the anterior ventricles of the brain, immediately below the corpus callosum. There was frequently the same kind of liquor in the third and fourth ventricles; but whether this is always the case, I cannot say, as I had not attended sufficiently to this circumstance. I never met with water between the* dura mater *and the brain, between the hemispheres of the brain, or immediately above the corpus callosum. Altho there seems to be a communication between the 2 anterior ventricles; yet, in 2 cases, I found one of them much distended, while the other contained but little water."* Whytt died at age 52, probably from complications of diabetes. His work was posthumously published in 1768 [8].

Louis Odier (1748–1817), originally from Geneva and trained in Edinburgh, was known for making variolation more widespread in France. He also returned to Whytt's clinical description [9]. The disease began with headaches, vomiting, and a low fever. The sick child was fussy, with sleep disturbed by cries or frightening dreams and teeth gnashing. At that time, physicians interpreted this clinical picture as the consequence of worms in the intestines. It lasted a few weeks to a few months, followed by an increase in all symptoms and the development of strabismus. *"The pupil, which had hitherto contracted in a healthy manner with the approach of light, now seemed immobile and very dilated."* Or the pupil spontaneously oscillated between contraction and dilation and in only one eye. Odier added that he had observed the clinical picture to alternate between the 2 eyes and considered this phenomenon to be specific to the disease. Finally, the terminal phase involved a strong fever, coma, trismus, and convulsions. Recovery was very rare and came with sequelae, most often a *"state of imbecility."* Upon autopsy, Odier observed *"a considerable quantity of clear serous fluid released into the anterior ventricles and also into the third and fourth ventricles, without any other apparent internal damage, except for some points of adherence between the* dura mater *and the skull."* For him, cases in adults were rare. He criticized earlier authors for neglecting to indicate that the disease particularly affected active, robust, and vigorous children, seeming to spare their *"scrofulous"* counterparts [10]. For Odier, brain trauma or intense fear seemed to be triggering factors.

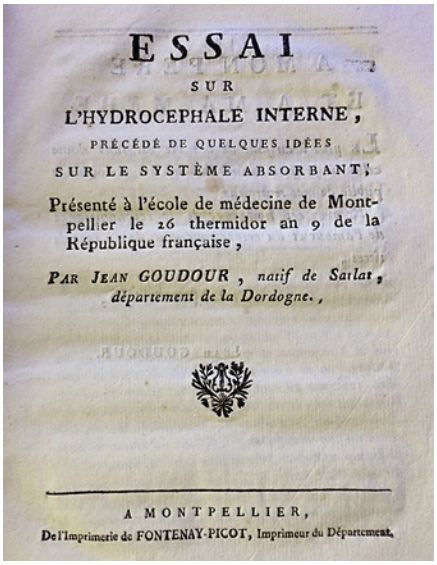
John Fothergill (1712–1780), a pharmacist then a physician who also trained in Edinburgh but worked in London, noted the same progressive phases as those suggested by Whytt, but criticized his contemporary for calling this disease *"acute hydrocephalus of the brain,"* creating confusion with chronic hydrocephalus, characterized by increased head volume. Fothergill thus suggested the term *"dropsy of the ventricles of the brain."* Clinically, the

description was the same. Fothergill wrote that the pulse rapidly switches from an extremely slow rate with irregularity to an extremely fast rate, and there is lethargy, insensitivity of the eyes to light, dilation of the pupil, and oscillations and convulsive movements of the eye itself. He believed that with early vermifuge treatment, the patients recovered after evacuation of the worms, whereas those who did not release them died of dropsy. Fothergill made aetiological suppositions. A blow to the head could cause the rupture of a lymphatic vessel in the brain. Recent measles or smallpox seemed to favour the headaches. He noted observing meningeal nodules during autopsy that he astutely recognized as possible tubercles. This made him the first since Willis to posit a link between the serous effusion observed and tuberculosis. As for the treatments he proposed, aside from blood-letting, they remain mysterious despite the poetry of the terms; in the French translation, we find *"la terre foliée de tartre et la liqueur de corne de cerf succinée"* (foliated earth of tartar and amber liquor of deer horn). Fothergill's book, published in London in 1781 [11], was translated into French by F.T. Bidault de Villiers (1775–1824), one of the first graduates of the elite Ecole Polytechnique. He received medical training in Edinburgh before returning to Paris, where he defended his thesis in medicine in 1803. He wanted to introduce French physicians to discoveries by English-language authors and translated several books including this one [12].

John Cheyne (1777–1836), trained in Edinburgh, practised surgery in Dublin in Ireland. His name remains familiar due to the eponym *"Cheyne–Stokes respiration"* [13]. He drew on the thesis defended by Charles William Quin (1755–1818) in 1779 [14], *De Hydrocephalo interno*, in order to suggest, in his 1808 *essay on hydrocephalus acutus, or dropsy of the brain*, a pathophysiological explanation for the abundance of intracranial serous fluid. He assumed there to be serous extravasation due to congestion in cerebral veins. Based on his practice, he concluded that this disease was always fatal [15].

French Theses in the Early 19th Century

Marcellin Chardel (1772–1847) was a student of Philippe Pinel (1745–1826) at La Salpêtrière (before the creation of the residency system in 1802). Before he became a champion of animal magnetism [16] and a pioneer in psychology [17], he defended his thesis on "16 Vendémiaire an VIII" (revolutionary calendar, 1799): *Observations pour servir à l'histoire de la fièvre cérébrale*

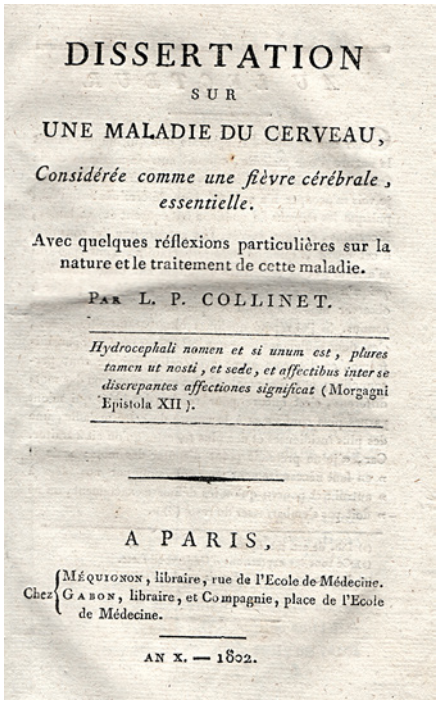

ESSAI
SUR
L'HYDROCEPHALE INTERNE,
PRÉCÉDÉ DE QUELQUES IDÉES
SUR LE SYSTÈME ABSORBANT;
Présenté à l'école de médecine de Montpellier le 26 thermidor an 9 de la République française,
PAR JEAN GOUDOUR, natif de Sarlat, département de la Dordogne.,
A MONTPELLIER,
De l'Imprimerie de FONTENAY-PICOT, Imprimeur du Département.

Color version available online

Fig. 1. Thesis of Jean Goudour 1801 (private collection of the author).

(observations relating to the history of brain fever) [18]. His patients were mostly elderly residents at the Hospice de la Salpêtrière along with a few young men. They were victims of fatal fevers, the symptoms of which resembled those mentioned above, notably the pulse variations, coma, and pupillary areflexia. He did not perform any autopsies. His observations suggest meningitis due to various causes, or other pathologies. However, these observations have historical value because they bear witness to the activities in Pinel's department of female patients, who were called *"citizens."*

Inspired by the hypothesis of a traumatic origin for dropsy of the ventricles, a young physician from Sarlat in the Dordogne region of France, Jean Goudour, developed in his thesis, defended in Montpellier on "26 thermidor an IX" (revolutionary calendar, 1801) (Fig. 1) [19], a pathophysiology of the serous effusion in the cerebral ventricles based on a functional disorder or rupture in the cerebral lymphatic vessels. Goudour drew on the discoveries of an Italian anatomist, Paolo Mascagni (1752–1815) from Siena [20]. Until only recently, this work may have seemed anecdotal because 20th century anatomists had determined there were no cerebral lymphatic vessels. However, new work has (re)discovered a conventional and functional lymphatic network within the central nervous system by means of *"intravital confocal"* microscopy and transgenic mice observed using fluorescence, associated with new methods of meningeal dissection in mice. This work has shown the presence of vessels expressing



DISSERTATION

SUR

UNE MALADIE DU CERVEAU,

Considérée comme une fièvre cérébrale, essentielle.

Avec quelques réflexions particulières sur la nature et le traitement de cette maladie.

PAR L. P. COLLINET.

Hydrocephali nomen et si unum est, plures tamen ut nosti, et sede, et affectibus inter se discrepantes affectiones significat (Morgagni Epistola XII).

A PARIS,

Chez { MÉQUIGNON, libraire, rue de l'Ecole de Médecine. GABON, libraire, et Compagnie, place de l'Ecole de Médecine.

AN X. — 1802.

Color version available online

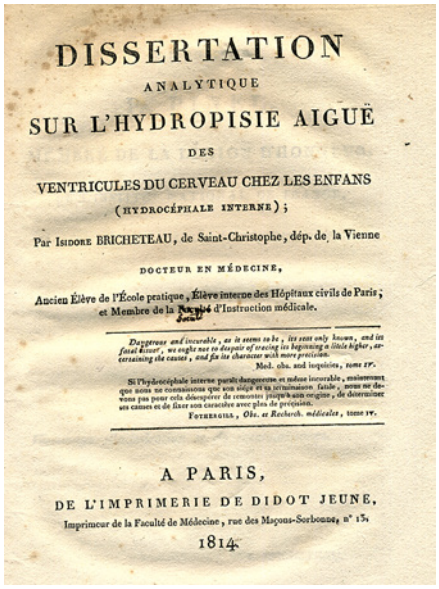
Fig. 2. Thesis of L.P. Collinet 1802 (private collection of the author).

all the molecular markers of peripheral lymphatic vessels that are located along the venous sinuses of the meninges. This circulatory system between the cerebrospinal fluid, the cerebral parenchyma, and the lymphatic vessels of the meninges, called the *"glymphatic system,"* involves the perivascular spaces and the astrocytes that drain interstitial fluid to and from cerebrospinal fluid [21]. Reading Goudour gives us some idea how this physiology was imagined 200 years ago, *"If we suppose that for whatever reason, these vessels lose their ability to pump the fluid released into the cavities and cells, serous fluid will build up there. These accidents will occur, meaning that the radicles of the lymphatic vessels fail due to a state of spasm (with or without inflammation) or a state of atonia and slackening that also works against their action."*

L.P. Collinet defended his thesis in 1802 in Paris, entitled "Dissertation sur une maladie du cerveau considérée comme une fièvre cérébrale essentielle (Dissertation on a Brain Disease Considered as a Fundamental Brain Fever)" [22] (Fig. 2). Collinet regretted being unable to obtain Whytt's work but nonetheless observed several cases of this same disease, thinking he was the first to describe it in France. His work is interesting in that it explicitly distinguishes between *"malignant brain fever,"* which was contagious and found among soldiers in the field and dropsy of the ventricles in children. Malignant brain fever had already been described by François Boissier de La Croix de Sauvages (1706–1767) in his 1768 nosology [23]. In the first case, Collinet observed *"purulent effusions and effusions containing a mixture of pus and blood"* during autopsies, whereas in the new form he described *"clear serous fluid, sometimes sanguinolent, in the ventricles."* In this way, he distinguished purulent meningitis from meningitis with clear cerebrospinal fluid. For him, this new form was easy to mistake clinically, especially at its onset: *"Preceded by sadness, a dark and worried attitude, a kind of apathy, with frequent headaches."* This clinical picture was not a cause for concern. Then the headaches worsened; they were continuous and exacerbated by lowering the head towards the ground. The patients cried out and developed a fever, with *"a kind of propensity to sleep."* Their rapid pulse became irregular, and their pupils were *"strongly dilated."* They went into a coma, and their gaze fixed, often with ocular divergence. This was followed by convulsions. Ten to 40 days after the disease started, the patients died. Children and young people were the most often affected, and several cases frequently occurred within the same family. According to Collinet, William Cullen (1710–1790) had described this pathology as *"hydrocephalic apoplexy"* in his 1772 nosology [24].

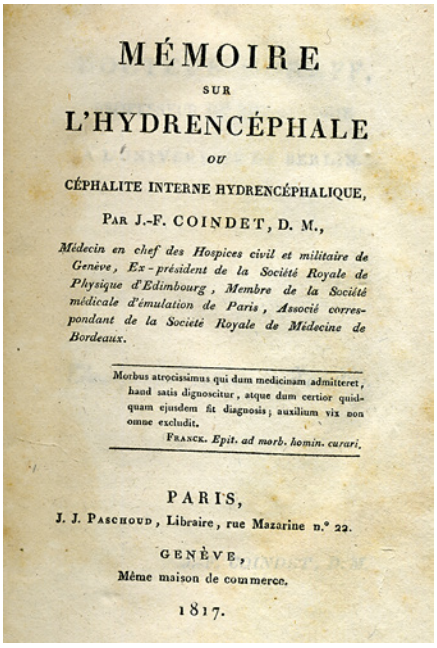
Antoine Bouchel was from Audenarde (former French administrative subdivision of the Escaut department, created on September 11, 1802, by Napoleon and no longer used from 1814 on, currently Audenarde, Oost-Vlaanderen, in Belgium). He defended his thesis in Paris on "4 Prairial an XIII" (May 24, 1805): "Dissertation sur l'hydrocéphale interne (R. Whytt), ou apoplexie hydrocéphalique (Cullen) (Dissertation on Internal Hydrocephalus (R. Whytt), or Hydrocephalic Apoplexy (Cullen))" [25]. Aside from its place in the history of 17th and 18th century writings, this thesis is interesting for its French summaries of the works of Paisley, Whytt, and Fothergill. It discusses how Erasmus Darwin (1731–1802) associated fever with the clinical picture of the new entity, distinguishing it from apoplexy [26]. He noted *"the discomfort experienced by the patient when they raise their head from their pillow and the desire they have immediately afterwards to lay it down again,"* a minimal form of the sign of Joseph Brudziński (1894–1917) [27, 28]. Bouchel is the first and only author to have proposed the use of electricity as a treatment.

Isidore Bricheteau (1787–1861), son of a banker in the central French city of Nevers, became a resident of the Paris hospitals in 1812 and defended his thesis in 1814:


DISSERTATION
ANALYTIQUE
SUR L'HYDROPISIE AIGUË
DES
VENTRICULES DU CERVEAU CHEZ LES ENFANS
(HYDROCÉPHALE INTERNE);
Par ISIDORE BRICHETEAU, de Saint-Christophe, dép. de la Vienne
DOCTEUR EN MÉDECINE,
Ancien Élève de l'École pratique, Élève interne des Hôpitaux civils de Paris;
et Membre de la Société d'Instruction médicale.
Dangerous and incurable, as it seems to be, its seat only known, and its final issue, we ought not to despair of tracing its beginning a little higher, ascertaining the causes, and fix its character with more precision.
Med. clin. and Inquiries, tome IV.
Si l'hydrocéphale interne paraît dangereuse et même incurable, malheureusement que nous ne connaissons que son siége et sa terminaison fatale, nous ne devons pas pour cela désespérer de remonter jusqu'à son origine, de déterminer ses causes et de fixer son caractère avec plus de précision.
FOTHERGILL, Obs. et Recherch. médicales, tome IV.
A PARIS,
DE L'IMPRIMERIE DE DIDOT JEUNE,
Imprimeur de la Faculté de Médecine, rue des Maçons-Sorbonne, n° 13.
1814.

Color version available online

Fig. 3. Thesis of Isidore Bricheteau 1814 (private collection of the author).


MÉMOIRE
SUR
L'HYDRENCÉPHALE
OU
CÉPHALITE INTERNE HYDRENCÉPHALIQUE,
PAR J.-F. COINDET, D. M.,
Médecin en chef des Hospices civil et militaire de Genève, Ex-président de la Société Royale de Physique d'Edimbourg, Membre de la Société médicale d'émulation de Paris, Associé correspondant de la Société Royale de Médecine de Bordeaux.
Morbus atrocissimus qui dum medicinam admitteret, haud satis dignoscitur, atque dum certior quidquam ejusdem fit diagnosis; auxilium vix non omne excludit.
FRANCK. *Epit. ad morb. homin. curari.*
PARIS,
J. J. PASCHOUD, Libraire, rue Mazarine n.° 22.
GENÈVE,
Même maison de commerce.
1817.

Color version available online

Fig. 4. Book's cover of J.F. Coindet (private collection of the author).

"Dissertation analytique sur l'hydropisie aiguë des ventricules du cerveau chez les enfants (Analytical Dissertation on Acute Dropsy of the Ventricles of the Brain in Children)" [29] (Fig. 3). He was one of Pinel's favourites and became his secretary in 1816. He collaborated on the *Dictionnaire des Sciences Médicales* and was elected to the French Academy of Medicine in 1822. Taken out of the running for any position during the restoration, he was appointed to Necker Hospital in 1830 after the July Revolution. Bricheteau delivered Pinel's eulogy before the Société d'Émulation of Paris (a learned society) in 1828. In his thesis, he reported on 18 observations of children ranging in age from 1 to 15 years old. This allowed him to underline the diagnostic difficulties, which related to symptoms that were not very specific. Only in one case did the disease last more than a month. He never mentioned a possible tuberculous origin. The only novel clinical trait that he added to the descriptions of his predecessors was the existence of *"repeated yawning during much of the disease; no other author mentions this symptom."* After an observation in 1824 [30], Bricheteau published another in 1830, including an argument aimed at demonstrating that *"acute hydrocephalus"* and meningitis were 2 distinct diseases [31]. However in a book published 5 years later, in 1835, which brought together the lessons he had taught at Necker Hospital, Bricheteau abandoned this interpretation and explicitly associated the neurological features of meningoencephalitis with the presence of tubercles in the nervous system as well as pulmonary tubercles [32].

In 1817, Jean-François Coindet (1774–1834), a Genevan physician trained in Edinburgh and Berlin who became famous for using iodine as a treatment for goitre in 1820 [33], was given an award by the Royal Society of Medicine of Bordeaux for his *"dissertation on hydrocephalus or hydrencephalic internal cephalitis"* [34] (Fig. 4). Coindet did not add anything new aside from mortality statistics for this disease. At the turn of the 19th century in Geneva, within the space of 10 years, at least 209 children apparently died of this disease. Coindet inconsistently observed meningeal tubercles during the autopsies, which led him to see them as a coincidence and not a cause. Several thousands were dying in Paris each year.

Hypothesis of a Tuberculous Origin

Jean-Marc-Gaspard Itard (1774–1838), another student of Pinel and René Théophile Hyacinthe Laënnec (1781–1826), wrote the *"hydrocephalus"* article for Panckoucke's dictionary of medical sciences in 1818. After a historical section focussed on classical Greek and Arab authors, he paid homage to English-language authors for having described the clinical picture for *"acute hydro-*

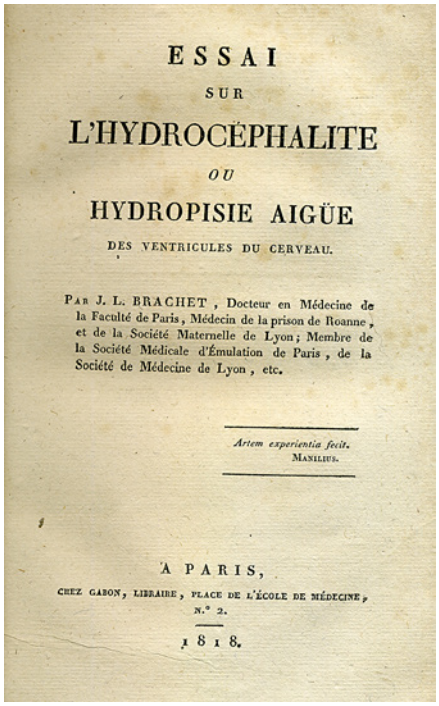


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Fig. 5. Book's cover of J.L. Brachet 1818 (private collection of the author).

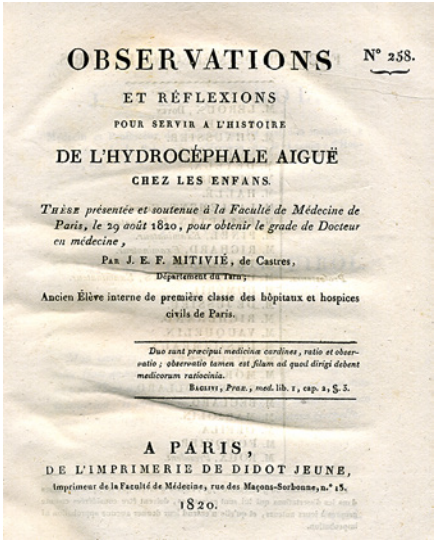

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Fig. 6. Thesis of J.E.F. Mitivié 1820 (private collection of the author).

cephalus." He provided no original clinical data but offered his personal observation of the epidemiological nature of the disease. Above all, he was one of the first authors to discuss aetiology: *"More modern research on pathological anatomy, due in large part to Laënnec, has shown tuberculous granulations of the substance of the brain and cerebellum, in the layers of the optical nerves, and even in the thickness of the meninges."* He described performing an innovative chemical analysis on the fluid abundantly present in the cerebral ventricles. His conclusion overturned the thinking of his predecessors: *"The effusion is not the disease, but merely its result"* [35].

In 1818, Jean Louis Brachet (1789–1858), both an exceptional physician and clinician and a pioneer of the physiology of the autonomous nervous system [36] (Fig. 5), supported Itard's conclusions concerning the disease's contagiousness. He criticized a view held *"in certain societies"* that is not without contemporary parallels: *"Since this disease has seemingly become more frequent as physicians have been better able to identify it, its cause has naturally been attributed to the introduction of the vaccine in medical practice. Before the vaccine was discovered, the thinking goes, acute hydrocephalus was not known; thus it did not exist. In this way, the vaccine replaced a scourge by a more terrible scourge"* [37]. Brachet discussed and contested the opinion Laënnec gave Itard, seeming to interpret the appearance of tubercles as *"consecutive to the accumulation of serous fluid in the ventricles."* In any case, the disease was incurable. His voluminous 208-page dissertation dealt in length with all the other data mentioned above.

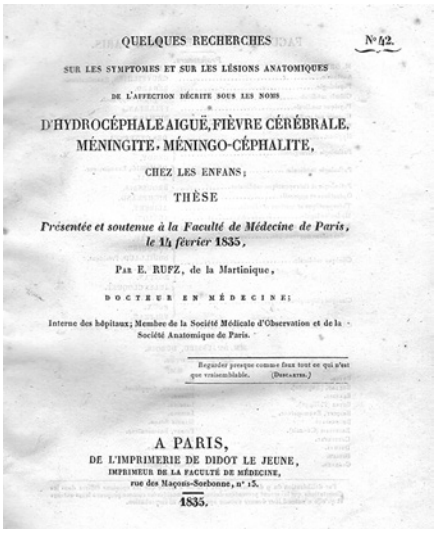
Jules-Étienne Mitivié (1796–1871) was part of the circle of students working under Jean-Étienne Esquirol (1772–1840), his uncle. An alienist at La Salpêtrière, he was Esquirol's associate in founding the Maison de Santé in Ivry, a renowned mental health centre in the suburbs of Paris. On August 29, 1820, Mitivié, who had passed the residency exam in 1815, defended his thesis: "Observations et réflexions pour servir à l'histoire de l'hydrocéphale aiguë chez les enfants (Observations and Thoughts Applied to the History of Acute Hydrocephalus in Children)" [38] (Fig. 6). Although he added no specific signs to those described in detail by Brachet, Mitivié used 26 cases with autopsies, which were only macroscopic, to differentiate between cases where only ventricular dilation was noted and those with inflammation of the various meninges, on which there were most often tubercles [39]. He did not draw any specific conclusions and presented no pathophysiological explanations in what was mainly a work of compilation.

In 1820, Louis Martinet (1795–1875) and Alexandre Parent-Duchatelet (1790–1836) presented a dissertation to the Royal French Academy of Sciences on inflammation of the arachnoid. They asserted that alongside cases

of general paralysis, *"tubercles, due to their development, may sometimes cause an inflammation of the arachnoid."* These authors deduced from the 140 cases analyzed in detail that they had described a specific, fundamental disease, *"arachnitis."* However, the causes of the meningeal inflammations observed actually stemmed from various aetiologies, primarily microbial, which they could not have identified at the time [40].

In 1825, the Genevan Louis Senn (1799–1873), a resident under Louis Benoit Guersant (1777–1848) at the Hôpital des Enfants-Malades in Paris, published a book covering the anatomopathological examinations of twelve children who had died of dropsy of the ventricles [41]. He clearly showed that these were cases of meningitis or meningoencephalitis, but did not indicate any lesions that would suggest tuberculosis.

In 1829, Jean Baptiste Hippolyte Dance (1797–1832) published a series of 26 cases, all adults, to show that the disease was not limited to children. He did not indicate in any of his autopsies the observation of miliary lesions (tiny spots resembling millet seeds) or tubercles [42].


QUELQUES RECHERCHES

N° 52.

SUR LES SYMPTOMES ET SUR LES LÉSIONS ANATOMIQUES

DE L'AFFECTION DÉCRITE SOUS LES NOMS

D'HYDROCÉPHALE AIGUË, FIÈVRE CÉRÉBRALE, MÉNINGITE, MÉNINGO-CÉPHALITE,

CHEZ LES ENFANS;

THÈSE

Présentée et soutenue à la Faculté de Médecine de Paris, le 14 février 1835,

PAR E. RUFZ, de la Martinique,

DOCTEUR EN MÉDECINE;

Interne des hôpitaux; Membre de la Société Médicale d'Observation et de la Société Anatomique de Paris.

Regardez presque comme faux tout ce qui n'est que vraisemblable. (DESCARTES.)

A PARIS,

DE L'IMPRIMERIE DE DIDOT LE JEUNE,

IMPRIMEUR DE LA FACULTÉ DE MÉDECINE,

rue des Maçons-Sorbonne, n° 13.

1835.

Fig. 7. Thesis of Étienne Rufz de Lavison (private collection of the author).

Tuberculous Origin Becomes Certain

In 1833, having passed the residency exam in 1829, Étienne Rufz de Lavison (1805–1884), born in Saint-Pierre on the island of Martinique, was also working as a resident under Guersant. He published a series of 10 autopsied cases of dropsy of the ventricles. In all of the cases, he noted miliary lesions or tubercles in various brain structures, considering them the probable cause of meningeal inflammation leading to the increased volume of the fluid present in the ventricles [43] (Fig. 7). He made this the subject of his thesis defended on February 14, 1835, with Jean-Baptiste Bouillaud (1796–1881) presiding over the jury. Working with his friend William Wood Gerhard (1809–1872) from Philadelphia, he added 14 new cases to those published in 1825 [44] and concluded that *"the disease described by the authors under the various names I have mentioned may be nothing other a tuberculous disease, a form of this fatal cachexia in men."* Gerhard published the same results once he returned to the USA [45]. Rufz autopsied all the cases and for each one discovered miliary lesions and tubercles in the meninges, ventricular dilation, and above all, tuberculous pulmonary lesions, which were a constant. This was pioneering work, and Rufz's writing is clear and concise [46]. It should be noted that Pierre Charles Alexandre Louis (1787–1872) published his seminal work on phthisis in 1825 [47]. A short time later, Rufz passed the *agrégation* exam, which opened the way to a career as a university professor. He then embarked on a political career in Martinique in 1856, going on to create the island's magnificent botanical gardens.

On December 4, 1837, Victor-Mathurin Le Diberder (1810–1891), a resident under Alfred Velpeau (1795–1867), defended his thesis, which corroborated the consistently tuberculous origin of this disease, *"the tuberculous affection of the* pia mater" [48]. The granulations were found *"most often in the base of the brain and extended in the Sylvian fissure, along the middle cerebral artery."* He correctly attributed the coma and ophthalmic disorders to the compression of nervous tissue by the increased volume of fluid around the brain, that is, intracranial hypertension.

Isidore Valleix (1807–1855) was convinced of the novelty and significance of the subject. *"The observations of Le Diberder will definitely be of great interest to the readers of the Archives. I intend to present them with the complete clinical picture of tuberculous meningitis"* [49]. In his publication, Valleix focussed on showing that all patients, whether children or adults, were phthisics for whom the autopsies always found the characteristic pulmonary lesions and very often peritoneal granulations together with meningeal tubercles. Tuberculous meningitis was a frequent cause of death in patients who, early in their disease, only suffered from pulmonary lesions. We can thus conclude that in 1838, physicians were mostly in agreement that dropsy of the ventricles was one of the (macroscopic) anatomopathological expressions of tuberculous infection in the nervous system.

In 1842, the lessons of Armand Trousseau (1801–1867) underscored the difficulty of diagnosing tuberculous meningitis, especially early on in the disease. In the advanced stage, *"patients uttered the hydrencephalic cry,"* a symptom that has since been forgotten. His conclusion called for modesty and confraternity: *"Such is the clinical picture of this terrible disease. You would be well served to always be vigilant, to pay attention to the slightest indispositions of childhood, to accept the diagnostic errors you may make, and above all, to be indulgent with your confrere who failed to recognize early on a disease that was later manifest for you. In such a case, we can all be forgiven and indulgence becomes our right"* [50].

Antoine de Barthez (1811–1891) and Frédéric Rilliet de Saladin (1814–1861) published their "Traité clinique et pratique des maladies des enfants (Clinical and Practical Treatise on the Diseases of Children)" in 1843, not only the first real paediatric treatise but a work containing pathological anatomy data. Physicians were provided with a specific chapter on tuberculous meningitis in children, testifying to this disease's definitive inclusion in the nosology [51].

Even though the pathophysiological explanation of tuberculous infection advanced by Georges Empis (1824–1913) turned out to be incorrect, in 1865 he proposed unifying a wide range of inaccurately named diseases, such as brain fever, granular meningitis, and acute hydrocephalus, under one name, *"la granulie"* (miliary tuberculosis) [52]. This was the final chapter in the history of the individualization of tuberculous meningitis [53].

Conclusion: Improved Diagnosis

Vladimir Kernig (1840–1917) improved the clinical diagnosis of the meningeal syndrome, describing the eponymous sign in 1882 [54]. As for Polish paediatrician Józef Brudziński (1874–1917), he proposed several signs after clinical observations and experiments in animals. The neck sign remains the most commonly used [55]. Recent evaluations indicate that the Kernig and Brudziński signs each have a sensitivity of 5% and a specificity of 95% [56].

Robert Koch (1843–1910) identified the causal agent, the eponymous bacillus, in 1882 [57]. Heinrich Quincke (1842–1922) developed lumbar puncture in 1891, initially for treatment, but which made it possible after that to perform biological and bacteriological analyses of cerebrospinal fluid and diagnose meningitis prior to death [58, 59].

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