Infundibulo-tuberal syndrome: the origins of clinical neuroendocrinology in France

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Abstract  The birth of clinical neuroendocrinology can be dated to the year 1900, when the French neurologist Joseph Babinski (1857–1932) described a particular syndrome of adiposity and sexual infantilism in an adolescent with a craniopharyngioma expanding at the base of the brain. This condition of adipose-genital dystrophy, also known as Babinski–Fröhlich syndrome, represented the first clinical evidence that the brain controlled endocrine functions. Adipose-genital dystrophy forms part of infundibulo-tuberal syndrome, which groups the endocrine, metabolic and behavioral disturbances caused by lesions involving the upper neurohypophysis (median eminence) and the adjacent basal hypothalamus (tuber cinereum). This syndrome was originally described by the French neuropsychiatrists Henri Claude (1869–1946) and Jean Lhermitte (1877–1959) in 1917, also in a patient with a craniopharyngioma. This type of tumor involves specifically the infundibulo-tuberal region of the hypothalamus, providing a clinical model to conceptualize the separation of hypophyseal and hypothalamic functions. The French School of Neurology analyzed and reported the symptoms associated with dysfunction of the basal hypothalamus by craniopharyngiomas and other types of tumors, influencing significantly the development of clinical neuroendocrinology. Experimental lesions performed in the tuber cinereum by the French physiologists Jean Camus (1872–1924) and Gustave Roussy (1874–1948) demonstrated unmistakably the anatomical origin of infundibulo-tuberal syndrome in the basal hypothalamus. This article reviews the original findings on infundibulo-tuberal syndrome reported by the French School of Neurology in the first decades of the twentieth century and the great influence this school had on modern conceptions of hypothalamic control over endocrine functions and behavior.

Keywords  Hypothalamus · Infundibulum · Tuber cinereum · Pituitary gland · Fröhlich syndrome · History endocrinology · Craniopharyngioma

Introduction

The infundibulo-tuberal area is the basal region of the hypothalamus formed by the infundibulum, the hollow, funnel-shaped proximal portion of the neurohypophysis and the tuber cinereum, the adjacent grey matter enclosed between the optic tracts and the mammillary bodies (Fig. 1a). A specialized anatomical region within this area is the median eminence, located along the midline of the infundibulum [1]. The lack of a functional blood-brain barrier allows this region to monitor the internal milieu and energy status of the organism and controls accordingly the endocrine output of the pituitary gland. Specifically, a cluster of neurons placed within the median eminence, the arcuate nucleus, plays a fundamental role in the regulation of feeding behavior linked to energy balance [2]. A second major role of the infundibulum is the regulation of sexual functions through the monitoring of circulating sexual
hormones and the control of hypophyseal secretion of gonadotropins [3]. The origin of Neuroendocrinology coincides with the identification of a clinical syndrome characterized by failed sexual development and abnormal obesity in patients with a particular pituitary tumor involving the infundibulo-tuberal area, the craniopharyngioma (CP) [4, 5]. Alfred Frohlich (1871–1953) called attention to this “adipose-genital” syndrome in 1901, by describing in detail a patient with these symptoms who eventually underwent an operation to remove a craniopharyngioma [6]. However, it was Joseph Babinski, the pioneering French neurologist, who first reported the association of sexual infantilism and obesity with a CP developing at the infundibulo-tuberal area [7]. In 1904, the Viennese pathologist Jakob Erdheim (1879–1937) defined the group of “hypophyseal duct tumors”, the category of epithelial tumors currently known as “craniopharyngiomas” (CPs), a term introduced by Harvey Cushing in the 1930s [8, 9]. Erdheim noticed that CPs developed preferentially at the infundibulo-tuberal area (IT). He also observed that the obesity manifested in patients with tumors involving the infundibulo-tuberal area was not related to damage to the pituitary gland, but rather to an injury to unknown centers within the third ventricle floor [8].

CPs developing primarily at the IT area or invading this region of the hypothalamus represent an adequate lesional model to differentiate symptoms due to hypothalamic dysfunction from those associated with functional disturbances of the pituitary gland [10, 11]. Harvey Cushing (1869–1939) challenged Erdheim’s theory and considered, erroneously, that Frohlich’s syndrome was caused by insufficiency of the pituitary gland, or “hypopituitarism” [12]. Numerous reports of patients with Frohlich’s syndrome caused by craniopharyngiomas involving the IT area and sparing the pituitary gland reported by members of the French School of Neurology supported Erdheim’s claims and opposed Cushing’s views. Despite Cushing’s mistaken interpretation being initially accepted, French authors stated that the adipose-genital dystrophy was an essential manifestation of an injury to the IT region of the hypothalamus. Through their detailed clinical reports
combined with a thorough analysis of anatomical distortions caused by craniopharyngiomas and other tumors involving the hypothalamus, the pioneers of the French School of Neurology definitely influenced the origins and development of clinical neuroendocrinology. Modern conceptualization of the hypothalamic control of metabolic homeostasis, endocrine functions and hormonal regulation of human behavior owes much to these original findings. This work summarizes their fundamental contributions to the field of neuroendocrinology.

Babinski’s “pituitary” case: a type of lesion evidencing the separation of hypothalamic and hypophysial functions

In 1900, Joseph Babinski (1857–1932), Charcot’s protégé and Chief of Neurology at La Pitie in Paris, reported the case of a 17-year-old female patient with headache, visual and memory disturbances, lack of sexual development and obesity (Fig. 2a, c) [7]. At her autopsy, a large pituitary tumor formed by epithelial tissue was found. The lesion, which occupied the base of the brain and expanded predominantly within the third ventricle, had destroyed the infundibulotuberal area (Fig. 2b). It replaced the tuber cinereum and protruded into the sella turcica, where it was tightly adhered to the intact body of the pituitary gland. This neoplasm had been examined histologically several years earlier, in 1892, by Babinski’s Russian pupil Jacques Onanoff, who used this study material as the basis of his doctoral thesis. Dr. Onanoff described this lesion as an “epithelioma” of Malpighian type (formed by stratified epithelium) containing areas of conjunctival stroma showing myxomatous degeneration [13]. He was the first author to point out the close resemblance of this tumor to that of adamantinomas of the jaw.

Joseph Babinski was intrigued because of the absence of acromegaly or gigantism in his patient, in spite of the presence of a large pituitary tumor. He knew about the relationship between atrophy of genital organs and tumors of the pituitary gland in adults, therefore he proposed any pituitary tumor could likewise lead to arrested development of genital organs in young patients. He acknowledged, however, that it would be necessary to know to what extent the gland had been functionally altered in cases such as these. Although he had been struck by the excess of adipose tissue in his patient’s body, Babinski was not able to link this clinical finding to the injury of the third ventricle floor caused by the tumor [7]. After Fröhlich’s seminal paper evidenced the frequent association of abnormal obesity and hypogonadism with large pituitary tumors, the symptoms of sexual infantilism and adiposity would later become known as Fröhlich’s syndrome [4, 5]. The priority of Babinski’s description led some authors to name this condition as Babinski–Fröhlich’s syndrome.

Over the following decades, the cause of Babinski–Fröhlich’s syndrome would be attributed, erroneously, to a primary disturbance of the pituitary gland. One of the main reasons for such an incorrect assumption was Harvey Cushing’s concept of pituitary insufficiency or “hypopituitarism” as the cause of Fröhlich’s syndrome. His dominant view was spread worldwide through his monograph “The Pituitary Body and its Disorders”, published in 1912 [12]. Cushing’s opinion resulted from his long experimental research on hypophysectomy in dogs, through which he had achieved the reproduction of a Fröhlich’s syndrome-like phenotype [14]. Cushing’s technique using a subtemporal approach, however, often caused a direct injury to the infundibulotuberal area of these dogs, as the layer of duramater interposed between the pituitary gland and the infundibulum is lacking in these animals [14]. The lesion of the infundibulotuberal area was the cause of progressive obesity and apathy in dogs after experimental hypophysectomy, as evidenced by the Viennese physiologist Bernhard Aschner (1883–1960), who employed a new transpalatal technique to cut the gland off from the infundibular stalk without damaging the hypothalamus [15]. Interestingly, the British neurologist Sir Byron Bramwell (1847–1931) had already observed in 1888 the association of obesity with gross distortion of the diencephalic area of the brain by large pituitary tumors [16]. His suggestion would be ignored until several members of the French school proposed, in the 1910s, the existence of “the infundibulo-tuberal syndrome”, caused by lesions restricted to the IT area of the hypothalamus [10].

The infundibulo-tuberal syndrome caused by craniopharyngiomas: description by the French School of Neurology

The original description of infundibulo-tuberal syndrome (“Syndrome infundibulaire”) appeared in an article published in 1917 by the French neurologists Henri Claude (1869–1946) and Julien Lhermitte (1877–1959) (Fig. 2d, f). These authors reported a 25 years-old man who died after suffering from headache, vomiting, polyuria, marked drowsiness and behavioral changes for 1 year, in addition to atypical alterations of the autonomic nervous system [10, 17]. At autopsy, a tumor was found within the third ventricle of the brain, above an intact pituitary gland, which did not cause obstructive hydrocephalus (Fig. 2e). This histologically benign, epithelial lesion corresponded to a CP. Based on the integrity of the pituitary gland, Claude and Lhermitte proposed the lesion of the infundibulum as the major cause of patient’s abnormal somnolence and diabetes insipidus.
Accordingly, they considered this region of the diencephalon as a primary brain center involved in the control of wakefulness and corporal water homeostasis [17]. Up to that time the pituitary gland had been considered the only organ involved in the regulation of corporal water balance. However, these authors sustained that psychiatric and memory disturbances in his patient were due to the impairment of other unknown brain centers, different from the infundibulum.

Shortly after this landmark study A. Salmon, from Florence, replied that disturbances in the control of the sleep-wakefulness cycle and water metabolism could be observed in lesions occurring either at the infundibulum or within the proper pituitary gland [18]. He based on Ramón y Cajal anatomical studies, in which he had traced a nervous bundle running downwards from the hypothalamus through the infundibulum toward the posterior lobe of the pituitary gland, and the lesion of this hypothalamus-hypophysial pathway at different levels could presumably account for the symptoms of the infundibular syndrome [19]. Consequently, Salmon proposed a “pituitary syndrome of infundibular origin” as a more appropriate term for the group of symptoms reported by Claude and Lhermitte [18].

In 1913, Jean Camus (1872–1924) and Gustave Roussy (1874–1948), the French pioneers of hypothalamus physiology were able to generate diabetes insipidus and the adiposogenital syndrome after injuring the region of the tuber cinereum in dogs [20, 21]. They used the definitive term “infundibulo-tuberal” to include the involvement of the tuber cinereum together with the infundibulum as the global region affected in Claude and Lhermitte’s infundibular syndrome [21]. The identification of CPs developing wholly within the third ventricle, above an
anatomically intact pituitary gland/stalk, which produced a constellation of symptoms similar to that reported by Claude and Lhermitte, allowed François and Vernier in 1919 and Lereboullet in 1921 the confirmation of the infundibulum as the region primarily affected in patients showing the infundibular syndrome [22, 23]. The findings reported by French authors were confirmed conclusively by one of Cushing’s most talented assistants, Percival Bailey (1892–1976), who forced Cushing to lastly accept the new doctrine of the preeminent role of the hypothalamus on the genesis of the adipose-genital syndrome [24].

In 1924, Jacques Jumentié (1881–1928) and L. Chausseblanche introduced a classification of the different clinical variants of the infundibular syndrome [10, 25]. They described a complete infundibular syndrome, which would include, in addition to a typical adipose-genital syndrome (Babinski–Fröhlich’s), the presence of abnormal somnolence, diabetes insipidus and disturbances of the autonomic nervous system (Fig. 2g, h) [25]. In addition, they proposed the theoretical existence of infundibular syndrome variants, termed “dissociated infundibular syndromes”, each characterized by the predominance of one symptom over the others. Among them, they mentioned the existence of a hypersomnic variant, characterized by abnormal daily somnolence, the dystrophic variant, in which Fröhlich’s syndrome was the predominant manifestation, and the frustrated types. The latter category would correspond to patients lacking obvious somnolence and Fröhlich’s syndrome because of the rapid evolution of other acute symptoms such as severe hydrocephalus or chiasm compression that allowed an early diagnosis of the tumor [25]. Jumentié was the first author to suggest that different topographical variants of tumors involving the hypothalamic-pituitary axis could produce different association of symptoms. In the case of CPs developing exclusively within the third ventricle the neural structures adjacent to the third ventricle walls would be involved first, causing hypothalamic and extrapyramidal symptoms, while the infundibular region below the tumor would be damaged at later stages of tumor development, leading to the diagnosis of frustrated variants of the infundibulo-tuberal syndrome (Fig. 2g, h).

**Craniohypophyngiomas: a clinical model of hypothalamic dysfunction**

The hypothalamus constitutes the fundamental neuroendocrine node that regulates endocrine output of the hypophysis and the brain center that monitors the changes of the internal milieu and integrates the behavior to restore the body homeostasis and support the survival of the individual [26]. The group of epithelial tumors presumably derived from remnants of Rathke’s pouch or craniohypophyngiomas have been classically regarded as lesions having a sellar and/or a suprasellar location. Nevertheless, up to 40% of CPs found at autopsy studies or exposed in surgical approaches are located primarily at the infundibulo-tuberal area, above an anatomically intact pituitary gland and pituitary stalk (Fig. 1b) [11, 27]. This subgroup of craniohypophyngiomas has been considered by some authors to be true hypothalamic tumors, though the most proper term for these lesions is infundibulo-tuberal CPs [11, 28, 29].

Infundibulo-tuberal CPs represent an adequate lesional model of the median eminence and its associate arcuate nucleus, the critical structures linking the neuroendocrine responses to changes in body homeostasis. Numerous well described examples of infundibulo-tuberal CPs identified at autopsic studies were reported by French clinicians at the different meetings of the Societe de Neurologie during the first half of the twentieth century [10]. Some of these authors identified Babinski–Fröhlich’s syndrome as the essential clinical manifestation of a lesion of the infundibulo-tuberal area. Curiously, it has not been remarked in medical literature that both Babinski and Fröhlich’s patients with adipose-genital syndrome did not present pituitary adenomas but rather infundibulo-tuberal CPs [30].

In a review of the historical cohort of CPs reported in French literature before the computed tomography/magnetic resonance imaging (CT/MRI) era we have conducted recently, it has been shown that specific neuroendocrine and hypothalamic disturbances are related to the topographical origin of the lesion [10]. In particular, the presence of the adipose-genital or Babinski–Fröhlich’s syndrome in addition to drowsiness and/or diabetes insipidus occurred in 75% of CPs developing primarily in or invading the infundibulo-tuberal area. In contrast, only 8% of CPs restricted within the sellar and/or suprasellar area, beneath an anatomically intact third ventricle floor, manifested symptoms of dysfunction of the infundibulo-tuberal region. This accurate concept of Babinski–Fröhlich’s syndrome as a manifestation of a lesion restricted to the infundibulo-tuberal region was provided by members of the French School of Neurology. This medical school should be recognized for its notable contribution to the comprehension of the hypothalamus and the new concept of the neural regulation of endocrine functions and metabolism, the true origin of neuroendocrinology.

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