History of the deficiency diseases of the nervous system

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ABSTRACT

Introduction. Mankind's earliest written accounts and images prove that deficiency diseases of the nervous system have been recognised throughout history. These diseases were originally caused by famines and armed conflict, and prisoners of war were frequent victims. Alcohol consumption, in addition to poor nutrition, became another cause of deficiency diseases of the nervous system from the late 19th century onward. The purpose of this article is twofold. Firstly, we wish to present the earliest descriptions of the deficiency diseases of the nervous system. Secondly, the article aims to show that diagnosing certain clinical entities, for example, vitamin B_{12} deficiency, requires an interdisciplinary approach.
Material and Methods. Our study is based mainly on initial descriptions of a specific syndrome or clinical feature. These articles were located in the the Spanish Society of Neurology's historical archive, and we also searched the MEDLINE and *Índice Médico Español* (IME) databases to gather additional literature.
Conclusions. A number of syndromes once regarded as separate clinical entities have been grouped together, as in the case of Wernicke-Korsakoff syndrome. However, some patients present clinical and pathological manifestations pertaining to several different entities: nutritional amblyopia, for example, may present with lesions specific to Wernicke-Korsakoff syndrome. The clinical features that have been described confirm that interdisciplinary studies are needed in order to gain more thorough knowledge of these entities.

KEYWORDS
Deficiency diseases of the nervous system, Wernicke-Korsakoff syndrome, pellagra, beriberi, Marchiafava-Bignami disease, central pontine myelinolysis, cortical cerebellar degeneration, nutritional amblyopia

Introduction

Since ancient times, poor nutrition has been known to cause several distinct neurological diseases. Alcohol abuse has also been linked to similar clinical entities, and over time, like poor nutrition, it gained recognition as the causal agent of numerous neurological syndromes. In his treatise on neurology, Brain describes Wernicke encephalopathy as follows:

> The thiamin deficiency may be due to various causes. An inadequate diet was the cause of Wernicke's encephalopathy occurring in prisoners of war, and in civil life the causes are the same which produce beri-beri, namely, inadequate diet, chronic alcoholism, gastrointestinal disorders, especially carcinoma of the stomach, and persistent vomiting of pregnancy.[1(p718)]

In *Merritt's Neurology*, Worrall and Rowland state that "alcohol abuse is a major cause of malnutrition and is associated with numerous neurologic syndromes".[2(p1092)] These considerations explain why several neurological syndromes are presented in chapters addressing deficiency diseases or alcoholism.

The purpose of this article is twofold. On the one hand, it will highlight the initial descriptions of different deficiency diseases of the nervous system. On the other hand, it demonstrates the complexity of certain clinical entities that require an interdisciplinary approach to diagnosis, for example, vitamin B_{12} deficiency.

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Material and methods

Most of the articles we have used in the present study constitute the initial descriptions of various syndromes or clinical features. These articles were located in the historical archive kept by the Spanish Society of Neurology. Our study draws from the classic literature on this topic, beginning in the 18th century with Casal's original studies and the contributions by Wernicke and Korsakoff in the late 19th century. We conclude with the description of such new entities as Marchiafava-Bignami disease, and also with Adams, Victor, and Mancall's account of central pontine myelinolysis in 1959 (Table 1). Additional references were collected using the Medline database.

Wernicke-Korsakoff syndrome

Wernicke encephalopathy (WE) is characterised by difficulty concentrating, confusion, and sleep disorders that may progress to stupor and coma. Examination reveals nystagmus and ophthalmoplegia. Some cases also display pronounced signs and symptoms of polyneuropathy.[3]

In 1881, Karl Wernicke (1848-1905) published the medical history of three patients whom he believed to show a new clinical entity. One had ingested sulphuric acid and presented vomiting and anorexia before dying 12 days later. The other two patients were long-term alcoholics who had been admitted to hospital with features of delirium tremens, and they also died several days later. Their clinical features included vomiting, sleep disorders, confusion, ophthalmoplegia, nystagmus, ataxia, and changes in short-term memory. Long-term survivors may ultimately present symptoms of confabulation and polyneuropathy. The neuropathology study revealed microhaemorrhages affecting the grey matter around the third and fourth ventricles and the cerebral aqueduct, and inflammation of the optic disk. Wernicke designated these features as 'polioencephalitis haemorrhagica superioris' and found the link between the symptoms and lesion location.[3]

Table 1. Main neurological diseases caused by nutritional deficiencies and chronic alcoholism

Disease	Initial description	Clinical manifestations
Wernicke encephalopathy	1881, Karl Wernicke	Deterioration of higher functions including lethargy, amnesia, ophthalmoplegia, and ataxia
Korsakoff syndrome	1887; Sergei Korsakoff	Dementia with amnesia and confabulation
Pellagra	1735; Gaspar Casal	Dermatitis, diarrhoea, amnesia, hallucinations, and dementia
Beriberi	1642; Jacobus Bontius	Peripheral polyneuropathy including paraesthesia ('burning feet'), hypoaesthesia, paresis, muscle atrophy (especially in the lower limbs), oedema, and heart failure
Marchiafava-Bignami disease	1903; Ettore Marchiafava and Amico Bignami	Emotional lability, delirium, tremor, aphasia, ataxia, stupor, and dementia
Central pontine myelinolysis	1959; Raymond D. Adams, Maurice Victor, Elliott L. Mancall	Behavioural disorders, dysarthria, mutism, ophthalmoplegia, dysphagia, paraplegia or quadriplegia, convulsions, and coma
Neurological diseases due to vitamin B_{12} deficiency	1887; Ludwig Lichtheim 1900; J. S. Risien Russell, Frederick E. Batten and James Collier	Painful paraesthesia ('burning feet'), loss of vibratory and arthrokinetic perception, Babinski reflex, and hyperreflexia or areflexia when peripheral neuropathy is very intense. Less frequently, deterioration of higher functions and optic neuritis. Lesions in the posterior funiculi of the spinal cord and corticospinal tract, paraplegia.
Cerebellar cortical	1959; Raymond D. Adams, Elliott L. Mancall	Ataxia without upper-limb dysmetria, occasional nystagmus
Nutritional amblyopia	1914; Heinrich Bickel 1944; Raymond D. Adams and Charles S. Kubik	Optic atrophy, central scotoma, and decreased visual acuity. It may also be associated with polyneuropathy and Wernicke-Korsakoff syndrome.
Alcohol dementia	1939; Ferdinand Morel	Intention tremor, hand stereotypies, irritability, insomnia, rigidity and spasticity, and dementia. Selective lesion in the third layer of the cortex, especially in the frontal lobe.

Figure 1. Karl Wernicke (1848-1905)

Figure 2. Sergei Korsakoff (1853-1900)

Similar clinical features had already been reported: in 1868, Dardel had described an alcoholic patient with delirium tremens who presented diplopia.[4] In 1875, Gayet described a clinical case similar to WE, although findings from the anatomical pathology report showed larger lesions affecting the pineal gland, tegmentum, and the upper part of the pons.[5] French authors then started to use the term '*encéphalopathie hémorragique de Gayet-Wernicke*' to describe similar cases.

Several years later, in 1896, Gudden described five patients presenting alcoholic polyneuropathy and psychiatric disorders whose lesions affected the mammillary bodies, the walls of the third ventricle, and the brainstem. He underlined the resemblance between WE and Korsakoff syndrome based on lesion topography.[6]

In 1928, Gamper studied the clinical symptoms and the neuropathology of 16 long-term alcoholic patients presenting Korsakoff psychosis. He concluded that those symptoms were closely linked to polioencephalitis haemorrhagica superioris. The three patients who lived the longest had lesions in the mammillary bodies, which he connected to memory disorders. Gamper also documented lesions affecting the grey matter in the diencephalon, the wall of the third ventricle, the nuclei of cranial nerves III, IV, and VI, the dorsal vagal nucleus, the inferior colliculi, and the anterior commissure. That author also detected polyneuropathy in several patients.[3]

In 1936, Neubürger described clinical cases of WE in 14 non-alcoholic patients. Most of them had carcinoma of the stomach or another part of the digestive tract.[7] In 1939, Campbell and Biggart described the connection between WE and malnutrition, especially in patients with vitamin B_1 deficiency.[8]

Sergei Korsakoff (1853-1900) presented his doctoral thesis on alcoholic paralysis in 1887, six years after Wernicke's contribution appeared. Between 1887 and 1891, that author published six articles on alcoholic patients. In one of the articles, he described memory disorders, cognitive decline, and polyneuropathy. Korsakoff used the term 'polyneuritic psychosis' to designate this set of features. In some cases, he observed the presence of ophthalmoplegia, dysarthria, and nystagmus. However, alcoholism was not the only cause for these symptoms; they also occurred in other diseases involving vomiting and severe diarrhoea, such as puerperal fever and typhoid fever. The hypothesis of

a toxic aetiology led Korsakoff to name it 'toxaemic cerebropathy'.[3]

In 1901, Bonhoeffer described a series of patients presenting Korsakoff psychosis followed by WE and vice versa.[9] This observation was corroborated by Kant many years later, in 1933.[10] The study by Ecker and Woltman confirmed the hypothesis that nutritional deficiencies are the cause of WE.[11]

In 1947, De Wardener and Lennox published a study of 52 prisoners of war who developed WE associated with vitamin B_1 deficiency.[12] Not long after that, in 1953, Girard, Garde, and Devic established an association between the symptoms, neuropathology, and aetiology of Gayet-Wernicke encephalopathy, and those of Korsakoff psychosis and Marchiafava-Bignami disease.[13] Several years later, in 1956, Malamud and Skillicorn confirmed yet another connection between WE and Korsakoff psychosis. The authors performed anatomical pathology studies of 70 cases of Korsakoff psychosis, and their findings included 24 patients with cerebellar lesions and a considerable loss of Purkinje cells, especially in the vermis.[14]

In 1971, Victor, Adams, and Collins studied 245 patients with chronic alcoholism, of whom 82 underwent an anatomical study. The authors demonstrated the clinical and anatomical similarities between these patients and those with Wernicke-Korsakoff syndrome. Additionally, 90% of WE patients presented mental symptoms, and 80% had polyneuropathy. Likewise, as the symptoms improved, patients experienced amnesia and confabulation, which are characteristic of Korsakoff syndrome. The authors concluded that WE and Korsakoff syndrome constituted a single clinical entity whose features merged as the syndrome evolved. In fact, these two descriptions belong to a single syndrome currently known by the eponym Wernicke-Korsakoff syndrome.[3]

Pellagra

Pellagra was first described by Gaspar Casal (1680-1759) in the 18th century. All his findings were published in 1735 under the title *Historia natural y médica del principado de Asturias* (A natural and medical history of the Principality of Asturias).[15] Pellagra was originally called *enfermedad de la rosa* because of the reddened skin of erythema, a characteristic feature of the disease. The current term for the disease, pellagra, was coined several years later, in 1771, by the Italian physician Frapolli. It refers to the rough skin caused by the disease (in Italian, *pelle*, 'skin', and *agra*, 'rough').[16]

The clinical features of pellagra are glossitis, gastroenteritis, diarrhoea, and erythema on areas of the skin exposed to light. Dermatitis takes the form of scaling and hyperpigmentation in the affected area. Lesions can appear in a collar pattern around the neck; known as Casal's collar, this finding is pathognomonic for the disease. Neurological and psychiatric manifestations include polyneuropathy, tremor, ataxia, Babinski reflex and signs of spinal cord and peripheral nerve lesions; delirium and dementia appear only in advanced stages of the disease. Throughout the first quarter of the 20th century, pellagra was endemic to certain areas in South America, the Midwestern United States, and several regions in Europe. During World War II (1939-1945), numerous cases were registered in prisoner-of-war camps.[17]

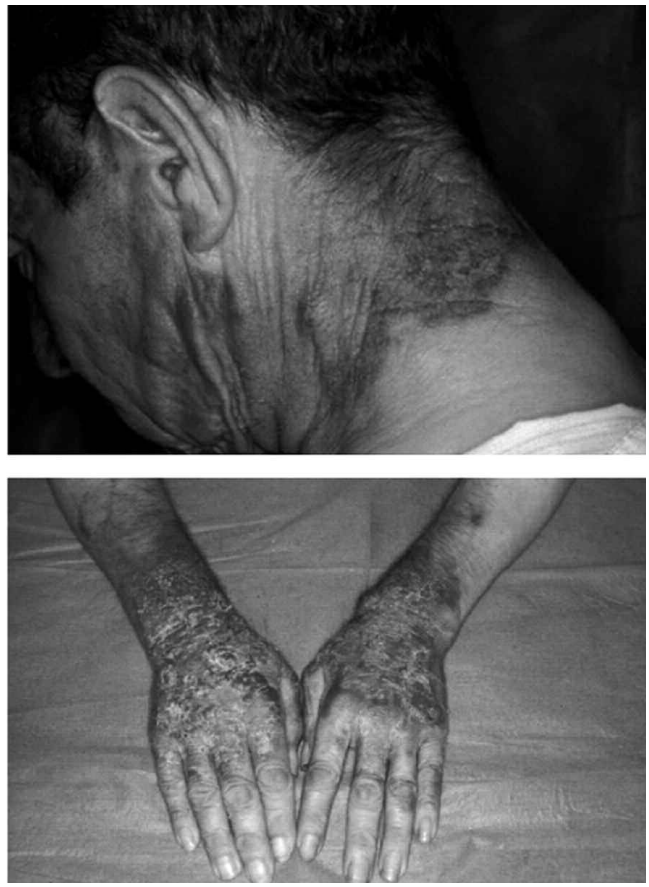

Figure 3. Two cases of pellagra. Images provided by Professor Castells.

Casal had suggested an association between pellagra and nutritional deficiency: "American corn or maize constitutes the staple diet for almost everyone with this disease...the people suffering this condition are poor farmworkers".[15] This hypothesis was confirmed in 1915 and 1920 by Goldberger and Wheeler, who completed two studies, in patients with dietary deficiencies[18] and in male convict volunteers.[19] Goldberger associated pellagra with black tongue, a canine disease similar to pellagra.

Leigh studied the psychiatric manifestations of pellagra and identified a group of psychoneurotic symptoms.[20] In 1940, Jolliffe, Bowman, Rosenblum, and Fein carefully studied the signs and symptoms of the disease. They described subacute presentation of diffuse brain lesions. Patients presented stupor, sucking and grasping reflexes, hearing loss, and retrobulbar neuritis. Most patients were elderly sufferers of some type of vascular disease, and they showed obvious signs of malnutrition.[21]

Clinical and psychiatric manifestations were studied and revised by Hardwick[22] in 1943, and Spillane's monograph on deficiency diseases is especially relevant.[23] Greenfield and Holmes studied patients with medullary lesions whose examinations revealed pyramidal syndrome, deep sensibility disorders, and symptoms of cerebellar dysfunction. Nicotinic acid administration elicited spectacular benefits in these patients.[24]

Pellagra results from low levels of nicotinic acid, a compound produced by the metabolisation of tryptophan in the intestinal tract.[25] In 1955, Rodnight and McIlwain described a set of clinical manifestations, including psychosis, indole-induced headache, photophobia, ataxia, and pellagra-like dermatitis.[26] In 1956, Baron et al. described hereditary pellagra-like features with aminoaciduria.[27]

Hersov and Rodnight definitively established the difference between pellagra and Hartnup disease in 1960. The disease was named after the Hartnup family, in which several cases of the disease had been described. It is caused by poor tryptophan absorption in the jejunum. Tryptophan is metabolised by colonic flora and transformed into indole compounds that are excreted in the urine, which leads to aminoaciduria. Since the tryptophan is not absorbed, it cannot be transformed into nicotinic acid. The resulting nicotinic acid deficiency has clinical features similar to those of pellagra. The formation of an argentaffinoma causes increased tryptophan metabolisation and nicotinic acid deficiency, a combination which gives rise to pellagra-like clinical features.[28]

Adolf Meyer completed one of the first pathology studies in 1901, and he described several degenerative lesions of the central nervous system.[29] These lesions were later confirmed by Leigh, in 1952. Leigh described lesions in Betz cells, pons nuclei, dorsal vagal nucleus, nucleus ambiguus, cuneate nucleus, gracile nucleus, the lowest portion of the trigeminal nucleus, and the oculomotor and vestibular nuclei. In some cases he discovered lesions in the cells of the anterior horn of the spinal cord.[20]

The most relevant neuropathological contributions were made by S.A.K. Wilson and presented to the Royal Society of Medicine in 1914.[30] Several years later, he published another comprehensive study on the same topic.[31] Wilson,[31] like Greenfield and Holmes,[24] described lesions in the posterior and lateral funiculi that affected the corticospinal and spinocerebellar tracts, as well as lesions in the anterior and posterior roots of the spinal cord and peripheral nerves. Severe lesions were found to involve both axons and myelin, whereas less evolved lesions affected myelin only.

Clinical features of pellagra associated with other B-vitamin deficiencies were observed among malnourished prisoners of World War II who participated in a study.[23]

Elvehjem, Madden, Strong, and Woolley cured black tongue in dogs by administering nicotinic acid and therefore concluded that nicotinic acid deficiency was the cause of pellagra.[32]

In 1955, Hicks demonstrated the presence of lesions in the ganglion cells, supra-optic nucleus, and pyramidal cells of Ammon's horn in experimental animals after administration of 3-acetylpyridine (a nicotinic acid antagonist). He also showed that those lesions did not develop when nicotinamide was administered.[33] In 1968, Truswell, Hansen, and Wannenburg found deficiencies of tryptophan and other amino acids in patients with pellagra. These authors found that pellagra could be caused not only by nicotinic acid deficiency, but also by destruction of the intestinal flora that metabolises tryptophan. They concluded that a third cause of pellagra was exclusive diet of maize with no tryptophan content.[34]

In 1968, Madhavan, Belavady, and Gopalan confirmed that nutritional deficiencies were one of the causes of the disease. Their study included numerous patients with pellagra from Hyderabad, in India, from a population whose staple diet was jowar (*Sorghum vulgare*), a type of millet containing little nicotinic acid and high levels of its antagonist, leucine.[35]

Beriberi

One of the first known descriptions of beriberi in Europe was written by Jacobus Bontius (1592-1631). This author compiled his experiences with tropical diseases in Java in a book which was published as *De Medicina Indorum*. Dated 1642, this treatise is regarded as the first one to address tropical medicine. Jacobus Bontius suffered from beriberi and was able to describe the clinical features of toxic/nutritional optic neuropathy, as it is known today.[36]

Beriberi was a well-known disease in the Far East. The name derives from the Sinhalese word for 'weakness', *beri*, and the repeated form means 'extreme weakness'. *Beri* may also derive from a Hindustani word meaning 'swelling' or 'sheep', as patients with beriberi display an insecure sheep-like gait. After World War II, many cases of beriberi were reported among prisoners of war in Asia and Europe.[36]

Malcolmson provided the first clinical descriptions of the disease in 1835, based on his experience diagnosing and treating several patients with beriberi in Madras (currently Chennai). Clinical symptoms appear progressively and include paraesthesia and lower limb pain, which sometimes resembles the pain of tabes dorsalis. Another frequent symptom is a burning sensation in the feet, which may extend to all four limbs at advanced stages. Other symptoms include distal paralysis, muscle atrophy, steppage gait, loss of reflexes, and decrease or loss of sensitivity.[37]

In 1897, Christiaan Eijkman (1858-1930) was posted to Batavia, a former Dutch colony currently known as Jakarta. He observed that chickens fed with polished rice suffered from beriberi, unlike those fed with brown rice. Eijkman thought that rice might contain some kind of toxic substance that was neutralised by the pericarp of brown rice. He found that brown rice prevented and cured beriberi in both chickens and humans.[38]

Growing clinical experience shed light on previously unknown features of beriberi, such as hoarseness, which is a less frequent symptom. Wright described a case of beriberi with aphonia. Autopsy revealed a large number of degenerated fibres in the left recurrent laryngeal nerve and, to a lesser extent, in the distal end of the vagus nerve.[39] Optic nerve degeneration as an early sign of the disease was reported by several Japanese authors, among them Hori (1888), Kono (1896), and Kagawa (1938).[40] The first descriptions of beriberi in children were presented by Hirota in 1897, in Tokyo[31]; in 1903, Wright also described acute cases of infantile beriberi which he called 'acute pernicious beriberi'.[41] Some years later, in 1958, Baron and Oliver described acute cases in adults and coined the term 'fulminating beriberi'.[42] Platt found severe protein and thiamine deficiencies in patients with fulminating beriberi.[43]

Dangerfield published a comprehensive monographic study of the symptoms and treatment of this disease in 1905. The autonomic nervous system is frequently compromised, and patients display hyperhidrosis, pupillary changes, and hypotension. When the heart is

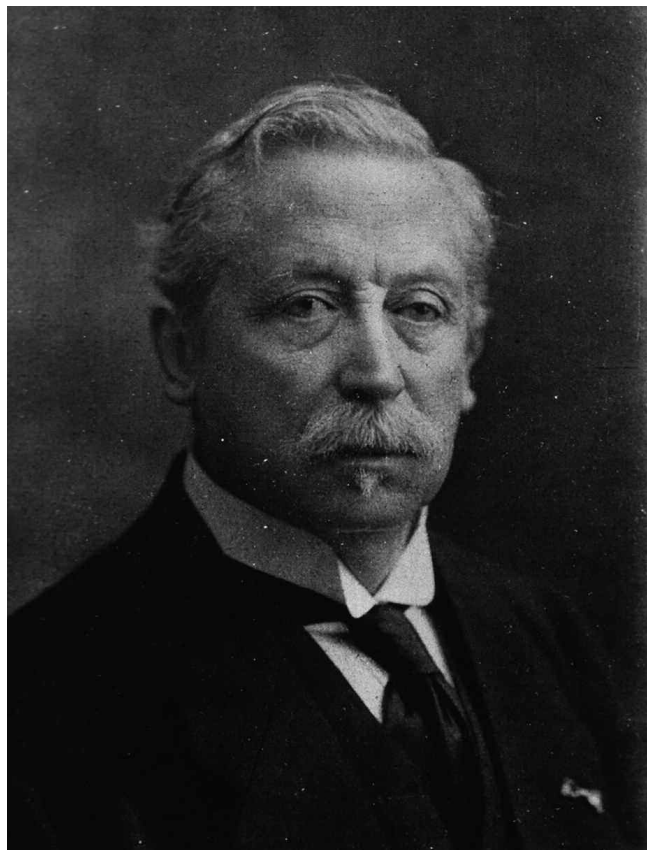

Figure 4. Christiaan Eijkman (1858-1930)

Figure 5. Casimir Funk (1884-1967)

affected, the patient experiences dyspnoea, tachycardia, palpitations, and oedema; these are features of what is called 'wet beriberi'. In contrast, 'dry beriberi' presents with mainly neurological symptoms. Acute forms of beriberi frequently cause death by heart failure. Early treatment results in nearly complete recovery. Otherwise, patients may present permanent sensory and motor deterioration.[44]

The study of beriberi led to the discovery of vitamins, termed 'accessory food factors' by English biochemist Frederick Hopkins (1861-1947). While working at Cambridge, Hopkins experimented with rats and noticed that a diet of artificial milk failed to support normal growth; additional substances, or accessory growth factors, were needed. He managed to isolate an active substance in the rice pericarp that cured beriberi. Casimir Funk (1884-1967) later termed these substances 'vitamines', as he thought that they all were amines, or compounds derived from ammonia.[38]

The term 'antineuritic vitamin' is a misnomer; vitamin B_1 deficiency does not cause beriberi unless there is an imbalance between vitamin B_1 and carbohydrates due to excessive carbohydrate intake. A total or relative deficiency of vitamin B_1 results in abnormal carbohydrate metabolism. This, in turn, leads to high concentrations of intermediate products, especially pyruvic acid, which have a negative impact on the nervous system.

In 1936, Williams and Cline synthesised vitamin B_1.[38] Platt in 1935 was the first researcher to find elevated pyruvic acid levels in the blood of patients with beriberi. His findings pointed to a link between carbohydrate metabolism and the disease when a pyruvic acid/ carbohydrate imbalance was present.[43]

The first neuropathological studies of beriberi, performed by Bälz (1882) and Scheube (1894), were frankly insufficient.[38] Chantemesse and Raymond presented more detailed observations in 1898, describing two cases in which they found peripheral nerve degeneration and vacuolation of the cells of the anterior horn of the spinal cord.[45] The most comprehensive neuropathological study was carried out by Greenfield, who described distal demyelination, occasionally with more proximal segmental demyelination. The same lesions were also found in the sympathetic nervous system. Cases of the disease in advanced stages display chromatolysis in the cells of the anterior horn of the spinal cord and those of the dorsal root ganglia, in addition to axonal degeneration in the posterior grey column of the spinal cord. More rarely, researchers may observe distal atrophy of the laryngeal nerves, occasionally with phrenic nerve degeneration. Greenfield described lesions in the spinal roots, dorsal root ganglion, posterior funiculi, and even the cells of the anterior horn. He stated that such lesions were secondary to dying-back degeneration of the peripheral nerve except for those resulting from a deficiency of other vitamins.[17]

In 1921, Buzzard and Greenfield studied several cases of heart disease, and found dilatation of the right cavities. Myocardial fibres were damaged and had been replaced by connective tissue. They also found oedema or anasarca (hence the designation 'wet beriberi'), congestion of the spleen, and chronic passive congestion of the liver.[46]

Marchiafava-Bignami disease

Marchiafava and Bignami described this disease in 1903, in their article '*Sopra una alterazione del corpo calloso osservata in soggeti alcolisti*'. Its symptoms were initially identified in Italian alcoholic patients who consumed a

specific type of red wine.[47] Clinical manifestations of Marchiafava-Bignami disease (MBD) included emotional lability, tremor, delirium, aphasia, cognitive impairment, stupor, coma, and death. Although the literature contains few studies on this particular topic, Bignami and Nazari observed identical brain lesions in different locations in 40 autopsied cases.[48] Cuban[49] and French[13] authors would later report similar findings in patients of non-Italian descent, but few cases seem to arise in the United States and the UK.

Marchiafava, Bignami, and later Mancall[49] suggested that long-term alcoholism was the cause of MBD. However, Gruner[50] and several Japanese authors[51] reported cases in non-alcoholic patients. In 1961, Ironside, Bosanquet, and McMenemey presented a literature review of 88 cases which led them to reconsider the racial incidence of the disease. Most patients showed signs of malnutrition, underscoring the connection between MBD and vitamin B_1 and other B-complex vitamins.[52]

The major finding in Marchiafava's anatomical pathology report was demyelination of the body of the corpus callosum. Axons were relatively well preserved and no inflammation was reported. Glial proliferation was more pronounced in the cases with longer survival times. In some cases, lesions extended to the chiasm, centrum semiovale, middle cerebellar peduncles, and neurons of the external pyramidal layer of the cerebral cortex.[53] Cases have been described in which MBD lesions appear with features of central pontine myelinolysis, and occasionally WE.[54,55]

Central pontine myelinolysis

Central pontine myelinolysis (CPM) was first described by Adams, Victor, and Mancall in 1959. These authors wrote:

> In the course of our studies of the neuropathology of alcoholism...two of us...observed three, perhaps four, cases in which the myelin sheaths of all the nerve fibers in the central part of the basis pontis had been destroyed in a single, large, symmetric focus. The nerve cells and axis cylinders were spared for the most part.... The disease had occurred on a background of alcoholism and malnutrition.... Case 1.–A chronic alcoholic entered the hospital with lobar pneumonia and delirium tremens. His symptoms were improving when...he developed flaccid quadriplegia, weakness of the face and tongue, and inability to speak and swallow. Death ensued on the 22nd hospital day....[56]

In 1977, Cambier et al. stated in their article that the disease was due to hyponatraemia caused by diuretic agents.[57] Burcar, Norenberg, and Yarnell reached similar conclusions regarding hyponatraemia.[58]

In 1980, Leslie, Robertson, and Norenberg studied 12 patients who had developed pontine myelinolysis due to a rapid increase in serum sodium concentration. However it was not hyponatraemia that caused the disease, but rather the rapid correction of that situation.[59] These authors reviewed 80 cases of hyponatraemia included in the literature; 51 of them underwent rapid correction of hyponatraemia and 22 showed neurological symptoms. Of the latter, 14 patients were diagnosed with CPM.

In 1983, Sterns, Riggs, and Schochet described 8 additional patients with hyponatraemia. Neurological disorder was present in two patients, the ones whose hyponatraemia had been corrected rapidly. The authors decided to term this disease 'osmotic demyelination syndrome'.[60]

Neurological diseases caused by vitamin B_{12} deficiency

The first descriptions of spinal cord diseases associated with metabolic pathways were provided by Hurst and Bell in 1922. These authors found that neurological symptoms were present in patients with achylia gastrica; low gastric acidity led to the proliferation of micro-organisms (especially streptococcus) in the digestive tract, by which route they could harm the spinal cord and the nervous system.[61] Some years before, in 1887, Lichtheim had described lesions in the posterior funiculi of the spinal cord in patients with pernicious anaemia, which were different from those of patients with tabes.[62] In 1917, Whipple managed to resolve anaemia in dogs by feeding them a raw liver diet.[63]

The first descriptions of anaemia-associated myelopathy were provided by Russell, Batten, and Collier in 1900. These authors used the term 'subacute combined degeneration of the spinal cord' to name the set of symptoms. However, they were not satisfied with that name and new designations appeared, such as 'funicular myelosis' and 'posterolateral sclerosis'. Although early observations linked spinal cord diseases to pre-existing anaemia, the authors soon found several cases of spinal cord disease in the absence of anaemia.[64]

Minot and Murphy were intrigued by anaemia, both with and without neurological signs. In 1925, following Whipple's observations, they treated patients with

pernicious anaemia with a diet rich in raw liver, which yielded impressive results. Minot and Murphy were jointly awarded the Nobel Prize in Medicine in 1934.[63]

In 1929, Castle found that gastric mucosa in anaemic patients secreted a factor that he called the 'intrinsic factor'. This factor, when combined with another present in food (or 'extrinsic factor'), elicited normal haematopoiesis and a properly nourished nervous system.[63] In 1948, the extrinsic factor was simultaneously isolated by Smith[65] and by Rickes, Brink, Koniuszy, Wood, and Folkers.[66]

In 1900, Russell, Batten, and Collier described the neurological symptoms, of anaemia which included paraparesis, paraplegia, loss of trunk and lower limb sensitivity, urinary incontinence, and sometimes trophic disorders. However, they found other cases in which neurological symptoms were not associated with macrocytic anaemia.[64]

In 1958, Richmond and Davidson stated that most cases of Addisonian anaemia were caused by polyneuropathy, although some cases were found in gastrectomised patients or those with gastric tumours, poor vitamin absorption due to intestinal diseases such as ileitis and gastric tuberculosis, or restrictive diet.[67] Richmond and Davidson described 10 cases of spinal cord disease with no anaemia. No autopsies had been performed on any of them. However, they later provided 3 additional cases including autopsy studies. As they presented neurological symptoms, the authors suggested the term 'vitamin B_{12} neuropathy'.[17]

In addition to pernicious anaemia, cases of myelopathy following partial gastrectomy were described by other authors including Olivarius and Roos.[68] In turn, Verjaal and Timmermans-van den Bos reported several cases of myelopathy in patients with dietary deficiencies.[69] Studies focusing on strict vegetarian patients have delivered contradictory results. Such diets are poor in vitamin B_{12} and low vitamin B_{12} levels have indeed been found in vegans; however, Wokes, Badenoch, and Sinclair described vegan patients with anaemia who did not present neurological symptoms.[70] In contrast, in 1954, Badenoch found neurological symptoms in a young vegan patient who later improved after vitamin B_{12} treatment.[71] In addition to medullary and polyneuritic symptoms, some authors have described cases of cerebral and optical nerve lesions. These findings are still subject to vigorous criticism more than 20 years later.

Visual disturbances caused by vitamin B_{12} deficiency were first described by Bickel in 1914.[72] In 1933, Benedict stated that 6% of patients with pernicious anaemia also suffered from retrobulbar neuritis.[73] The article by Adams and Kubik addressing this subject was decisive. Patients had scotoma, reduced perimetry, and papillary pallor.[74] According to Benham, visual field defects can at times precede manifestations of vitamin B_{12} deficiency in the spinal cord or peripheral nerves.[75]

Regarding psychological manifestations caused by vitamin B_{12} deficiencies, different authors express conflicting points of view. The first statistical data provided by Woltman[76] in 1924 and Goldhammer et al.[77] in 1934 differed considerably: psychiatric symptoms were reported in 4% to 64% of all patients with vitamin B_{12} deficiencies. Some years later, in 1960, Eilenberg conducted a critical study on the subject and established a list of requirements for psychiatric disorders to be considered linked to vitamin B_{12} deficiency: no prior history of psychiatric symptoms or premorbid personality traits, true psychiatric symptoms, pernicious anaemia, and recovery or improvement after treatment with vitamin B_{12}. Eilenberg found that these requirements were met by only 4 out of 20 patients admitted to a psychiatric hospital.[78]

Adams and Kubik studied the psychiatric complications of vitamin B_{12} deficiency. The neuropathological study showed multiple foci of perivascular demyelination in the white matter with reactive gliosis. These authors also found that psychiatric manifestations were frequently associated with spinal cord lesions.[74]

The study conducted by Herman et al. in 1937 provides useful data on vitamin B_{12} deficiency and mental changes. These authors found that 40% of patients with pernicious anaemia and mental symptoms also experienced symptoms of spinal cord disease.[79]

In 1956, Holmes studied 14 patients with pernicious anaemia and psychiatric symptoms. He found that all patients presented the same type of discrete spinal cord lesions, and one of them also presented epilepsy. After vitamin B_{12} treatment, 12 individuals showed substantial improvements.[80]

Russell, Batten, and Collier studied the anatomical pathology of the disease and found that lesions were located in the middle thoracic region of the spinal cord. The bundles of the posterior and lateral columns of the spinal cord presented demyelination. In contrast, only the

fibres of the posterior funiculi and spinocerebellar bundles were demyelinated in the superior spinal cord. Exceptionally, pyramidal tracts degenerated in the medulla oblongata. Axons displayed degeneration at a later stage. In advanced stages, researchers observed ruptures of the myelin sheaths and axon loss that left free spaces and gave the bundles a vacuolated appearance. Wallerian degeneration of the spinal cord bundles was more prominent in the cervical and lumbar regions. However, spinal grey matter, meninges, and nerve roots presented minimal lesions.[64]

While Adams and Kubik had already described perivascular demyelination foci in the central nervous system,[74] one of the first studies addressing lesions in the peripheral nervous system was conducted by Russell, Batten, and Collier. Their study found scarce lesions in the peripheral nervous system, but it did identify distal degeneration of nerve fibres, especially in muscle, in patients with a prolonged history of the disease. Greenfield and Carmichael studied smaller peripheral nerves of the skin, especially at the level of the anterior tibial nerve, and found a marked decrease in the number of myelin sheaths.[81]

There are discrepancies with regard to the pathogenesis of neurological symptoms in vitamin B_{12} deficiency. The outstanding study by Cox and White[82] suggests that myelopathy is caused by the toxic effect of methylmalonic acid accumulation. Large amounts of this acid are excreted in the urine, but it also accumulates in the peripheral nerves in the case of vitamin B_{12} deficiency. Other authors, such as Wilson and Langman, underscore a connection between cyanide metabolism and detoxification and vitamin B_{12}. They also recognise that, in certain cases (for example, tobacco use), vitamin B_{12} deficiency facilitates cyanide's toxic effect on the nervous system.[83]

Cerebellar cortical degeneration

The most comprehensive study on cerebellar cortical degeneration (CCD) was conducted by Victor, Adams, and Mancall in 1959.[84] These authors described 50 chronic alcoholics with cerebellar syndrome; neuropathology studies were available in seven cases. All patients presented ataxic gait, changes in bipedal position, and dysmetria on the heel-to-knee test. There was relatively little impairment of upper-limb function, speech, or ocular motility, and most patients did not present nystagmus. Patients were classified into three groups according to how the disease had progressed. Patients in the first group had presented clinical symptoms within weeks or months, after which the disease remained stable for years. Patients in the second group experienced gradually progressing symptoms over several years, which later stabilised. The third and least numerous group was characterised by a stable condition with periodic exacerbations, usually occurring with intercurrent processes. Exacerbations were followed by partial recovery.

Anatomical pathology findings included degeneration of neurons in the cerebellar cortex, especially Purkinje cells. Lesions were limited to the anterior areas of the cerebellar hemispheres and vermis. The authors found much less pronounced loss of Purkinje cells in the brains of four 70-year-old patients used as a control sample. There were lesions in the olivary body and, to a lesser extent, in the fastigial, globose, emboliform, and vestibular nuclei. Spinocerebellar bundles and white matter in the peduncles and both hemispheres showed no lesions. In addition to cerebellar lesions, five patients showed polyneuropathy, four presented lesions specific to WE, and six displayed hepatic encephalopathy.

The authors pointed to the precise clinical and pathological correlation based on previous findings on cerebellar somatotopy. They also examined several possible aetiological factors, especially alcohol consumption and nutritional deficiencies, and described complex situations, including the example of six patients who presented symptoms of CCD several weeks after completely discontinuing alcohol use. Doctors observed malnutrition in 16 patients in the first consultation, while others had had a poor diet for several years before onset of CCD, and a third group of patients presented clinical symptoms after having eliminated alcohol and improving diet.

Taking into account the long-term alcohol consumption and slow progression of clinical symptoms, the authors concluded that these patients exhibited a specific clinical-pathological entity. However, they placed more emphasis on nutritional deficiencies than on alcohol abuse, even if they suggested that alcohol might directly affect cerebellar atrophy.

Victor, Adams, and Mancall also conducted a review of the literature on cerebellar disorders in which neuronal degeneration occurred exclusively or predominantly in the cerebellum. In addition to the studies included in the review, they mentioned the paraneoplastic cerebellar degeneration described by Brain and Henson in 1958,[85]

hereditary cerebellar degeneration illustrated by Mathieu and Bertrand in 1929,[86] and patients with atrophy but no family history of the disease, as presented by Thomas[87] in 1905 and Lhermitte in 1922.[88]

Cases of non-alcoholic patients with cerebellar atrophy have also been published. We should mention the patient with chronic dysentery described by Houssiau in 1930.[89] Mancall and McEntee highlighted the role of nutrition in cerebellar atrophy. In their article they described a 18-year-old male with no prior history of alcoholism who presented symptoms of malnutrition due to congenital volvulus. The patient showed clinical and neuropathological signs of WE and cerebellar cortex degeneration was identified in the anatomical pathology study.[90]

Nutritional amblyopia

Alcoholism has historically been considered a cause of visual impairment. One of the first contributions to this field is owed to Bickel, who described optic nerve lesions, myelitis, and polyneuropathy.[72] In 1934, Benedict and Wagener found optic neuritis in 6% of patients with pernicious anaemia.[91] Some years later, in 1944, Adams and Kubik studied these symptoms more exhaustively and concluded that the cause was vitamin B_{12} deficiency and tobacco consumption.[74]

Amblyopia is characterised by difficulty distinguishing red and green. Patients experience decreased visual acuity and bilateral scotoma without loss of visual field. Temporal pallor of the optic disk is typical. The anatomical pathology study shows axon demyelination, gliosis in the optic nerve and chiasm, and neuronal loss in the lateral geniculate nucleus. In some cases, cell degeneration in the macular region has also been described. Several patients with amblyopia also display lesions characteristic of Wernicke-Korsakoff syndrome and polyneuropathy.

In 1958, Heaton et al. reported that some patients with amblyopia also presented vitamin B_{12} and riboflavin deficiencies.[92] In 1961, Freeman and Heaton postulated that optic neuritis in conjunction with pernicious anaemia was caused by tobacco use, given the cyanide content of that substance. These authors found that patients with amblyopia improved significantly after treatment with B-complex vitamins, even if tobacco and alcohol use continued. Tobacco and alcohol were therefore relegated to a secondary role within the aetiology of the disease in these patients.[93] These findings 'restored' the article published by Carroll[94] in 1936 addressing the aetiology of nutritional amblyopia.

In a more recent review, Mancall[49] supported the nutritional aetiology of tobacco-alcohol amblyopia, stating that the disease is caused by vitamin deficiencies.

Alcoholic dementia

Encephalopathies secondary to alcoholism can be divided into WK syndrome, pellagra, Marchiafava-Bignami disease, and encephalopathy secondary to beriberi on the one hand, and alcohol dementia not associated with any other similar encephalopathies on the other.

Morel was the first author to investigate this topic.[95] In 1939, he described the symptoms and anatomical pathology of four patients experiencing intention tremor, hand stereotypies, mumbling, writing disorders, depression, irritability, insomnia, oneirism, disorientation in time and space, weight loss, anorexia, decreased strength and muscular flexibility, rigidity and spasticity, absent or increased Achilles reflexes, episodes of acute alcohol intoxication, and minor delirium tremens.

Macroscopic post-mortem examination revealed meningeal thickening and enlargement of the ventricles, which Mott[96] had already described in 1910. Microscopic examination also showed glial hyperplasia and neuronal cell loss in different brain regions. Morel described these findings as cortical laminar sclerosis in the third layer of the cortex, especially in the frontal lobe.

In 1989, Charness et al.[97] found neuronal cell loss in the nucleus basalis of Meynert in patients with alcohol dementia, although these findings were not confirmed by subsequent studies. Even today, the aetiology of the lesions found in patients with alcohol dementia is a topic for debate.

Conclusions

A number of syndromes once considered to be separate clinical entities have been grouped together, as in the case of Wernicke-Korsakoff syndrome. However, some patients may present clinical and pathological manifestations of multiple entities, as in the case of nutritional amblyopia, which can present with typical Wernicke-Korsakoff lesions. The clinical features described here confirm that interdisciplinary studies are needed in order to gain a better knowledge of these entities.

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