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A historical approach to hereditary spastic paraplegia

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ABSTRACT

Hereditary spastic paraplegia (HSP) is a group of rare neurological disorders, characterised by their extreme heterogeneity in both their clinical manifestations and genetic origins. Although Charles-Prosper Ollivier d’Angers (1796–1845) sketched out a suggestive description in 1827, it was Heinrich Erb (1840–1921) who described the clinical picture, in 1875, for “spastic spinal paralysis”. Jean-Martin Charcot (1825–1893) began teaching the disorder as a clinical entity this same year. Adolf von Strümpell (1853–1925) recognised its hereditary nature in 1880 and Maurice Lorrain (1867–1956) gained posthumous fame for adding his name to that of Strümpell and forming the eponym after his 1898 thesis, the first review covering twenty-nine affected families. He benefited from the knowledge accumulated over a dozen years on this pathology by his teacher, Fulgence Raymond (1844–1910). Here I present a history across two centuries, leading to the clinical, anatomopathological, and genetic description of hereditary spastic paraplegia which today enables a better understanding of the causative cellular dysfunctions and makes it possible to envisage effective treatment.

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1. Introduction

Spastic paraplegias are a large group of rare inherited neurological disorders that share the primary symptom of walking difficulties due to muscle weakness and muscle tightness in the legs. As for other diseases of the nervous system, they were described throughout the 19th century, mainly in France, England and Germany. Benefiting from advances in the understanding of medullary physiology, clinicians gradually learned to identify the various causes of spinal cord diseases, including infectious (tuberculosis, syphilis), vascular, carcinogenic, and structural (syringomyelia, degeneration) causes, or those secondary to nutrient deficiencies. We start with a discussion of how a hereditary pathology, referred to as spastic paraplegia, was recognised, notably by Adolf von Strümpell in 1886.

2. Foundations: 1820–1876

Reading the thesis of Antoine-Barthé Clot, known as Clot-Bey (1793–1868), defended on 24 July 1820 and entitled Recherches et observations sur le spinitis ou inflammation de la moelle épinière (Research and observations on spinitis or inflammation of the spinal cord) [1], one cannot help but
agree with the comments of Charles-Prosper Ollivier d’Angers (1796–1845) in the introduction to his own thesis, entitled Essai sur l’anatomie et les vices de conformation de la moelle épineuse chez l’Homme (Essay on the anatomy and conformational defects of the spinal cord in humans) [2]. Ollivier d’Angers argued that “most spinal cord diseases were observed by physicians in antiquity [Hippocrates and Galen]; this aspect of pathology has remained more or less the same since that time”. In 1818, John Abercrombie (1780–1844) in Edinburgh published Observations on the Diseases of the Spinal Marrow [3]. He also limited himself to describing “the inflammation of the spinal marrow” and “the softening of the spinal cord”, disturbances which seem to have been infections, probably syphilitic or vascular conditions.

Ollivier d’Angers can be considered a pioneer in his attempt to comprehensively understand the embryology, anatomopathology, and nosology of spinal pathologies on the whole [4]. Among other coinages, we owe him the word “syringomyelia”, even though he did not really describe the disease [5]. After defending his thesis on 12 June 1823, he published an expanded version in 1827, a true treatise on spinal cord diseases [6] that was further expanded and published in a new edition in 1837 [7], making the French translation of Abercrombie’s book by Augustin-Nicolas Gendrin (1796–1890) obsolete when it was released in 1832.

In the section on chronic myelitis, Ollivier d’Angers presented a clinical picture suggestive of spastic paraplegia: “These patients have a characteristic gait: they struggle to lift their foot from the ground, and in their effort to lift it entirely and move it forward, their trunks straighten and are thrown back, as if to offset the weight of the lower limb, which shakes involuntarily before it is returned to the ground. In this progression, the front tip of the foot can be either lowered, dragging more or less against the ground before lifting from it, or raised suddenly at the same time the foot bends toward the outside [...]. When the paralysis has existed for some time, ordinarily the affected limbs stiffen and retract little by little, remaining in a permanent contraction that it is difficult to overcome”.

In a December 1875 lesson, Jean-Martin Charcot (1825–1893) reviewed this initial clinical description that he taught under the term “spasmodic dorsal tables” [8]. The word “tables,” meaning “disintegrate” in Latin and a synonym of “phthisis” in Greek, was purely descriptive of the macroscopic appearance of the spinal cord and gave no indication of aetiology. Charcot credited his German alter-ego in Heidelberg, Heinrich Erb (1840–1921), with the initial term “spinales Symptomencomplex” and with the complete description shortly before Charcot’s lesion [9]. Based on sixteen observations he had compiled, Erb baptised as “spastischen Spinalparalyse”, or “spastic spinal paralysis”, a gradually progressing association of symptoms with “growing weakness in the lower limbs, later invading the upper limbs [...]. There are multiple spasmodic phenomena which consist in more or less pronounced rigidity of the limbs with spontaneous jerking, tonic contractions, initially temporary, and clonic shaking in the lower limbs [...]. Their gait is hesitating and slightly vacillating. The soles of the feet stick to the ground and the patient drags his leg as he walks, which he does with small steps, keeping the legs held closely together. The front tip of the foot collides with the slightest obstacle [...]. The tendon reflexes are almost always exaggerated” [10].

For Charcot, this condition points to “an undeniable organic substratum, an anatomical lesion at a more or less deep location in the spinal cord. It is also certain that this lesion specifically affects the lateral spinal tracts”; he had previously referred to “symmetrical and primitive sclerosis of the lateral tracts of the spinal cord” [11]. The clinical manifestations enabled him to eliminate amyotrophic lateral sclerosis, “common transversal myelitis”, and multiple sclerosis. The absence of searing pain, motor incoordination, amblyopia, and so forth also eliminated the diagnosis of locomotor ataxia as described by Guillaume Duchenne de Boulogne (1806–1875). Charcot used this lesson to teach his students “spontaneous or provoked tremor”: brought about “by raising the front tip of the foot or the ends of the toes”. Unlike Erb, he did not observe any sensory disturbances. With his gift of expression, he described the difference between this tabes and ataxia as follows: “In spasmodic tabes there are not these excessively flexible limbs, sometimes seeming dislocated, which give the ataxic’s gait its special hallmark”. Finally, the inexorable ascending progression, with muscular trophicity maintained, completed the clinical picture described by Charcot, who, in December 1875, did not indicate the age of onset or the role of heredity, even though heredity was, according to him, the cause of most diseases affecting the nervous system.

As was his habit for subjects under exploration but not totally elucidated, Charcot suggested to one of his students, Isidore Bérous (1852–?), who was from Caupenne d’Armagnac in southwest France and would go on to work in the Barèges thermal treatment centre [12], that he use this topic for his thesis. On 18 May 1876, Charcot presided over the defence of the thesis [13], entitled Étude sur le tabes dorsal spasmodique. Based on four detailed observations, Bérous presented the clinical information exactly as Charcot did in his lesson, highlighting the differential diagnostic criteria for locomotor ataxia and multiple sclerosis. His view of the prognosis was rather positive, given the very slow and long progression. As none of the four patients had died, Bérous made no anatomopathological argument to support Charcot’s hypothesis of lateral column damage. The following year, Erb added nineteen other purely clinical observations, still awaiting anatomopathological confirmation of localisation in the lateral column [14]. After these publications and until World War I, the synonym “Erb-Charcot paralysis” was in current use, replacing spasitic spinal paralysis, but was most often used incorrectly to refer to a rare form of neurosyphilis. Charcot had nonetheless clearly indicated that spasmodic dorsal tabes was “fundamentally distinct from all other forms of chronic myelitis”.

3. Doubts and uncertainties: 1880–1885

In 1883, Adrien Proust (1834–1903) identified “spasmodic spinal lathyrism”, after having observed, while travelling, an epidemic of spasmodic paraplegia “in an indigenous population” that he linked to the consumption of a supposedly toxic plant (lathyrus cicera) following a famine in Kabylia. His colleague at the Académie de Médecine, Alfred Le Roy de Méricourt (1825–1901), correctly considered these cases to be
beriberi; Proust admitted he knew nothing about this disease. The idea of vitamins and vitamin deficiency was still unknown [15].

Fernand Jubineau (1858–1943), in his 1883 thesis, reported observing spasmatic dorsal tabes with sclerosis in the lateral columns, illustrating the hypothesis of Charcot and Erb [16]. But the paraplegia had been preceded by delirium, suggesting syphilitic general paralysis instead, as Karl Friedrich Westphal (1833–1890) had reported several times before him [27].

In 1885, Fulgence Raymond (1844–1910) [18] authored the “spasmodic taws” entry of the Dictionnaire encyclopédique des Sciences médicales [19]. He admitted right away that “this name is the source of unfortunate confusion” between syphilitic tabes and spastic spinal paralysis due to other causes. The confusion was aggravated by the absence of specific anatopathological features, such as primitive sclerosis in the lateral columns, as assumed by Erb and Charcot. Raymond listed multiple sclerosis, “diffuse myelitis”, amyotrophic lateral sclerosis, hysteria, and childhood spastic paralysis (Little’s disease) as liable to be confused with the initially described pure form, the aetiology of which remained a mystery for him. He expressed doubt regarding the results of a few published anatopathological examinations which, for the most part, did not describe the expected sclerosis in the lateral columns. For example, in her first publication, as an externe under Alfred Vulpian (1826–1887), Augusta Klumpke (1859–1927), future wife of Jules Dejerine (1849–1917), found the spinal cord to be normal at autopsy in a paraplegic woman with contraction, qualified as hysterical and which had progressed over several years [20].

In summary, cases of spastic paraplegia up to 1885 were never attributed to heredity and were, for the most part, very likely secondary to syphilis.

4. Adolf von Strümpell: 1886

In 1880, Adolf von Strümpell (1853–1925) published the first observation of hereditary spasmatic paraplegia in two brothers of the Gaum family in Estonia. In the older brother, onset was at around age 56 with slow progression [21]. The younger brother developed a pure form of the disease at around age 37 and died of tuberculosis at age 61. Strümpell published his autopsy in 1886: the spinal cord was normal to the naked eye, but under the microscope, in the dorsal and lumbar regions, there was “primitive combined sclerosis of the pyramidal tract, spino-cerebellar tract, and Goll tract (gracile tract)” in the absence of any cerebral anomaly [22]. He likened his results to those published by Raymond in 1882 [23], Jubineau in 1883, and Johannes Naef (1863–1915) in Zürich. In his 1885 thesis on Little’s disease, directed by Oscar Wyss (1840–1918), Naef relates the story of three brothers with isolated spasmatic paralysis [24]. In 1893, Strümpell added new data after examining a 27-year-old man whose brother, father, grandfather, and two uncles had spasmatic paraplegia, without sensory or sphincteric disturbances [25]. In this last publication, he stressed his certainty that the condition was hereditary. Otto Adolph Seeligmüller (1837–1916) had long claimed he had provided the first description, in 1876, but the muscular atrophy and medullary paralysis he described in three brothers is not part of the clinical picture for pure spasmatic paraplegia [26].

In 1891, the German Martin Bernhardt (1844–1915), a student of Rudolf Virchow (1821–1902) and known for having described meralgia paresthetica, reported the history of a family where, of eight children, four were affected after age 30 and two others died before this age, suffering from spasmatic paraplegia with medullary deficits and muscular atrophy [27]. The following year, Richard von Krafft-Ebing (1840–1902) in Vienna added a series including two boys and one girl with spasmodic paraplegia [28]. In 1897, Ernő Jendrassik (1858–1921) in Budapest compared three families with consanguinity, in which several adolescents had spasmodic paraplegia associated with ocular paralysis and cognitive impairment [29].

Raymond’s lesson on 18 January 1895 covered “spasmatic taws”, faithfully keeping the name given by his teacher, and presented his audience with “two familial cases of childhood spasmotic paraplegia” [30]. He drew much material from the recent publication of his senior resident, Achille Souques (1860–1944), in La Revue Neurologique, for the clinical description of the two cases [31]. Focused on his responsibility as a teacher, a role he enjoyed, his main goal was to show how to distinguish this new nosological entity, still uncertain for him, from Little’s disease. This lesson also served as an introduction to his subsequent lessons on “heredity in nervous pathology”. In 1895, Raymond and Souques observed another family in which two sisters suffered from spastic paraplegia (Fig. 1). They compared their observation with those already published, which they accorded little credit, believing them to be “based on diagnostic errors!” Here are some of their own conjectures: “Spasmotic paraplegia could be considered a disease of the centrifugal protoneuron […] It is possible that the degeneration starts in the lumbar region, then reaching the dorsal and cervical regions; that it thus resembles ascending sclerosis, less evident in the cervical region than in the subjacent regions; and that it ascends more or less according to the resistance of the pyramidal fibres and the duration of the disease” [32]. They also referred to “an innate fragility of the centrifugal protoneuron which may begin to degenerate at its spinal extremity, i.e. at its least nourished, weakest part […]. The longest fibres would appear to be affected first.” They classified this entity alongside Friedreich’s ataxia. Another idea they had was that the predisposing factor was “conception of the child in a state of inebriation”.

In 1895, Giulio Melotti (1857–?), student of Charcot and of Ignazio Cantalamessa (1855–1896), a professor of pathological anatomy in Bologna, published cases observed in a family of ten children, eight of whom reached adulthood. Among them, two boys and a girl had spasmotic paraplegia [33].

In 1896, Charles Achard (1860–1945) and Henri Fresson (1870–1942) also identified two affected sisters, part of a large family where more than half of the children died at a young age from infectious diseases [34]. The progression was typical. Achard and Fresson suggested that disease onset occurred shortly after an infectious disease, smallpox and measles for their patients. Raymond challenged this hypothesis based on his own cases.

In most publications mentioned above, the authors refer to Sigmund Freud (1856–1939) for his numerous publications on “spastic diplegia or Little’s disease” [35–37], a pathology that was then considered for differential diagnosis, as was multiple
sclerosis. In fact, Little’s disease has nothing to do with HSP, being a form of dystonic diplegia due to lesions in the basal ganglia.

In his lessons on spinal cord diseases published in 1892, Pierre Marie devoted two of them to “spasmodic dorsal tubes”. According to him, only Little’s disease could cause this spasticity in the lower limbs, and he seemed unaware of the hereditary nature of the disturbances [38]. When Édouard Brissaud (1852–1909) temporarily occupied the Chair of Nervous System Diseases after Charcot’s death, he focused a lesson on amyotrophic lateral sclerosis or “Charcot’s disease”. At the end, he explained how Strümpell let him examine the slides of a deceased patient: “What is undeniable is that the degeneration of the spinal cord and capsule occupies precisely the pyramidal tract region. And the clinical history of this patient is that of an eminently progressive disease. His rigidity did not occur in a predetermined time, as if it were a secondary hemiplegic double contraction. The spasmodic phenomena generalised gradually and very slowly” [39].

5. Maurice Lorrain: 1898

Maurice Lorrain (1867–1956), who passed the residency examination in 1893 in the same class as Léopold Chauveau (1870–1940), was the son of a Parisian lace dealer (Fig. 2). His posthumous fame, based solely on the eponym associating his name with Strümpell, faded as this way of naming diseases stopped being used. He was Pierre Marie’s resident in 1894. After working under Raymond as an externe, he was his resident in 1897. Raymond gave him his thesis subject, the study of hereditary spasmodic paraplegia, and presided over his defence on 3 March 1898 (Fig. 3) [40].

This thesis was the first review of the subject, bringing together clinical aspects as Charcot and Erb had established them, and a demonstration of hereditary aspects through the comparison of twenty-nine observations. “The laws of heredity are still too mysterious for us to attempt a study”. As a result, Lorrain did not use the term “hereditary disease” but rather “familial disease”, the characteristics of which were, according to Léon-Charles Pauly (1870–1936) and Charles Bonne (1872–?), as follows: “Without changing form, it must affect several children of the same generation, start at around the same age in all children of this generation, be clinically independent from any outside influence, from an acquired condition or intrauterine accident; these various characteristics must be the rule and not the exception” [41].

After a review of previous publications from which he excerpted twenty-three observations of spasmodic paraplegia, Lorrain added six personal observations, including one of two sisters, recorded at Hôpital Saint-Antoine by Georges Gilles de

Fig. 1 – Two sisters examined by F. Raymond and A. Souques in 1896 (OW Collection).
la Tourette (1857–1904). He considered only one aetiology: heredity. Girls and boys could be affected, with the onset most often between age 8 and 15. A trauma or infectious disease seemed to be the notable aggravating factors, but motor difficulties preceded them.

Lorrain detailed the clinical aspects, highlighting clubfoot (Fig. 4), the absence of sensory deficit, incoordination, speech difficulties, sphincteric problems, trophic problems, and cognitive impairment. Currently, the dynamic nature of spasticity (exaggerated in standing position, reduced in prone position) is used to distinguish HSP from multiple sclerosis, where spasticity is permanent. Lorrain had already noted this: “Very marked flexion of the feet, such that the foot during walking can only rest on the toes, since the heal is raised a few centimetres from the ground. Sometimes, after a few seconds, this spasmatic state partially ceases, the muscles relax, and the foot can gradually come to rest completely on its sole”.

The progression of the disease is irregular and very slow, alternating between periods of aggravation and stability. Lorrain distinguished two forms: “One resembling spasmatic tabes, the other multiple sclerosis”. To this day, clinicians are always aware of the differential diagnosis.

He reviewed in detail the result of the autopsy of Strümpell’s patient before presenting the one he carried out with the help of Claudien Philippe (1866–1903): “There are lesions along the full length of the spinal cord, from the medullary cone up to the medulla. These lesions are clearly predominant in the white matter (anterolateral columns and posterior columns); they consist in more or less sclerotic areas”. He also described the colours used to bring out the details: “Slightly sclerotic nodular location: certain nervous tubes often have a dilated sheath, sparsely myelinated and slightly yellowed by picrocarmin; the nerve fibre is small, poorly coloured, often at the periphery of the sheath…” (Fig. 5).

With spasmotic paraplegia, differential diagnosis should eliminate compression from a spinal tumour, vertebral metastasis, and Pott’s disease. The presence of pain and of sensory and sphincteric disturbances are the clinical elements that enable diagnostic certainty. Gilles de la Tourette [42] and his senior resident Georges Gasne (1868–1910), the latter in his 1897 thesis [43], raised the difficulty of clinically distinguishing hereditary spasmatic paraplegia from spinal syphilis after intrauterine fetal infection, with manifestations during childhood (sphincteric disturbances only in the case of syphilis). Aside from infectious or toxic myelitis (Lorrain included pellagra and beriberi), two diagnoses to eliminate right away were syphilitic paraplegia, on which Jules Sottas (1866–1945) [44] wrote his 1894 thesis [45], and multiple sclerosis. Strümpell had suggested multiple sclerosis upon seeing the first of the Gaum brothers: “Spasmotic paraplegia always has a familial characteristic; until now, it has been the exception for multiple sclerosis”. Lorrain proposed that differential diagnosis involved multiple sclerosis and Friedreich’s ataxia.

Lorrain admitted that unfortunately he could not provide any anatomopathological proof. The treatment he proposed amounted to hot baths and massages. As a last resort and for reasons of hygiene, he suggested “tendon section, or even section of the obturator nerve, resulting in paralysis of the adductors”.

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Fig. 2 – At La Salpêtrière in 1898: Henri Herbet (1873–1909) is standing on the left and Maurice Lorrain on the right. Raymond Cestan is seated on the left and Paul Froussard (1870–1927) on the right (OW Collection).

Fig. 3 – Cover of Lorrain’s thesis (OW Collection).

In 1888, after Strümpell’s seminal publication of the case of two brothers, the observations compared by Lorrain and indirectly, through him, by Raymond, who had been interested in this pathology for more than ten years, confirmed the “hereditary essence” of Charcot’s spastic paraplegia and Erb’s spastic paraplegia. In 1886, Dejerine had briefly mentioned heredity in “spastic dorsal tubes (Erb, Charcot)” in his agrégation thesis, L’hérédité dans les maladies du système nerveux, referring to the study of a family of seven children, three with paraplegia, and a fourth with “locomotor ataxia with epilepsy”, reported by Ernst Bloch in Germany in 1881 [46].

The paediatrician Samuel Jones Gee (1839–1911), who described celiac disease in 1888, is credited with reporting the first series of three children of the same family with spastic paraplegia in Great Britain in 1889 [47]. In 1893, Léo Newmark (1861–1943) in San Francisco observed two affected families. In the first, a 15-year-old girl, a 5-year-old boy, and their cousin had gait problems characteristic of isolated spasticity in the lower limbs. In the second family, with eleven children, eight survived, including seven boys and girls with clinical spasticity or exaggerated reflexes with spinal tremor. Newmark compared this hereditary feature to that of Friedreich’s ataxia and Huntington’s disease [48].

In 1897, W. D. Bayley, in the US, mapped out the genealogical tree of a family affected over five generations [49]. On 2 March 1905, Valentin Magnan (1835–1916) and his resident Félix Dreyfus-Rose (1877–?) presented to the Société de Neurologie of Paris a family with three affected members, having “a familial spastic condition with spinal and medullary symptomatology”, contraction of all four limbs, cerebellar syndrome, and “dazed, inert physiognomy and physiognomy of crying”, which they included in “familial spastic conditions”; that is, complex HSP [50]. In 1907, Ernst Jones (1879–1958) reported on the largest affected family, with eight sick boys and one healthy girl. Their parents were healthy and not blood relatives. The disease started in all the affected children around age 2. They showed the hallmark symptoms, with involvement of only the lower limbs [51]. Once again in 1909, Raymond and Rose published an observation of a family with the same clinical picture, spanning three generations [52].

In 1922 in Germany, F.W. Bremer was able to cover six generations, suggesting the dominant character of transmission [53]. In 1916, John Rhein, a neurology professor in Philadelphia, compared all literature up to that point (111 families) and showed the heterogeneity of the forms of HSP within the same family, some patients having retinal degeneration, others extrapyramidal syndrome or dementia [54].

In 1909, Dejerine and André Thomas (1867–1963), in their treatise on spinal cord diseases, seemed to doubt the reality of this disease, oscillating between cerebral palsy (Little’s disease [55,56]) and multiple sclerosis, adding that involvement “in several members of the same family does not necessarily prove the existence of a special familial condition” [57].

The medical literature gradually added to the number of families described during the following half-century without improving pathophysiological knowledge of HSP [58,59]. This included a vast review by Gabriel Schwartz in 1952 [60]. Another example is Edwin R. Bickerstaff (1920–2008) who, in 1950, examined a large family with seventy-six members over four generations, twenty-seven of whom had HSP. He noted the consistency of the clinical picture over the first three generations and the occurrence of retrobulbar neuritis in the fourth generation [61]. Genetics only really started to emerge in literature reviews in the 1970s [62,63].

7. Current state of knowledge: era of genetics

Epidemiological data on hereditary spastic paraplegia are scarce. Highly variable prevalence values for HSP are reported across the world. This variation reflects the different genetic
make-up of different populations, but also methodological heterogeneity. From the available data, around 1:10,000 people are affected by HSP. In spite of advances in genetic research, most families in population-based series remain without identified genetic mutations after extensive testing [64].

HSP are characterised by extreme heterogeneity both in their clinical manifestations (increasing motor weakness and progressive spasticity) and their genetic origins. The pure form is characterised by pyramidal signs, i.e. weakness, spasticity, brisk tendon reflexes, and extensor plantar responses, predominantly affecting the lower limbs and with possible association of sphincter disturbances and deep sensory loss; and in the complex form by the addition of variable neurological (sensory disturbances, cerebellar syndrome, nystagmus, cognitive impairment, epilepsy, mental retardation) or non-neurological features (retinitis, deafness, ichthyosis, etc.) [65].

The various types of HSP are classified according to a) the mode of inheritance (dominant, recessive, X-linked, maternal); b) the gene in which the mutation occurs; and c) the clinical syndrome (pattern of symptoms and neurological findings). HSP syndromes are classified as “uncomplicated” when symptoms are confined to leg weakness and tightness and urinary urgency; they are classified as “complicated” when leg weakness and tightness (spasticity) are accompanied by other neurological disturbances such as peripheral

Fig. 5 – Illustration from Lorrain’s thesis, anatomopathological examination (OW Collection).
nerve impairment, muscle atrophy, or intellectual impairment. MRI can detect cerebellar atrophy and OCT (Optical Coherence Tomography) can detect macular degeneration, whereas the clinical manifestations may point to pure HSP. During the slow progression, ataxia or ophthalmoptlegia can occur at a later stage, which shows how the pure HSP classification is only approximative. HSP is also characterised by pathological anatomy data, i.e. retrograde axonal degeneration in the corticospinal tracts and posterior columns, first evident in the longest neuronal pathways (lower limbs). It was initially considered to affect the first motor neuron (upper motor neuron disease), but current research is discovering forms with involvement of the second motor neuron (SPG11) [66].

The chromosome locations (“loci”) of HSP genes are designated “SPastic paraplegia, loci (“SPG”) and numbered in order of their discovery (for example, SPG1 through SPG80). Currently 80 different forms and 64 genes have been identified. Genetic studies have also identified cellular dysfunctions affecting axonal homoeostasis: urea cycle anomalies and other innate metabolic errors disturbing the permeability of the neuron membrane, formation of endoplasmic reticulum, lysosome physiology, myelination, and so forth. Several mutations affect these interconnected functions. The mechanisms, clinical features, and imaging abnormalities are different according to the mutated gene [67,68]. Differentiating HSP from other genetic diseases associated with spasticity can be challenging. A wide group of neurological acquired and inherited disorders should be included in the differential diagnosis and properly excluded after a complete laboratorial, neuroimaging, and genetic evaluation [69].

There is currently no specific treatment for these disorders. While available therapies are exclusively for symptom relief and aimed at reducing spasticity to improve gait, symptomatic management continues to evolve as researchers’ understanding of the pathophysiological basis of individual HSP subtypes improves. There are emerging opportunities to provide targeted molecular therapies and personalised medicine.

In 2004, a team at Oxford published a novel anatomopathological study after histopathological examinations of six HSP spinal cords compared with thirty-two controls, quantitatively assessing the corticospinal axons from the medulla to the lumbar region. A reduction of axonal density was shown at all levels of the spine. In contrast, the axons of the sensory pathways were only rarefied at the cervical level. The authors argued that neuron loss had occurred that was length-dependent, symmetrical, and retrograde [73].

In 2006, a German HSP treatment network proposed a scale for assessing spastic paraplegia, developed to clinically quantify the disorder’s progression. These measurements, validated in the progressive stages of the disorder, are useful for understanding its natural history as well as evaluating as objectively as possible the effects of treatment and validating future clinical trials.

In 2015, a Tübingen imaging team, studying the most frequent variant of HSP, showed for the first time using 3T MRI the extensive diffusion of anomalies to brain areas, involving both grey matter and white matter, notably the corpus callosum, mediodorsal thalamus, parieto-occipital areas, and cerebellum [74].

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