Historical overview of hereditary ataxias with an annotation on the legacy of Hans Joachim Scherer

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ABSTRACT

Introduction. This paper presents a historical overview of the evolution of knowledge of degenerative cerebellar disorders and hereditary spastic paraplegias over the last one-and-a-half centuries.

Development. Original descriptions of the main pathological subtypes, including Friedreich ataxia, hereditary spastic paraplegia, olivopontocerebellar atrophy and cortical cerebellar atrophy, are reviewed. Special attention is given to the first accurate description of striato-nigral degeneration by Hans Joachim Scherer, and his personal and scientific trajectory are clarified. Pathological classifications of ataxia are critically analyzed. The current clinico-genetic classification of ataxia is updated by taking into account recent molecular discoveries.

Conclusions. There has been enormous progress in the understanding of the nosology of hereditary ataxias and paraplegias, currently encompassing about 180 genetic subtypes.

KEYWORDS

Ataxia, autosomal dominant cerebellar ataxia, autosomal recessive cerebellar ataxia, cortical cerebellar atrophy, episodic ataxia, Friedreich's ataxia, Hans Joachim Scherer, hereditary spastic paraplegia, idiopathic late onset ataxia, multiple system atrophy, Nazism, non-progressive congenital ataxia, olivopontocerebellar atrophy, parkinsonism, SCA genes, SPG genes, striato-nigral degeneration

Introduction

The umbrella term "ataxia" encompasses an increasing number of degenerative syndromes, which may be inherited or sporadic, and are basically characterized by loss of cerebellar control of movement.[1] In this paper I analyze the historical evolution of the understanding of degenerative ataxias and paraplegias, dividing this review into four parts[2]: *1)* the first is devoted to reviewing the origin and meaning of the term ataxia; *2)* the second focuses on the main clinico-pathological entities (namely Friedreich's ataxia [FA], hereditary spastic paraplegia [HSP], olivopontocerebellar atrophy [OPCA], and cortical cerebellar atrophy [CCA]), following the chronological order of their publication; 3*)* the third is an annotation on the contributions of Hans Joachim Scherer (HJS) on OPCA and striato-nigral degeneration; and *4)* finally, the different proposals of classification are reviewed.

Development

Semantics and etymology of ataxia

The semantics of the term ataxia was masterfully analyzed in a seminal paper by Bell and Carmichael.[3] Therefore, I quote several passages from it below. The term ataxia, literally meaning irregularity, confusion, or disorderliness, was used in this sense from the days of Hippocrates or before; thus Hippocrates (*Precepts*, XIV) says that ataxia, that is, irregularity, in a disease signifies

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that it will be a long one. Byfield, writing on angels in 1615, says: "we are not to thinke there is any ataxie among those glorious creatures." As late as 1853, Mayne's *Lexicon* describes ataxia as a term for irregularity, want of order, occurring in the progress of diseases or in natural functions, thus emphasising its application to medical states in general, but making no reference to a particular application to the nervous system. Althaus, in his textbook on nervous diseases in 1877, refers to the fact that:

> The term ataxia is as old as that of tabes, for it also originated with Hippocrates, and it has likewise entirely changed its meaning in the course of time. Some authors have applied it to chorea, others to fevers, others to various nervous disorders. At present, however, we understand by ataxy, not a disease itself, but merely a symptom to which various disorders may give rise and which essentially consists of a want of coordination of voluntary movements and a tendency on the part of the patient to lose his balance, but without actual loss of power, and apart from tremor, chorea or paralysis.

Any further change in the use of the word has consisted in the increasing tendency to apply it to designate a particular disease, of which it is a prominent symptom, rather than to confine it to the description of the symptom, thus Locomotor ataxia, Friedreich's ataxia, cerebellar ataxia and hereditary ataxia occur frequently throughout medical literature of today. It is worth noting that Bell and Carmichael's[3] paper was the point of reference for including HSP within the ataxias despite the fact that this disorder does not usually include ataxia as an outstanding semiology. The reason for such inclusion was twofold: first, in some ataxia pedigrees there may be patients with almost pure pyramidal signs; and second, the need for distinguishing cases with absence of deep tendon reflexes (characteristic of FA) from those with present or exaggerated deep reflexes (characteristic of spastic ataxia or HSP).

Friedreich's ataxia

In a series of five papers published between 1863 and 1877, Friedreich[4-8] described a distinctive clinical syndrome in nine patients (seven male and two female) belonging to five sibships. The age of onset was around puberty. The established clinical picture consisted of progressive gait and limb ataxia and dysarthria. Other symptoms and signs in the course of the disease included nystagmus, areflexia (cases II, VI, VII and IX examined after the description of tendon reflexes in 1875), sensory loss, muscle weakness, scoliosis, diabetes and tachycardia. Autopsy in four cases showed a uniform pathological picture consisting of degeneration of the posterior funiculus, posterior spinal roots, Clarke's columns, and the spinal lateral funiculus. Furthermore, Friedreich described cardiomyopathy in three cases. The proposal that the disorder he reported was a distinct entity, called hereditary ataxia, initially met with considerable opposition. In 1868 Charcot considered that Friedreich's patients suffered from multiple sclerosis[9]. In 1876 Friedreich[7] wrote that:

> It is incomprehensive that anyone can still speak of disseminated sclerosis when I have given the results of three detailed studies. I am pleased to know that some French pathologists (Bourdon and Topinard) have recognized my cases as examples of authentic non-complicated ataxia […] and I hope that Charcot, in the vast field of observation which he commands, will sooner or later find a case analogous to those I have described.

Ironically, Charcot recognized hereditary ataxia two years after Friedreich's death, which occurred in 1882.[1,9]

Nikolaus Friedreich not only introduced the concept of hereditary ataxia but was also the first author to precisely describe a clinico-pathological study of a form of spinocerebellar degeneration. Because of this, Brousse's proposal to apply the term Friedreich's ataxia to hereditary ataxia was soon accepted.[9]

Figures 1 and 2 illustrate the pathological background of a classic FA patient studied by the author.

Hereditary spastic paraplegia

In a series of four successive papers Strümpell[10-13] described two families with a uniform clinical picture characterized by vertical transmission (at least in the Polster family) and progressive lower-limb spasmodic pseudoparalysis, that is, predominance of dynamic spasticity over pyramidal weakness and at-rest hypertonia, a clinical finding later on recognized as a semiological characteristic of HSP.[14,15] Onset of symptoms occurred between 34 and 56 years of age. Two autopsy studies revealed degeneration of the pyramidal tracts, posterior columns, and spinocerebellar tracts.

In short, Adolf Strümpell reported a clinicopathological entity. Despite this in the literature there has been a tendency to call the syndrome by the eponym Strümpell-

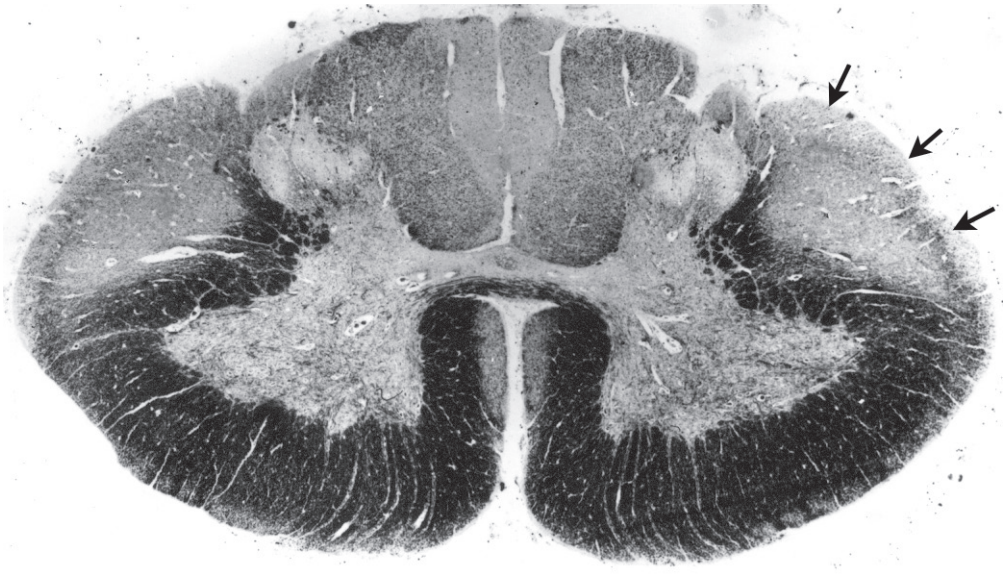

Figure 1. Thoracic spinal cord from an FA patient with the classical phenotype, studied by the author. The myelin stain reveals pallor of the dorsal columns, the crossed pyramidal tracts, the direct pyramidal tracts, and the dorsal spinocerebellar tracts (right, marked with arrows). Note that the gracile fasciculi are more demyelinated than the cuneate fasciculi, indicating that posterior column degeneration is length dependent. Klüver Barrera.

Lorrain disease.[16,17] This merits a brief comment. Lorrain's[18] thesis can be divided into three parts.[19] The first is a general review addressing the question of what a familial disorder is. The second is a description of personal observations including four sporadic cases (no. I, II, III and XXI) and two familial cases (case XXII corresponding to a doubtful spastic paraplegia and case XXVIII suffering from familial spastic ataxia); furthermore in this second part Lorrain carried out a literature review encompassing 20 publications. In the third part of his doctoral thesis Lorrain describes the pathology of HSP translating the case of F. Gaum reported by Strümpell and presenting histological features of a personal sporadic case. Lorrain concluded that familial diseases have numerous transitional forms, and that HSP and hereditary spasmodic tabes are synonymous disease designations.

It is obvious that Strümpell defined a hereditary disorder characterized by pure spastic paraplegia, now known as "pure" HSP,[14,15] with a uniform neuropathological framework. Lorrain carried out a literature review reporting a heterogeneous personal series; in fact, none of his patients could retrospectively be included within "pure" HSP. For historical reasons and in order to avoid semantic confusion, the eponym "Strümpell disease" should be used to designate "pure" HSP and such an eponym should not be used to designate other "complicated" forms of the disease.[19]

Olivopontocerebellar atrophy and the case of the original description of striato-nigral degeneration

The term OPCA was introduced by Dejerine and Thomas[20] in 1900, to designate the pathological framework in a sporadic case with progressive cerebellar ataxia. Nine years before, however, Menzel[21] had reported a family with a complex clinical picture characterized by progressive cerebellar ataxia, spasmodic dysphonia, rigidity in the lower limbs, dysphagia and dystonic posture of the neck. Onset of symptoms was around 30 years of age. There were four affected members over two generations. Autopsy revealed olivopontocerebellar lesions together with degeneration of the posterior and

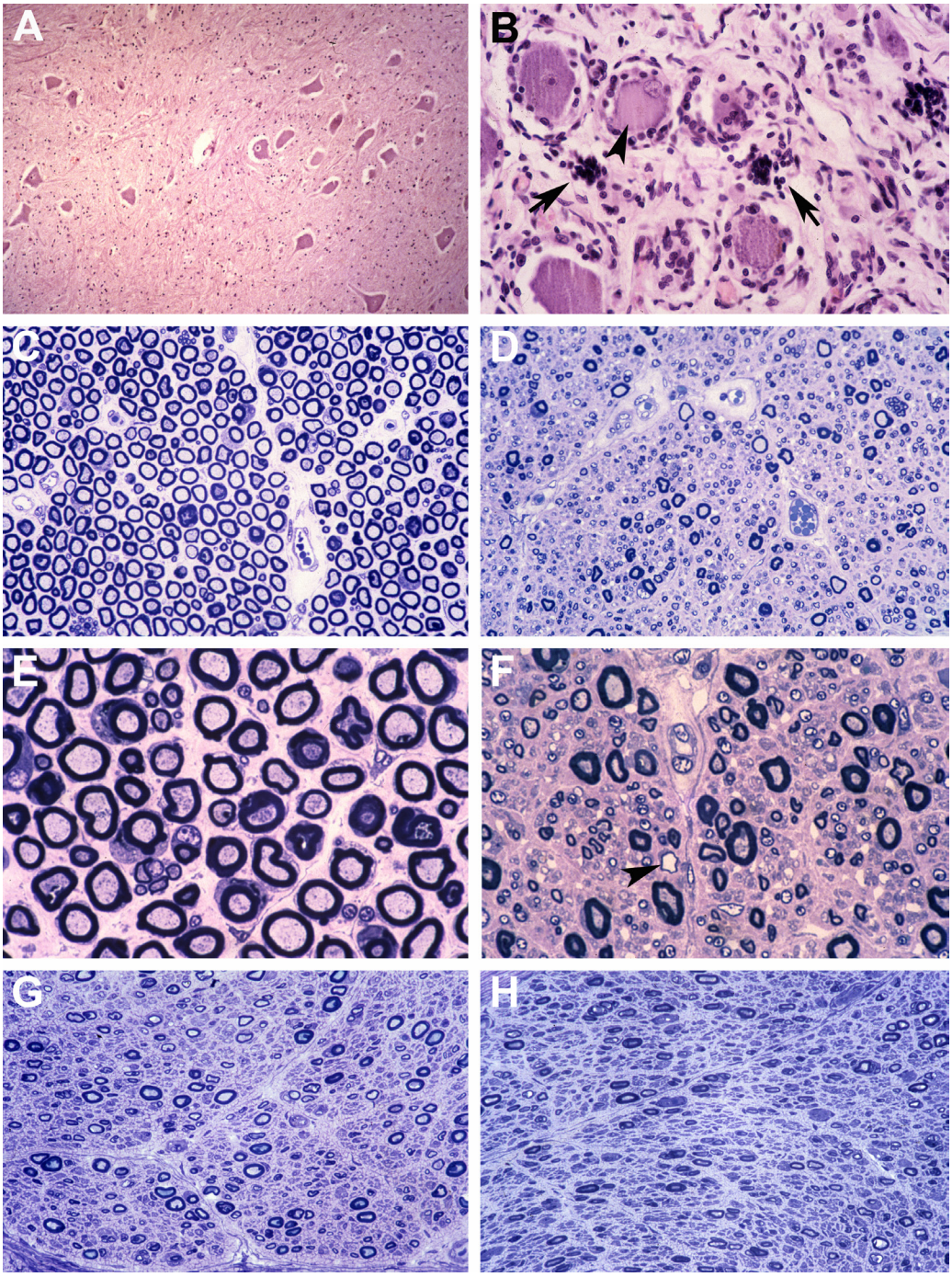

Figure 2. Spinal and peripheral nerve lesions in the same FA patient as the previous figure. A) Neurons in the anterior horn of the spinal cord at L5 level are preserved (HE, 16× objective). B) L5 spinal ganglion showing loss of nerve cells with presence of nodules of Nageotte (arrows) and proliferation of capsule cells; note also central chromatolysis in one of remaining nerve cells (arrowhead) (HE, 40× objective). Semithin sections of L5 ventral (C) and dorsal (D) roots showing normal population of myelinated fibres in the ventral root and marked reduction in the dorsal root (Toluidine blue, 40× objective). At higher magnification, note the preservation of myelinated fibres in the L5 ventral root (E), whereas in the L5 dorsal root (F) there is an almost complete loss of larger myelinated fibres; note also the presence of remyelinated fibres (F, arrowhead) (Toluidine blue, 63× objective). G) Semithin transverse section of the sural nerve at midcalf showing marked loss of myelinated fibres, particularly of the large ones (Toluidine blue, 40× objective). H) Semithin transverse section of the sural nerve at ankle showing massive loss of large myelinated fibres (Toluidine blue, 40× objective). This proximal-to-distal gradient loss of myelinated fibres gives support to the notion of a dying-back process, degeneration of the peripheral sensory axons slowly progressing from the distal portion of the fibre toward its cell body.

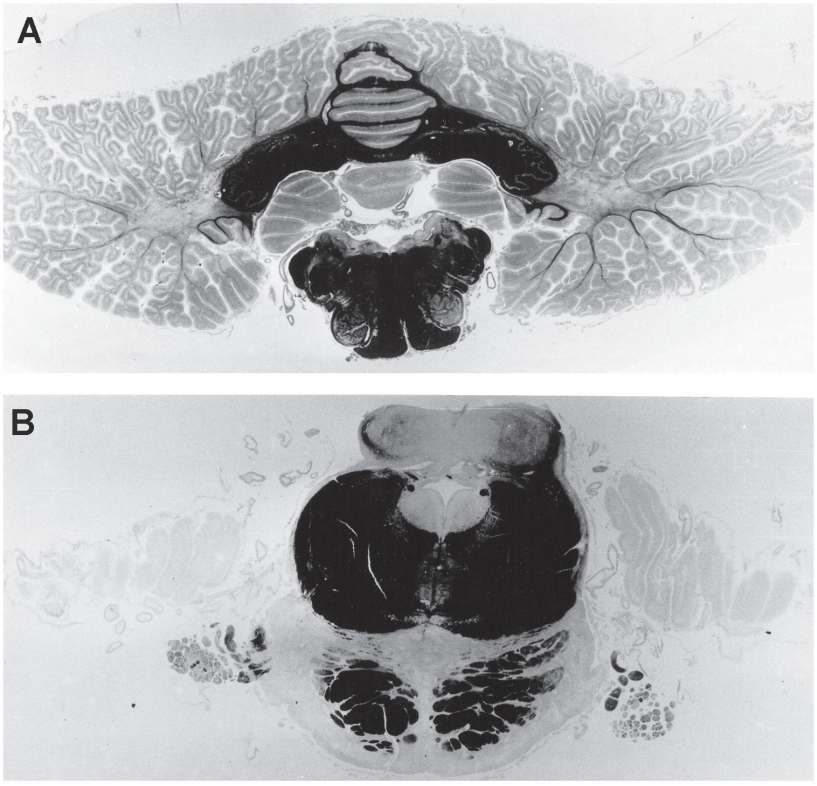

Figure 3. Olivopontocerebellar lesions in the case reported by Dejerine and Thomas[20] and reviewed by Berciano.[22,23] Both transverse sections are stained with the Weigert-Pal method. A) This section through the medulla and cerebellum shows demyelination of the cerebellar white matter and olivo-cerebellar fibers. B) This section through the upper half of the pons shows demyelination of the middle cerebellar peduncles

Clarke's columns, pyramidal and spinocerebellar tracts, and substantia nigra. Menzel found "very flattened and reduced subthalamic nuclei" but unfortunately he did not give any microscopic description of these structures; demonstration of luysian atrophy would have been of great interest in view of the dystonic postures of the patient. Be that as it may, this family is a good example of autosomal dominant cerebellar ataxia (ADCA) type I in Harding's classification (*vide infra*). Dejerine and Thomas[20] described a sporadic case with progressive cerebellar ataxic gait, dysarthria, impassive face, hypertonia, hyperreflexia, and urinary incontinence beginning at the age of 53. Two years later, autopsy showed advanced degeneration of the basis pontis, inferior olives, middle cerebellar peduncles, and to a lesser degree the inferior cerebellar peduncles. There was severe atrophy of Purkinje cells, more marked in the cerebellar hemispheres than in the vermis. Neither the basal ganglia nor substantia nigra are mentioned. According to the authors, OPCA is a non-familial disease that should be included among primary cerebellar degenerative disorders. Berciano[22,23] revised the pathological material of this case ("Vais D.V." Dejerine Laboratory, Paris), with the available preparations stained with the Weigert-Pal or carmine methods being as follows: seven transverse sections of the spinal cord, six transverse sections of the brainstem and cerebellum through medulla, pons and *isthmus rombencephali*, and one horizontal section of the basal ganglia through the anterior commisure. While confirming the reported olivopontocerebellar lesions (Figure 3) and the absence of apparent lesions of the putamen, it was not possible to establish whether or not the substantia nigra was degenerated. This finding would have been of great interest because the patient had had an incipient parkinsonism.

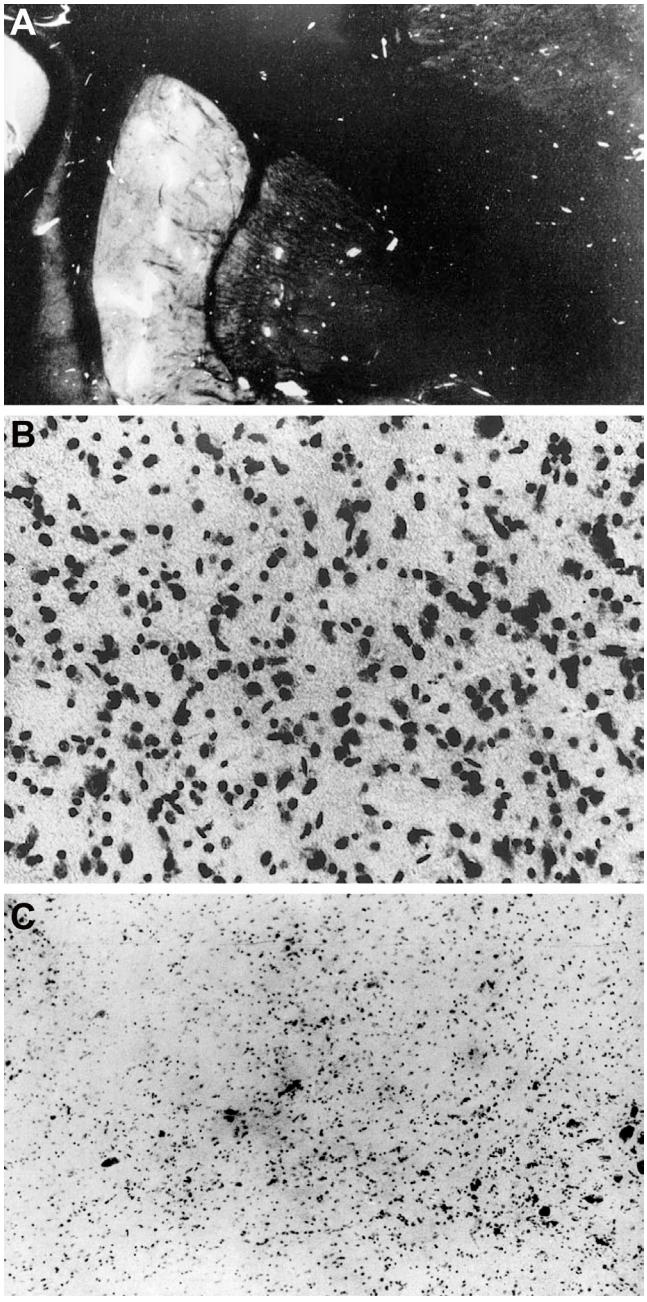

Figure 4. Reproduction of figures 2-4 from Scherer,[29] as reported by Berciano et al.[33] A) Coronal section of the brain showing severe demyelination of the putamen (Spielmeyer). B) At higher magnification, note severe putaminal gliosis with complete loss of small neurons and relative preservation of large ganglion cells (Nissl). C) Transverse section of the mesencephalon showing severe loss of neurons in the substantia nigra with marked gliosis (Nissl)

The early reports of Dejerine and Thomas[20] and later Loew's[24] thesis, developed under the tutelage of Dejerine himself, considered OPCA to be atypical when there was a hereditary factor (as is the case for aforementioned family reported by Menzel), lesions extending beyond the olivopontocerebellar framework, or a clinical presentation not limited to cerebellar symptoms. However, the concept of atypical OPCA fell into disuse with the recognition of familial OPCA[25,26] and of the many lesions that frequently accompany olivopontine atrophy.[27]

As outlined in the original case of Dejerine and Thomas (*vide supra*), extrapyramidal rigidity and nigro-striatal lesions are outstanding features of OPCA.[22,23,28-30] Based upon clinicopathological study of two cases, Guillain et al.[31,32] proposed the hypothesis of a cerebellar origin for extrapyramidal rigidity in OPCA. This hypothesis was prevalent until 1933, when Scherer[29] addressed the question of pathophysiology of rigidity in OPCA, starting from the clinicopathological study of four sporadic OPCA cases. Two patients had severe parkinsonism masking cerebellar semiology. Pathologically, both cases displayed marked degeneration of the striatum and substantia nigra (Figure 4) and non–fully developed olivopontocerebellar lesions. Cerebellar ataxia was the outstanding symptomatology in the other two, their pathological study showing severe OPCA and incipient striato-nigral atrophy. Scherer stated that severity of parkinsonism in OPCA correlated not with the degree of cerebellar degeneration but with that of striatum and substantia nigra. Furthermore, Scherer compared striatal degeneration in his patients with that previously described reported in Huntington's disease and considered, leaving aside the question of hereditary factors, that both diseases should be included under the same nosological umbrella. Indisputably, with these superb papers Scherer not only ruled out the erroneous concept of cerebellar parkinsonism in OPCA but gave the first accurate description of striatonigral degeneration.[33]

As illustrated in Figure 5, OPCA may be the pathological framework of several ADCAs.[22,23,34-38]

Hans Joachim Scherer: an excellent neuroscientist and entirely honest man

The biography of HJS (1906-1945) has been summarized by Martin (Figure 6).[39] He was a German neuropathologist who, between 1930 and 1933, trained in neuropathology and general pathology with Prof. Spielmeyer (Münich) and Rössle (Berlin), respectively. An active opponent of National Socialism (*vide infra*), in August 1933 he left Germany because he wanted to escape the Nazi

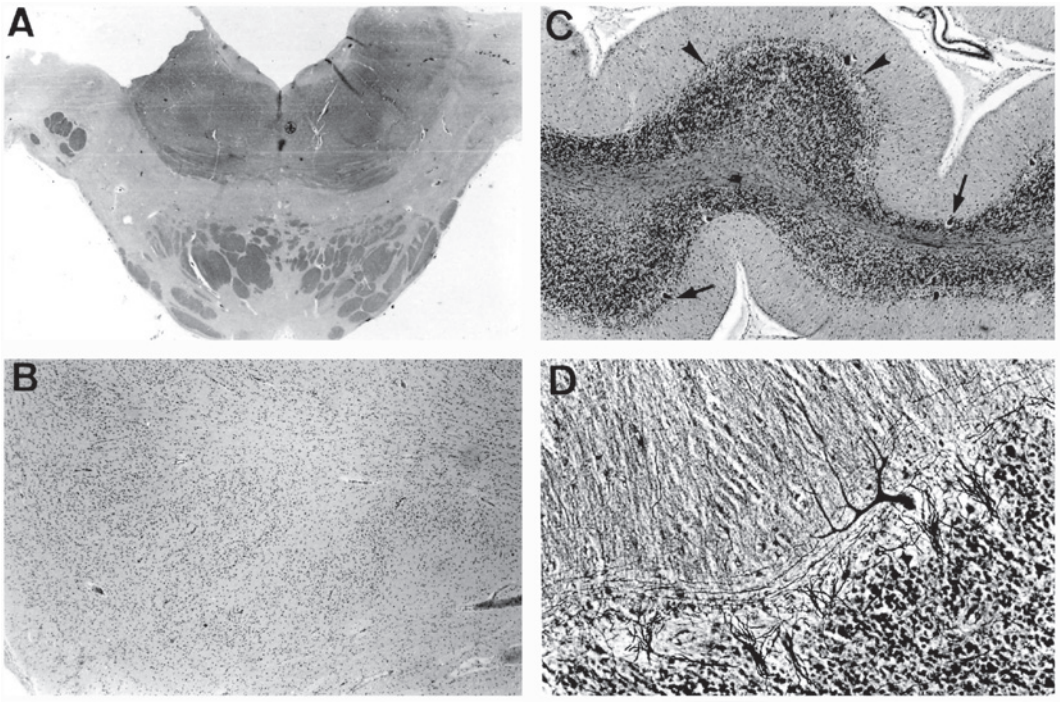

Figure 5. Microscopic olivopontocerebellar lesions in a case of familial OPCA studied in 1976 by the author[22,23,34]; afterwards, SCA2 mutation was found in this pedigree.[34-37] A) Transverse section through the middle pons showing complete demyelination of transverse pontine fibers (Spielmeyer). B) Disappearance of neurons and severe gliosis in the inferior olive (Nissl). C) Marked loss of Purkinje cells in the cerebellum (arrows indicated a few cells remaining) with prominence of the Bergmann glia (arrowheads) (phosphotungstic haematoxylin). D) Empty baskets (Naumenko-Feigin)

censorship. He worked at the Bunge Institute (Antwerp, Belgium), directed by Nestor van der Stricht with Ludo van Bogaert being member of the Management Board ("Conseil de Direction"), from January 1934 to January 1941. After the invasion of Belgium by German forces in May 1940, Scherer was arrested by the Belgian police and transferred into the camp of St Cyprien (France), being freed two months later. In April 1939 he was working part-time at Ghent University with Professor Vernieuwe. Two years later, HJS left the Bunge Institute after a quarrel with Ludo van Bogaert and continued his research at the University of Ghent. In December 1941, the German Occupation Authorities ordered him to go back to Germany because a shortage of medical doctors. HJS went to Magdeburg where his parents lived; while staying there, he was invited by Prof. Viktor von Weizsäcker to work at the Neurological Institute in Breslau; here, as stated by Professor Weizsäcker, HJS was forced to fulfil the requirements the regime imposed on him. On April 16, 1945, he was killed during an air raid on the railway station of Landshut. It is worth of noting that, in June 1939, HJS was offered by Charles Aring the position of neuropathologist at the University of Cincinnati (Ohio, USA). HJS could not accept the proposal of Aring because the US consul in Antwerp decided that he should be considered a Polish citizen, even though he had a German passport and was born in Bromberg, which in 1906 was a German town. The consul justified his decision because after the Treaty of Versailles, Bromberg became a Polish town called Bydgoszcz.

His main investigation focused on the morphology and biology of malignant gliomas, although his contribution to the nosology of OPCA/SND (*vide supra*) represents an incommensurable legacy. HJS was a very active investigator: from 1929 to 1944, he published 59 papers and four books (the complete list of papers is available in the reference by Martin[39]).

Figure 6. Hans Joachim Scherer playing piano in his house, Magdeburg, 1923. Courtesy of Marc Scherer

Scherer's reputation was tainted with the publication of a historical note on HJS by Peiffer and Kleihues[40] in 1999. Although recognizing that HJS was among the most creative and productive neuropathologists of his time, they expressed discrediting comments about him; in short:

> "Scherer was a controversial personality, who at the end of World War II became entangled in the Nazi euthanasia programme" (as argued below, this allegation has been entirely disarmed).
>
> "In contrast to other political émigrés, his German passport was extended and after the invasion of Belgium by German troops, he was not arrested" (as indicated above, this assertion is false).
>
> "Instead, he made an attempt to push Professor Van Bogaert, who had given him asylum in the Bunge Institute, out of the position of Institute Director, to assume the position himself" (this assertion is also false, given that by then HJS had been appointed to a full position at Ghent University).

As of the publication of Peiffer and Kleihues's paper, the name of Hans Joachim Scherer appeared in the list of Nazi perpetrators of neurological eponyms.[41,42]

In 2013, Marc Scherer, the youngest child of HJS, responded to the aforementioned historical annotation by providing compelling evidence that his father strongly opposed the political agenda of the Nazi party and that HJS's own career was negatively impacted by this regime (see below for further details).[43] Despite these convincing arguments, Kleihues wrote a rejoinder, including the following statements[44]:

> It is therefore difficult to assume that a person of van Bogaert's reputation would invent such an episode. However, as Marc Scherer points out, there are no documents supporting van Bogaert's allegation… Scherer did not publish the results obtained by investigating the brains of euthanized children. His fate was to find himself working in an environment where medical research was bereft of compassion for the dignity of mentally ill and the disabled.

In a letter to the editor of the Jerusalem Post, Marc Scherer wrote a very significant and insightful article that is literally reproduced below[45]:

> On July 14 you reported the proposal of Dr. Matthew Fox ("Israeli researcher launches campaign to note history of Nazi doctors alongside diseases named for them." Fox called Hans Joachim Scherer (1906-1945) a Nazi doctor or Nazi sympathizer. I asked him about his evidence. I never received an answer.
>
> Since Scherer has been maligned and since dead men cannot participate in their own defense, I would like to mention a few facts that will give your readers a fairer image of my father.
>
> While working in Berlin, Scherer was known as an explicit and imprudent opponent to National Socialism. In August 1933 he was arrested by the Gestapo. After his release he left Germany for Belgium.
>
> In February 1939 he asked to relinquish his German citizenship and started the procedure for obtaining Belgian citizenship; unfortunately, this could not be completed because of the German invasion of Belgium in May 1940.
>
> In 1941, after repeated interrogations by the Gestapo, Scherer was ordered back to Germany, and the physiologist Viktor von Weizsäcker invited him to Breslau, where he continued to be considered a political suspect.
>
> Many of his contemporaries have declared that after his return he didn't change his opinion about the Nazis.
>
> Scherer signed 209 post mortem reports of children euthanized in Lublinitz and whose brains were examined in Breslau. Nothing gives anyone the right to say he ordered these children to be killed or that he participated in their killings.
>
> Documents belonging to my personal archives seem to suggest that he could not have refused to perform these examinations without running the risk of being killed or imperiling the safety of his family.
>
> In 1947 von Weizsäcker wrote: "...he [Scherer] certainly was forced to fulfil the requirements the regime has imposed upon him."
>
> I would also like to quote Philipp Schwartz (1894-1977), a pathologist and Jewish founder of the wartime Emergency Association of German Scientists Abroad, who in 1959 wrote: "I was and still am proud to have shaken hands with him [Scherer] since he was one of the few Aryan colleagues who emigrated voluntary because they didn't accept the injustice which hit innocent people."
>
> MARC SCHERER
> Alsemberg, Belgium
> The Jerusalem Post, October 22, 2014

In reference to HJS, the editorial by Arie Perry,[46] entitled "Practising neuropathology under great adversity", is particularly exciting; the following paragraph is quoted:

> I greatly admire Dr Scherer's remarkable insights on gliomas despite the many challenges of practicing neuropathology during this period. These included secondary structure formation (ie, patterns of tumor spread) and primary vs. secondary glioblastomas, concepts that were only possible to validate with molecular studies many decades later. One can also only wonder how much brighter Dr Scherer's star might have shone had he simply been born in a different place and time.

Over 2017 and 2018, I have kept in close contact with Marc Scherer via e-mail. He has provided me a wealth of information on his father. Marc has just written a comprehensive paper entitled "The very unfortunate lot of Hans Joachim Scherer (1906-1945). Pioneer in glioma research. A plea for more circumspection and accuracy in biographical notes." After reading the draft, I can only state that I am deeply touched by HJS's trajectory, including a unique combination of scientific talent, human endeavor, and integrity. I look forward to reading it in a peer-reviewed journal, as it entirely "disentangles" the "entangled" allegations by Peiffer and Kleihues.[40]

Cortical cerebellar atrophy

Holmes in 1907 described a family with an autosomal recessive disorder giving rise to cerebellar ataxia and hypogonadism.[47] The sibship included four affected members (three male and one female) with onset of symptoms in the fourth decade of life. Autopsy study of one case showed cerebello-olivary degeneration. Greenfield[48] erroneously classified this family together with autosomal dominant pure CCA. Since then the eponym "Holmes type" has been used to designate familial cerebello-olivary degeneration (or CCA) without any reference to hypogonadism. A sporadic and idiopathic form of the disease was later reported.[49]

Classification of the ataxias

Unravelling the classification of the ataxias was not an easy task. Suffice it to say that none of the neurology textbooks published up to a few years ago had ever coincided on this point. In this connection, it is timely to remember the reflexion made by Refsum and Skre[50]: "From the clinical viewpoint, it is not an exaggeration to state that there are as many classifications and there are authors on the subject."

1. Pathological classification of the ataxias

As outlined before, the first serious attempt at classification was made by Greenfield,[48] based on pathological criteria. He divided the underlying anatomical basis of heredoataxia into three groups: *1)* predominantly spinal forms (FA and hereditary spastic ataxia); *2)* spino-cerebellar forms (Menzel-type hereditary ataxia and subacute spino-cerebellar degeneration); and *3)* predominantly cerebellar forms (Holmes-type hereditary ataxia, diffuse atrophy of Purkinje cells, OPCA and dentato-rubral atrophy).

In his comprehensive literature review, Greenfield[48] separated autosomal dominant pedigrees into two main groups: type A (Menzel), which would enter into the general category of OPCA, and type B (Holmes). Concerning OPCA, this was, therefore, divided into hereditary type (Menzel) and sporadic type (Dejerine and Thomas). The publication of cases with uncommon clinico-pathological findings (eg, dementia or blindness) led to the identification of a new type of OPCA called "special,"[51] or "variant."[52]

Using genetic, clinical and pathological data, Konigsmark and Weiner[53] classified OPCA into five categories (type I, dominant; type II, recessive; type III, with retinal degeneration; type IV, Schut and Haymaker type; and type V, with dementia, ophthalmoplegia and extrapyramidal signs). They added a further two categories for sporadic observations and for those which do not fit the previous five, although in their opinion such cases probably belong to type II.

Berciano[22,23] indicated that OPCA is a complex clinico-pathological syndrome which made it difficult to sustain any classification based on clinical and pathological criteria. Thus, for example, the creation of "special types" or "variants" ignores the fact that mental deterioration or atrophy of the anterior gray horn is seen in half the cases of familial OPCA. Furthermore, he indicated several omissions in the study by Konigsmark and Weiner[53] making the borderlines of their "types" somewhat hazy.

Pathological classification of the ataxias has several drawbacks. It is not particularly helpful to clinicians who, not unnaturally, prefer to make some sort of working diagnosis before the autopsy results are available.[1] Pathological classification ignores the fact that genetic heterogeneity affects not only the clinical picture but also the pathological framework,[2,36] that is, this classification is impossible within reported families in which autopsy findings were not consistent.[36] Finally, it is hardly surprising that in a well-known symposium on spinocerebellar degenerations, when Oppenheimer was asked to say something about the neuropathological contributions to this symposium, he said: "I am painfully aware that histopathology seems to add very little to our understanding of the ataxic disorders."[54]

2. Clinico-genetic classification

We have seen that for almost a century clinico-pathological studies of hereditary ataxias contributed to delineate a static but also confusing nosology of these syndromes. To find a new classification was a pressing need. This task was achieved by Harding,[1,55] culminating in a series of exceptional contributions to the field of hereditary ataxias and related disorders. She proposed starting from genetic and clinical features which are, certainly, the tools used by neurologists in clinical practice. In this way she proposed the clinico-genetic classification that appears in Table 1, which was soon universally accepted. Leaving aside ataxic disorders with known metabolic or other causes, we will briefly update the remaining ataxic groups.

Using Harding's classification we have established a prevalence ratio in Cantabria (Northern Spain) of 20.2 cases per 100 000 population.[56] The most frequent phenotypes were "pure" HSP and FA.

2.1 Non-progressive congenital ataxias

The term "non-progressive congenital ataxia" refers to a clinically and genetically heterogeneous group of disorders characterized by congenital or early-onset ataxia, but no progression or even improvement on follow-up.[1,57] Ataxia is preceded by muscular hypotonia and delayed motor and language milestones. The six original phenotypes (see Table 1) have now evolved into 18 entities.[57]

2.2 Friedreich's ataxia and other non-Friedreich's ataxia syndromes

FA is the commonest form of autosomal recessive early-onset cerebellar ataxias (EOCA). Harding divided EOCA into two main groups[58,59]: FA and EOCA syndromes other

Table 1. Harding's clinico-genetic classification of the hereditary ataxias and paraplegias[1]

I. Congenital disorders of unknown aetiology

i. Congenital ataxia with episodic hyperpnoea, abnormal eye movements and mental retardation (Joubert's syndrome)
ii. Congenital ataxia with mental retardation and spasticity (includes pontoneocerebellar hypoplasia)
iii. Congenital ataxia ± mental retardation (includes granule cell hypoplasia)
iv. Congenital ataxia with mental retardation and partial aniridia (Gillespie syndrome)
v. Dysequilibrium syndrome
vi. X-linked recessive ataxia with spasticity and mental retardation (Paine syndrome)

II. Ataxic disorders with known metabolic or other cause

A. Metabolic disorders

1. Intermitent ataxic disorders (syndromes with hyperammonaemia, aminoacidurias withouth hypermmonaemias and disorders of piruvate and lactate metabolism)
2. Progressive unremitting ataxic syndromes (e.g., abetalipropteinemia, hypobetalipoproteinemia, hexominidase deficiency, cholestenolosis, etc)
3. Metabolic disorders in which ataxia may occur as a minor feature (e.g., sphingomyelin storage disorders, metachromatic leucodystrophy, adrenoleucodystrophy, etc)

B. Disorders characterised by defective DNA repair

Ataxia telangiectasia
Xeroderma pigmentosum
Cockayne's syndrome

III. Ataxic disorders of unknown aetiology

A. Early onset cerebellar ataxia (usually before 20 years)

i. Friedreich's ataxia
ii. Early onset cerebellar ataxia with retained tendon reflexes
iii. With hypogonadism ± deafness and/or dementia
iv. With myoclonus (Ramsay Hunt syndrome, Baltic myoclonus)
v. With pigmentary retinal degeneration ± mental retardation and/or deafness
vi. With optic atrophy ± mental retardation
vii. With cataracts and mental retardation (Marinesco-Sjögren syndrome)
viii. With childhood onset deafness and mental retardation
ix. With congenital deafness
x. With extrapyramidal features
xi. X-linked recessive spinocerebellar ataxia

B. Late onset cerebellar ataxia (onset usually after 20 years)

i. Autosomal dominant cerebellar ataxia with optic atrophy / ophthalmoplegia / dementia / extrapyramidal features / amyotrophy (probably includes Azorean ataxia) (ADCA type II)
ii. Autosomal dominant cerebellar ataxia with pigmentary retinal degeneration ± ophthalmoplegia and/or extrapyramidal features (ADCA type II)
iii. "Pure" autosomal dominant cerebellar ataxia of later onset (over 50 years) (ADCA type III)
iv. Autosomal dominant cerebellar with myoclonus and deafness (ADCA type IV)
v. Periodic autosomal dominant ataxia
vi. "Idiopathic" late onset cerebellar ataxia

IV. Hereditary spastic paraplegia

1. "Pure" spastic paraplegia

i. Autosomal dominant: age of onset usually before 35 (type I)
ii. Autosomal dominant: age of onset usually after 35 (type II)
iii. Autosomal recessive
iv. ? X-linked recessive

2. Complicated forms of spastic paraplegia

i. With amyotrophy
- of the small hand muscles
- resembling peroneal muscular atrophy
- Troyer syndrome
- Charlevoix-Saguenay syndrome
- Resembling amyotrophic lateral sclerosis

ii. Spastic quadriparesis with mental retardation
iii. Sjögren-Larsson syndrome
iv. With macular degeneration and mental retardation (Kjellin syndrome)
v. With optic atrophy
vi. With extrapyramidal features
vii. With ataxia and dysarthria
viii. With sensory neuropathy
ix. With disordered skin pigmentation

than FA. This distinction is most appropriate because under the rubric of FA a hotchpotch of syndromes has sometimes been included that we now know are genetically separate entities.

As we saw earlier, Nikolaus Friedreich outlined the main characteristics of "his" disease. Nowadays, the most used FA diagnostic criteria are those proposed by Harding[58] in 1981. An important step in the disease was the location of the gene on chromosome 9p.[60] Afterwards, links to chromosome 9 markers in families with onset later than 25 years or with retained tendon reflexes were recognized.[56,61-65]

In 1996 Campuzano et al.[66] reported that the molecular basis of FA is an intronic GAA triplet repeat expansion in frataxin gene. The majority of patients were found to be homozygous for this dynamic mutation, a few having an expansion in one allele and point mutation in the other. Screening of patients with progressive ataxia for GAA expansion in the frataxin gene has demonstrated that the clinical spectrum of FA is broader than previously recognized, to the extent that about one-quarter of patients, despite being homozygous, had atypical clinical picture.[67]

Other EOCA syndromes usually recognize an autosomal recessive transmission; because of this they are now designated with the acronym of ARCA (autosomal recessive cerebellar ataxia) or SCAR (spinocerebellar ataxia recessive). With the advent of the next generation sequencing technologies, the panorama of ARCA has been in a state of constant flux at present comprising pathogenic mutations in 50 genes.[68-70] In short, ARCA encompasses three main syndromic groups:

— Friedreich's ataxia-like: FA, ataxia with vitamin E deficiency, abetalipoproteinemia, posterior column ataxia and retinitis pigmentosa, and Refsum disease.

— Friedreich's ataxia-like with cerebellar atrophy: DNA polymerase γ disorders, late-onset Tay-Sachs disease, cerebrotendinous xanthomatosis, and spinocerebellar ataxia with axonal neuropathy.

— Early-onset ataxia with cerebellar atrophy: ataxia telangiectasia, ataxia telangiectasia-like disorder, ataxia with ocular apraxia (types 1 and 2), autosomal recessive ataxia of Charlevoix-Saguenay, infantile-onset spinocerebellar ataxia, Cayman ataxia, and Marinesco-Sjögren syndrome.

2.3 Autosomal dominant cerebellar ataxia

ADCA is clinically and genetically heterogeneous. Harding[1,55,71] distinguished four main phenotypes (ADCA I-IV), studying separately episodic ataxias (EA) (see Table 1). Afterwards, it was established that ADCA IV is a type of mitochondrial cytopathy.[72] At present the acronym SCA is used for the designation of dominant cerebellar ataxia phenotypes.

Recently, the panorama of ADCA has also been drastically changed with substantial molecular discoveries, first with the location of several responsible genes, and later with identification of dynamic mutation as the commonest molecular basis of gene mutation[73,74]; conventional mutations are relatively rare. To date 47 SCA subtypes have been identified, SCA2 and SCA3 being the most common in Cantabria.[35] It is worth noting that two genotypes have been identified in Spain: SCA36 (Costa da Morte ataxia), caused by a GGCCTG repeat expansion in intron 1 of *NOP56*,[75] and SCA37, caused by an $(ATTTC)_n$ insertion in a polymorphic ATTTT repeat in the non-coding region of *DAB1*.[76,77] The most frequent forms are polyglutamine (polyQ) expansion diseases (*ATXN1*/SCA1, *ATXN2*/SCA2, *ATXN3*/SCA3, *CACNA1A*/SCA6, *ATXN7*/SCA7, *TBP*/SCA17, and *ATN1*/DRPLA). The main disease mechanisms of these SCA include toxic RNA gain-of-function, mitochondrial dysfunction, channelopathies, autophagia and transcription dysregulation.[74] These diseases manifest above a threshold number of CAG repeats, which is different for each gene. Disease onset generally occurs between the ages of 20 and 40 years, and age at onset and CAG repeat expansion size are inversely correlated.[35,73,74] A correlation between ADCA phenotypes (see Table 1) and SCA is as follows[74]:

— ADCA 1: SCA1-4, 8, 12-14, 15, 17-22, 25, 27, 28, 31, 32, 34-37, 38,42-44, 46, 47, DNMT1 and DRPLA.

— ADCA II: SCA7.

— ADCA III: SCA5, 6, 11, 23, 26, 30, 37, 41 and 45.

2.4 Idiopathic late onset cerebellar ataxia (ILOCA)

ILOCA is characterised by sporadic progressive pure cerebellar or cerebellar-plus ataxia beginning after 20 years of age.[78] Judging by computed tomography or magnetic resonance imaging, the usual presumptive pathological framework here is CCA for cases with pure cerebellar ataxia and OPCA for cases with cerebellar-

plus syndrome.[79] The most complex nosological problem of ILOCA is probably its relation to multiple system atrophy (MSA). Although there is some overlap between both processes, we have proposed that a subset of ILOCA cases does not fit in well within MSA and therefore should be considered as a separate entity until any biological marker becomes available.[36,80]

2.5 Episodic ataxia

EA is a clinically heterogeneous group of disorders that are characterized by recurrent spells of truncal ataxia and incoordination lasting minutes to hours.[80] Most have autosomal dominant transmission. To date eight subtypes have been defined, and five genes are linked to EA. Only EA1 associated with point mutations in *KCNA1* and EA2 associated with mutations in *CACNA1A* have been reported in multiple families of different ethnicities.

2.6 Hereditary spastic paraplegia

The last nosological entity in the clinicogenetic classification is HSP, divided by Harding into two main categories[2,14,55]: pure and complicated forms (see Table 1). Transmission may be autosomal dominant or recessive, and is rarely X-linked. On the basis of age of onset, two types of dominant pure HSP can be defined: type I, with onset before 40 years, and type II, with later onset.[14,15] However, this age separation has not always been found. Ironically, despite its limited semiological repertoire, HSP is genetically the most complex neurodegenerative syndrome, to date comprising 70 genetic subtypes, designated with the acronym SPG derived from spastic gait (for review, see references 82 and 83). Molecular diagnosis should be guided by pattern of inheritance, clinical features and epidemiological data. In this way, we should bear in mind that SPG4 is by far the most common phenotype, accounting for 50% of cases, with SPG3 being specially common in young-onset cases. For recessive HSP, the most common phenotypes are SPG7 and SPG5. De Souza et al.[83] have provided useful tables for molecular diagnostic purposes.

Conclusions

This historical overview of the ataxias illustrates the enormous evolution of the knowledge of degenerative cerebellar disorders over the last century and a half. Original descriptions of the main pathological subtypes, FA, HSP, OPCA, and CCA, are revised. Special attention is given to the first accurate description of SND by Hans Joachim Scherer, and his personal and scientific trajectory are clarified. Pathological classifications of ataxia are critically analyzed. The current clinico-genetic classification of ataxia is updated by taking into account recent molecular discoveries.

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Conflicts of interest

The author has no conflicts of interest to declare.

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