Neurological research at Hospital Universitario Marqués de Valdecilla: a personal and retrospective analysis (1974-2021)

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ABSTRACT

Introduction. Modern clinical neurology started by the mid-1960s, coinciding with the launch of a post-graduate programme at Clínica Puerta de Hierro in Madrid, where the author specialised between 1969 and 1973.

Objectives. I chronologically analyse my pre-graduate training, the creation and development of Clínica Puerta de Hierro, my post-graduate training at that centre, and my research career at Hospital Universitario Marqués de Valdecilla between 1974 and 2021.

Development. The excellent pregraduate neuroanatomical instruction was decisive in my decision to specialise in neurology at Clínica Puerta de Hierro, a pioneering centre in post-graduate training within the Spanish social security system. My research activity has fundamentally focused on the study of ataxia, Charcot-Marie-Tooth disease, Guillain-Barré syndrome, and various syndromes involving unknown or rare neurological features.

Conclusion. My career has spanned almost five decades of uninterrupted neurological research, largely derived from my solid post-graduate training and the inestimable help of my colleagues. This research activity soon garnered international recognition, which has unquestionably served as great encouragement.

KEYWORDS

Ataxia, botulism, Charcot-Marie-Tooth disease, cheiro-oral syndrome, Chiari malformation, Clínica Puerta de Hierro, Creutzfeldt-Jakob disease, epidemiology, Friedreich ataxia, Guillain-Barré syndrome, hereditary spastic paraplegia, Hospital Universitario Marqués de Valdecilla, Marie ataxia, motor neuron disease, moyamoya syndrome, multiple sclerosis, neurological research, occipital dysplasia, olivopontocerebellar atrophy, posterior column ataxia-retinitis pigmentosa syndrome, post-graduate training, SCA, Sneddon syndrome, striatonigral degeneration, syringomyelia, young stroke.

We can only know what we are if we determine how we became what we are
(Fusi JP. Historia mínima de España. Madrid: Turner Publicaciones; 2012. p. 9)

Introduction

In *Todo lo que era sólido* (Everything that was solid), Muñoz Molina wrote[1(p197)]:

> Those of us who knew the world before have the duty to recount how it was: not seeking pity due to the scarcity we suffered, but so that those who were born later and have taken everything for granted might know that that world has not existed forever, and was very hard to create, and that losing it may be infinitely easier than creating it. If we truly care about it, we must commit to defending and preserving it.

Modern clinical neurology in Spain began in the mid-1960s. As neurologist starting my career during that period, I would like to leave my testimony of the difficulties I faced to continue clinical neurological research

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over time; I will only very briefly mention healthcare and teaching aspects, which have been analysed elsewhere.[2]

With the aim of providing a global view of my academic activity, this work is divided into five sections: *i)* undergraduate training; *ii)* creation of the Clínica Puerta de Hierro (CPH): a historical milestone for Spanish medicine; *iii)* post-graduate training at the CPH; *iv)* arrival at Valdecilla; and *v)* research activity (1974-2021). In this last section, with the aim of being as impartial as possible, I will only focus on the research published as lead author, main co-author, or author for correspondence.

1. Undergraduate training

I completed my medical degree (1962-1968) at the School of Medicine of the University of Zaragoza. Of this period, I will only highlight the excellent teaching in neuroanatomy (1963-1964 academic year) by Prof Luis Jiménez-González,[3] which was decisive in my decision to specialise in neurology.

During my six years at the School of Medicine, I lived at the Pedro Cerbuna college, where both the human and the cultural atmosphere was extraordinary. Prof Pascual López-Lorenzo (director between 1957 and 1964) recalls in his memoirs: "Being part of the aspiration and interests of young students, being immersed into their future and education, in their destiny somehow, is a most satisfying adventure and a risk that is worth taking." Certainly, both López-Lorenzo and his successor Prof Celso Gutiérrez Losa (director from 1964 to 1971) organised life at the college in such a way that students had the most complete training possible in a liberal environment, unprecedented at that time. Among other facilities, the college was equipped with a photography laboratory in which I took my first steps in the art of film development, which was of great value to me later on.

In July 1962, Prof Diego Figuera Aymerich was appointed chair of surgery at the University of Zaragoza. In October of the same year, Prof Figuera Aymerich and his assistant Prof José Luis Inchausti Teja joined the university's teaching staff, and lived at the Cerbuna college (the first floor was reserved for lecturers and doctorate students). Both soon became involved in collegiate life. I clearly remember one of the first days of the 1962-1963 academic year: three students were having breakfast at a table for six, when Prof Figuera came and asked us if he could join us. We immediately stood and answered "yes, of course." For us, this was an exceptional occurrence, as numerary professors always ate at the presidential table of the dining hall, which had an individualised service. We sat back down, and he introduced himself as the new chair of surgery and started a relaxed conversation with us, showing an interest in our activities at the university and at the college. Professors Figuera and Inchausti quickly became authentic stars of the college. By late 1963, Dr Inchausti informed us that he and his superior were moving to Madrid to launch an unprecedented hospital project at the CPH, which included a novel programme for interns; he encouraged us to continue studying hard, as interns would be selected based on their academic performance and personal interviews.

2. Creation of the Clínica Puerta de Hierro: a historical milestone for Spanish medicine

Since 1944, healthcare had been provided by the former residences of the compulsory health coverage system (SOE for its Spanish initials) under the Spanish National Institute of Social Insurance (INP for its Spanish initials); these were not designed as modern hospitals but rather as large sanatoriums, mimicking the private sanatoriums used by wealthy people.[4] These residences lacked central services (eg, clinical records, general laboratories, or anatomical pathology departments) and were not authorised to provide post-graduate training. In fact, during the 1960s, Spain had only a few centres whose organisation was adapted to the growing needs of medicine; I may mention Fundación Jiménez Díaz in Madrid, Hospital de la Santa Creu i Sant Pau in Barcelona, Casa de Salud Valdecilla (CSV) in Santander, Hospital de Basurto in Bilbao, and Hospital General de Asturias in Oviedo. However, these centres did not belong to the SOE; rather, they operated under healthcare provision contracts with the INP.

Analysing the relevant contributions of these institutions to the development of neurology is beyond the scope of this work; the contributions of the CSV are detailed elsewhere.[2]

However, hospital medicine in Spain was born due to a series of circumstances that I will analyse below.[5] After the Second World War, the Order of Preachers (Dominicans) received war reparations from Japan for the destruction of the buildings belonging to the Order in the Philippines. With this money, they built a luxury sanatorium in the elite area of Puerta de Hierro in Madrid, which would be equipped with the most advanced

medical-surgical facilities and directed by Prof Gregorio Marañón y Posadillo. Unfortunately, Marañón died in March 1960 when the building was already complete but medico-surgical facilities were still being installed. At this juncture, the Japanese authorities demanded that the Dominicans invest the war reparations in the Philippines. As a result, the building was made available for sale, and was purchased in 1964 by the Ministry of Labour (led by Jesús Romeo Gorría) for 180 million pesetas. Romeo Gorría's team, which included the distinguished José María Guerra Zunzúnegui (general delegate at the INP) as a collaborator and Prof Carlos Jiménez Díaz as an advisor, launched a plan for this luxury sanatorium to become the starting point of a unique project for the Spanish healthcare system. To that end, Prof José María Segovia de Arana (chair of Medical Pathology at University of Santiago de Compostela from November 1962) was designated director of the centre, and Prof Figuera Aymerich director of the surgical department. The centre began operating in June 1964 under the name Clínica Puerta de Hierro, under an unprecedented special centre statute (Spanish National Centre of Medico-surgical Research of the Social Security System). Years later, Prof Segovia de Arana recalled the founding principles of the CPH[5,6]:

— Complete and exclusive dedication of the whole staff to the clinic; progressive contracts; morning and afternoon shifts; and limited possibility to work in private practice.

— Organisational structure of several medical and surgical specialties into departments and services coordinating with one another through the creation of specialised technical sections, resulting in highly operational functional units.

— Implementation of post-graduate medical training for resident medical interns (MIR for its Spanish initials) for the first time in public hospitals, followed in 1968 by undergraduate training as a university hospital associated with the School of Medicine of the Universidad Autónoma de Madrid.

— Introduction of clinical research, with experimental immunology, biochemistry, endocrinology, and surgery services, which included basic researchers working in close collaboration with clinicians.

— The hospital grew slowly, achieving a robust healthcare organisation, and extending its teaching activities with the creation of schools for nurses and laboratory and radiology technicians. It also incorporated new general services (central archives of clinical records, dietetics service, in-hospital infection control), as well as new systems for hospital administration.

The CPH was a true reference for modern hospitals in Spain, which Prof Segovia de Arana described as follows:

> The Spanish Social Security System slowly incorporated a large amount of the experiences acquired into its other hospitals, a process called "hierarchy establishment" that transformed healthcare residences into modern hospitals. Very decisive was the help of young specialists, who, after training under the MIR system (already extended to other Spanish public hospitals), shared the newly created hospital positions with more experienced, specialised professionals.

3. Post-graduate training at the CPH

My post-graduate training took place at the CPH between January 1969 and December 1973. These five years were exciting, as I will briefly describe. In a recent symposium at Fundación Areces in homage to Prof Segovia de Arana, Dr Pilar España Saz (former head of oncology at the CPH), gave a precise account of life at the CPH during her MIR years in internal medicine (1968-1971):

> There was an extraordinary working atmosphere, promoting dedication and study; science dominated consultations and visits to admitted patients, as well as the unforgettable clinical sessions; we learnt by osmosis in every corner of the hospital. These were wonderful years for us and for medicine, which unquestionably can never be repeated.[A]

I have two very special memories from my first year as an intern (1969): *i)* the rotation at the anatomical pathology department, in which Dr Josefina Menéndez Sánchez (Pepita) reviewed and corrected with endless patience our preliminary biopsy reports of the day; and *ii)* the rotation at the Internal Medicine department with Dr Juan Martínez López de Letona (Dr Letona) and his assistant Dr Ciriaco Aguirre Errasti, where we learnt the clinical method at great speed: how to draft a guided clinical history including pertinent positive and negative data; how

[A]The lecture by Dr Pilar España Sanz may be consulted at: https://www.fundacionareces.tv/ciencias-de-la-vida-y-de-la-materia/el-profesor-segovia-de-arana-persona-clave-en-la-sanidad-esp/el-profesor-segovia-y-su-apoyo-a-la-oncologia/

to determine the potential severity of each patient and therefore prioritise complementary studies; how to confirm every detail by ourselves (we should remember the aphorism on research [here, quality clinical practice], according to which "we require commitment with little or no delegation"[7(p36)]); how to perform and correctly report routine follow-up; and how to dictate well-structured treatment schedules. Dr Letona carefully supervised everything and we knew that every little mistake would be detected: we were aware that false positives were very poorly tolerated and that it was infinitely better to acknowledge our ignorance that to feign knowledge that we lacked. Successful performance in this rotation marked a turning point in my professional career.

In the second year (1970), after the first year of residency (R1), interns had the chance to choose a specialty or to continue working in three-month rotations. I chose the latter option, thus rotating through the cardiology, nephrology, and endocrinology services. I especially remember Dr Manuel Artaza Andrade, who, with great mastery, offered a solid foundation in electrocardiography and cardiac auscultation. This was a very productive year that put me on the track of internal medicine. However, in the last quarter I arrived at the neurology department directed by Dr Alberto Gimeno Álava, becoming fascinated by the neurological method, which I could learn more easily thanks to the excellent teaching I had received on neuroanatomy (see above). I decided to remain at this department to specialise in neurology (1971-1972). I owe a debt of gratitude for the excellent teachings of Dr Gimeno Álava and his three assistants (Dr Hugo Liaño Martínez, Dr Félix López López, and Dr Eduardo Zaragozá García).

The position of head of the on-call service was created at the CPH in 1972. Prof Segovia de Arana chose me, among others, to occupy this position in 1973, which had the associated benefit of the renewal of my residency contract for an additional year. This was an extraordinary opportunity to further my training in clinical neurophysiology (with Dr Eduardo Cocero Oviedo at Hospital Clínico, and Dr Alfonso Rodríguez de Castro at Hospital La Paz), neuroradiology (Dr Juan Parera Simonet at the CPH), and neuropathology (Dr José Ramón Ricoy Campos at the CPH).

4. Arrival at Valdecilla

In 1973, upon the initiative of Dr Segundo López Vélez (director of the CSV), the Centro Médico Nacional Marqués de Valdecilla, a special centre similar to the CPH, began operating. It combined two public hospitals in Santander: the CSV, founded in 1929 and belonging to the provincial government of Santander, and the Residencia Sanitaria Cantabria, inaugurated in 1969 and belonging to the INP.[8] The school of medicine was founded the same year; for this reason, the name of the centre was changed soon to its current designation, Hospital Universitario Marqués de Valdecilla (HUMV).

I joined the HUMV in February 1974 as head of the neurology unit, where I worked until my retirement in December 2015. I was assigned a ward with 23 beds (increasing to 33 in 1993) and a polyclinic with three consultation offices, increasing to six in 2013. One of the first patients was a woman in her thirties with transient ischaemic attacks in the left carotid territory with normal findings in the neurological examination at admission; however, cardiac auscultation revealed fixed splitting of the second heart sound and a mild systolic pulmonary ejection murmur. A chest radiography revealed pulmonary hyperflow, a prominent pulmonary arch, and enlarged right atrium; the ECG showed a complete block of the right branch. Diagnosed with atrial septal defect, the patient was transferred to the cardiology department; this was the first case of congenital heart disease to be treated surgically in Valdecilla, by Dr Carlos Gómez-Durán Lafleur, who had just become head of the cardiovascular surgery department.

Until 1979, when a neuroradiologist (Dr Fernando Quintana Pando) joined the hospital, we had to perform neuroradiological studies ourselves (brain angiography, pneumoencephalography, and myelography). We initially had the help of an internist (Dr Manuel Ortiz Ortiz), who six months later would be replaced by a neurologist (Dr Ricardo Navarro Izquierdo), and two residents (Dr José Miguel Polo Esteban and Dr Mariano Rebollo Álvarez-Amandi). The unit became a department in 1989, coinciding with my appointment as chair of neurology, after three years as full professor. The incorporation of statutory staff was very slow: in 1982, the unit included four consultants (chronologically, Dr Rebollo and Dr Polo, Dr Onofre Combarros Pascual, and Dr Carlos Leno Camarero); between 1988 and 1994, after being assigned the patient population of four outpatient neuropsychiatry clinics, two other consultants (Dr Julio Pascual Gómez and Dr Agustín Oterino Durán) joined the department. Obviously, the department's first 20 years were not easy. From 2000, with the implementation of

the post-MIR contracts of the Río-Hortega (Instituto de Salud Carlos III) and López Albo programmes (Instituto de Investigación Universitario Marqués de Valdecilla [IFIMAV; IDIVAL in its current Spanish initials]), as well as the creation of on-call neurology services, there was a slight increase in staffing numbers; the department currently includes a head of department, a head of unit, and 18 consultants.[B] Specialised units were gradually implemented, including stroke, cognitive impairment, headache, multiple sclerosis, neuromuscular disease, and Parkinson's disease units. The HUMV is also a Reference Centre of the Spanish National Health System for ataxias and hereditary paraplegia. From early 1974, Spain's National Neurology Commission authorised the unit to train two MIR residents per year, which meant that by 2015 a total of 82 specialists had been trained in neurology at the centre.

As mentioned above, it is beyond the scope of this work to analyse my healthcare and undergraduate teaching activity. However, I would like to provide a few general details on this subject. According to the annual reports of the department, and considering the patients attended at the outpatient clinic (new and successive), patients admitted to hospital wards, and consultations, the total number of patients attended was 6763 in 1981, 12 605 in 1998, and 23 642 in 2014. In 2013, there were four university positions linked to the neurology department (two chairs [myself and Onofre Combarros] and two full professors [José Miguel Polo and Mariano Rebollo]), and one position of senior lecturer obtained by Jon Infante, who that same year was accredited by the ANECA to obtain a position as full professor of Neurology. I taught pathophysiology of the nervous system (third year), medical pathology of the nervous system (fifth year), and clinical medicine (sixth year).

From 1983 to 2014, I participated in 22 competitive research projects, being the main researcher in nine of them.

Since my arrival at Valdecilla, it was always very clear to me that the comprehensive development of neurology requires active collaboration with related specialties. Thus, we contacted Dr Fernando Val Bernal (head of the anatomical pathology department), who helped one of his consultants (Dr Javier Figols Ladrón de Guevara) to work in neuropathology after a one-year stay with Dr Jordi Cervós-Navarro (Free University of Berlin, Germany). We were in close contact with the clinical neurophysiology (Dr Jesús Calleja Fernández), neurosurgery (Dr Guillermo Dierssen Gervás), and neuroradiology departments (Dr Quintana Pando), with whom I held weekly meetings. With the collaboration of professors Miguel Lafarga Coscojuela and María T. Berciano Blanco (Cell Biology and Anatomy department, University of Cantabria [UC]), we established a nerve histopathology laboratory. With the invaluable help of the Maintenance Service of the HUMV and occupying the space of a toilet, we installed a photography laboratory with a Durst M605 enlarger, which enabled us to develop conventional negatives and electronic microscopy plates. In 1994, in collaboration with Dr José Luis Fernández Luna (Molecular Genetics department, HUMV), Dr Combarros Pascual founded the neurogenetics laboratory, which is currently located at the School of Medicine directed by Dr Jon Infante Ceberio.

Thanks to our research activity, the Neurodegenerative Diseases Research Team is part of the following research networks: CIBERNED (Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas), IDIVAL (Instituto de Investigación Sanitaria Valdecilla), EUROSCA (European Integrated Project on Spinocerebellar Ataxias), MSA-SG (Multiple System Atrophy Study Group), CMT Consortium (Charcot-Marie-Tooth Disease Consortium), and IGOS (International Guillain-Barré Syndrome Outcome Study).

5. Research activity (1974-2021)

I will detail my research activity from my arrival at Valdecilla in 1974 to today, which includes four years as ordinary emeritus professor at the UC (2016-2020) and my current position as emeritus professor ad honorem (since 2020). To facilitate this analysis, I will divide my contributions into the following sections:

— Ataxia and hereditary paraplegia
— Charcot-Marie-Tooth disease (CMT)
— Guillain-Barré syndrome (GBS)
— Other contributions
— Postscript: in recognition of Dr Onofre Combarros Pascual.

[B]Available from: http://www.humv.es/index.php?option=com_content&task=view&id=183

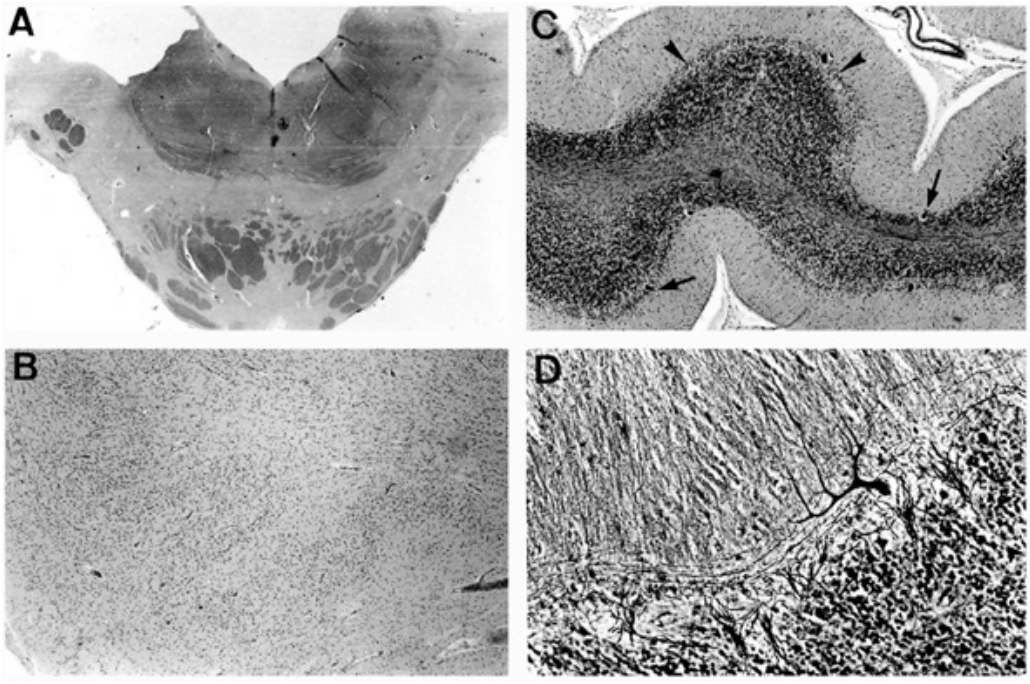


Figure 1. Histological findings in Menzel-type olivopontocerebellar atrophy.[19] **A**) Transverse section of the pons showing complete demyelination of the pontocerebellar fibres (Spielmeyer). **B**) Detail of the olivary body, showing complete neuron loss; in fact, the wavy contour seems to indicate intense gliosis (Nissl). **C**) Cerebellar folium showing an almost complete loss of Purkinje cells (arrows indicate two remaining cells) and pronounced proliferation of Bergmann glia (arrowheads) (phosphotungstic acid haematoxylin). **D**) The loss of Purkinje cells originates the presence of empty baskets (Naoumenko-Feigin).

5.1. Ataxia and hereditary paraplegia

After my arrival at Valdecilla in 1974, Dr Juan F. Díez Manrique (head of the psychiatry service at HUMV) provided me with the records of several patients with hereditary ataxia (HA) and hereditary spastic paraplegia (HSP), which had been studied decades before by the former head of the department, Dr José María Aldama Truchuelo (head of neuropsychiatry at the CSV until his death in 1970). These records included detailed clinical and genealogical information.

5.1.1. Olivopontocerebellar atrophy

In the analysis of the proband of one of the families with HA with an autosomal dominant inheritance pattern, the pneumoencephalography study showed the characteristic pattern of olivopontocerebellar atrophy (OPCA). The clinical picture of this patient combined generalised ataxia with inability to remain standing, dysarthria, dysphagia, ocular apraxia, emotional lability with loss of sphincter control, areflexia, and disseminated fasciculations. The patient died due to aspiration pneumonia. Dr Ricoy Campos examined her brain in February 1975 at Hospital 12 de Octubre in Madrid. The examination showed the typical pattern of OPCA (Figure 1) and associated lesions in the substantia nigra and spinal cord (dorsal columns, spinocerebellar bundles, and anterior horn neurons). A diagnosis of Menzel-type OPCA was established.

During the summer of 1975, Dr Dierssen Gervás organised an International Symposium in Santander entitled "The cerebellum." The symposium was attended by renowned neuroscientists, including Dr Raymond Escourolle (head of the Laboratoire de Neuropathologie Charles-Foix, Hôpital de la Salpêtrière, Paris), who delivered a masterful speech entitled "Les atrophies cérébelleuses." With Dr Ricoy Campos as co-author, I presented

our clinico-pathological study of the case of Menzel-type OPCA. During the break, Dr Escourolle approached us to compliment our study, which was very gratifying as he was such an authority on neuropathology. With his characteristic spontaneity, Dr Ricoy Campos suggested to Dr Escourolle that I may write my doctoral thesis on the topic of OPCA, using our histological material together with his from the series at La Salpêtrière. It was no sooner said than done, and my stay at his laboratory for the months of June-July 1976 was organised, without help from any institution.

We designed the study by performing an exhaustive clinico-pathological review of familial (Menzel-type), and sporadic (Dejerine-Thomas type) OPCA, creating different tables for clinical and pathological data, and making a statistical analysis of the differences. It should be noted that no previous study on OPCA had used a similar approach.

My stay at the Laboratoire de Neuropathologie Charles Foix (renamed after Raymond Escourolle after his death in 1984) was an unforgettable experience. Madame Simonneau (head of the laboratory) provided us with a list of the 15 neuropathological studies of OPCA performed between 1897 and 1976, including:

— Cases IV and V from André Thomas's thesis[9];
— a case published by Dejerine and Thomas[10];
— another case published by Thomas[11];
— a case published by Ley,[12] Geis. Prosper, reviewed by Guillain et al.[13];
— the case of Bil. Henry published by Guillain et al.[13];
— another case published by Guillain et al.[14];
— five cases from Veron's thesis[15];
— a case published by Bonduelle et al.[16]; and
— two unpublished cases of Shy-Drager syndrome with associated OPCA.

When reviewing the test slides, we noticed that the histological material from the first four cases was missing[9-11]; like the remaining cases, these had been reported at La Salpêtrière. When I asked Dr Escourolle about this, he said that the material was at the Dejerine Laboratory of the Faculté de Médecine, Paris V. Several days later we went together to visit that laboratory and explained the aim of our projects to those in charge, requesting the corresponding histological preparations. It was surprising that such a large part of the OPCA series should be outside La Salpêtrière, but I was not aware at the time of the sordid history behind this circumstance. With my pathological study already well underway, Dr Escourolle offered me the images I wished to use to illustrate the thesis: I had no doubts in selecting two of those included in the initial report by Dejerine and Thomas (Figure 2).[10]

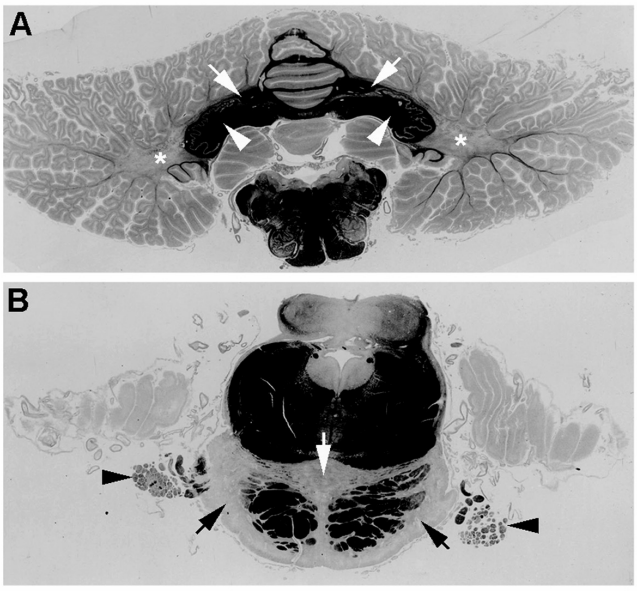


Figure 2. Histological findings from the princeps case by Dejerine and Thomas.[10,17] **A**) Transverse section of the spinal bulb and cerebellum showing demyelination of the olivocerebellar tract and cerebellar white matter (asterisks); however, note preservation of amiculum (arrows) and efferent fibres (arrowheads) of dentate nuclei (Weigert-Pal). **B**) Transverse section of the upper part of the pons, at the root of trigeminal nerves (arrowheads), showing complete demyelination of pontocerebellar fibres (arrows); note the preservation of the pontine vault and corticopontine fibres at the base of the pons.

With the approval of Dr Escourolle and Madame Simonneau, before starting the study I drafted a worksheet with the existing preparations for every case, so that the stock of materials could be consulted at the beginning and at the end of the study. This question, as we will see below, was especially relevant in one of the cases analysed.

The doctoral thesis included 16 cases of OPCA for which I had personally reviewed the histopathological material, and another 101 reported in the literature up to 1976[17-19]: 54 were familial forms of OPCA (Menzel-type) and the remaining 63 were sporadic forms (Dejerine-Thomas type). The results showed that the mean age of onset of Menzel-type OPCA was significantly younger than in the Dejerine-Thomas-type OPCA (28.5 [13.7] years vs

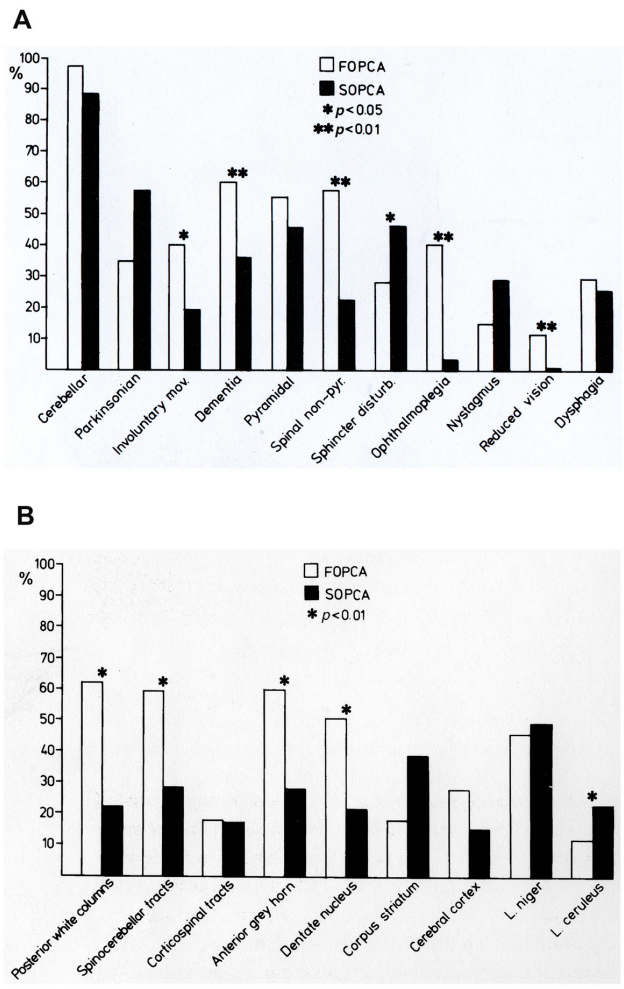


Figure 3. A) Histogram of the frequency of symptoms in Menzel-type (familial, FOPCA) and Dejerine-Thomas–type (sporadic) olivopontocerebellar atrophy (SOPCA). **B**) Histogram of frequency of lesions associated with olivopontine lesions. Adapted from Berciano.[18]

49.5 [10.7]; $P < .001$); however, mean disease duration was longer in familial OPCA (15.1 [8.31] vs 6.3 [4.8]; $P < .001$).

Figure 3A shows the frequency of OPCA symptoms. As expected, the most frequent is static cerebellar ataxia and appendicular ataxia with scanning dysarthria. However, in the great majority of cases, extracerebellar signs were also present, including movement disorders (especially parkinsonism), dementia, spinal signs, sphincter dysfunction, decreased visual acuity, or dysphagia, with frequent significant differences between familial and sporadic forms. Figure 3B illustrates the lesions associated with OPCA (constant by definition), showing significant differences between both forms.

The classification of OPCA was a topic under constant debate. After analysing the disadvantages, if not glaring mistakes, of some proposals for classification, we agreed with the recommendation of subdividing the disease in the simplest way possible[20]: familial forms, typically with an autosomal dominant inheritance pattern (Menzel-type); and sporadic forms (Dejerine-Thomas type).

Let us now address two historical questions that are relevant to understand certain intricacies of neurology.

Dr Jules Dejerine is one of the giants of the history of neurology and neuropathology.[21] First *chef de clinique* and later *professeur agrégé* at Hôpital Bicètre, he joined La Salpêtrière in 1887, and obtained the chair of neurology (1910), defeating Dr Pierre Marie in the selection process; the latter became the leader of his worst and most feared scientific enemies. Dr Dejerine collaborated with Dr André Thomas, the head of his laboratory since 1897, and with his wife Dr Auguste Marie Klumpke, who was the first woman to obtain the position of *interne des hôpitaux*. Dejerine suffered a chronic kidney disease, which coincided with his early retirement in 1913 at the age of 64; until his death, in 1917, he was temporarily replaced by André-Thomas. From that year, the chair of neurology was occupied by Pierre Marie, whose first measure was to dismiss certain individuals (including Dr Klumpke) from La Salpêtrière and to get rid of some objects that reminded him of his predecessor (I highly recommend reading the insightful text by Serge Duckett [1926-2020], former neuropathologist at La Salpêtrière, published in the "Pioneers in Neurology" section of *Journal of Neurology*, 2000).[22] This included Dejerine's famous histological collection, which was promptly taken to its current location at the Faculté de Médecine, Paris V. Therefore, more than 20 years later, I finally understood the miserable reasons for which the first studies of OPCA at La Salpêtrière should be located outside of their original archive.

During a stay at La Salpêtrière, Dr Rodolfo Ley (a Belgian neurologist who presided the Société Belge de Neurologie, 1950-1951) reviewed the Geis. Prosper case of OPCA with parkinsonian symptoms and nigral degeneration.[12] Soon after, Guillain et al.[13] reviewed this case and that of Bil. Henry, another patient with parkinsonism, reporting that the substantia nigra was normal in both,

which led them propose that rigid-akinetic signs were of cerebellar origin (effort-induced parkinsonism of cerebellar origin). In our pathological review of the case of Bil. Henry, we observed, together with the olivopontocerebellar lesions, neuronal loss in the substantia nigra, especially in the medial portion, pigment in the interstitium, and mild gliosis, but no Lewy bodies or striatal lesions. In the case of Geis. Prosper, we faced the fact that there were no histological preparations of the midbrain; the striatum also appeared normal. This observation had been reported by Dr Jean de Recondo (*chef de service*, Hôpital Saint Anne, Paris) in his doctoral thesis,[23] with no reference to the locus niger. After I had talked about this with Dr Escourolle, he spoke on the phone with Dr de Recondo, who went to La Salpêtrière and confirmed that he had also observed nigral lesions. Following the directives of his thesis director, Dr Raymond Garcin, son-in-law of Dr George Guillain, the midbrain preparations did not leave Garcin's office. Thus, this is an example of the principle that states that once the cause is removed, the effects automatically disappear.

It is Scherer[24,25] whom we must truly acknowledge for having demonstrated that the presence and severity of parkinsonism in OPCA depends on the nigrostriatal involvement rather than on the degree of cerebellar atrophy. Furthermore, almost two decades earlier, Scherer had given an excellent description of striatonigral degeneration (SND), a fact that was very well-known to Ludo van Bogaert,[26-29] but was deliberately overlooked in the original studies of this nosological entity.[30-32] As we have described elsewhere, behind this omission lies a miserable story of envy and persecution towards Hans Joachim Scherer, another giant of neurology.[28]

It should be noted that, as in the cases of Geis. Prosper and Bil. Henry, parkinsonism in OPCA or multiple system atrophy (MSA) may be pre-synaptic. We have shown this both in cases of sporadic OPCA and in MSA with parkinsonism, which both respond well to levodopa. Autopsy examinations revealed nigral degeneration with no Lewy bodies and integrity of the striatum; furthermore, in the case of OPCA, striatal D2 receptors were intact in the radiometric study.[33,34]

My thesis included a review of 31 cases of Shy-Drager syndrome, and 48 of SND; olivopontine degeneration occurred in 58% and 33% of cases, respectively.[17] Shy-Drager syndrome, SND, and a subgroup of sporadic OPCA are currently classified as MSA; these entities share the feature of presenting glial inclusions with positive immunoreactivity for synuclein.[34-39]

The classical literature used the term Marie ataxia,[40] created to distinguish Friedreich ataxia, which distinctively progresses with areflexia, from other familial ataxia syndromes with preserved or overactive reflexes. It is interesting to highlight that Marie ataxia was included in the International Classification of Diseases, version 8 (ICD-8, section 332.1, hereditary cerebellar ataxia, 1968), despite strong criticism from Holmes, who argued that familial cerebellar ataxia exclusively included OPCA and olivocerebellar atrophy.[41] After a detailed review, we reached the conclusion that, in fact, Dr Pierre Marie had the merit of calling attention to the existence of ataxia forms with preserved reflexes but lacking specific neuropathological signs.[17,27,42] During the 13th World Congress of Neurology (Hamburg, 1985), Dr Bruce S. Schoenberg convened a panel of neurologists interested in degenerative ataxias with the aim of preparing a new edition of the ICD (ICD-9-CM); the panel was presided by Dr Anita Harding. After an intense debate with a French colleague and analysing Marie's findings, the term Marie ataxia was excluded from the ICD-9, giving way to a clinico-genetic classification described shortly before by Harding[43,44]; this classification remains in effect today.

5.1.2. Other types of ataxia and hereditary paraplegia

According to the chronological order of publication, I will analyse now the two new phenotypes with an autosomal recessive inheritance pattern. The first was the description of a family with ataxia and hypogonadotropic hypogonadism, which included two patients, siblings (a man and a woman), of 39 and 34 years of age, respectively.[45] Repetitive stimulation with luteinising hormone–releasing hormone (LHRH) was followed by an increase in gonadotropin levels, which suggested for the first time that the hormonal defect in this syndrome may be hypothalamic rather than pituitary; in fact, the OMIM catalogue includes it under the name "ataxia with LHRH deficiency" (OMIM #212840). The second phenotype corresponds to the novel association of Friedreich ataxia and congenital glaucoma[46] (OMIM #229310).

In her doctoral thesis, Dr Ana Ramos González performed CT studies of 35 patients with progressive ataxia, classified according to Harding's clinico-genetic classification, and 36 controls.[47,48] Atrophy was quantified by measuring the number and amplitude of cerebellar

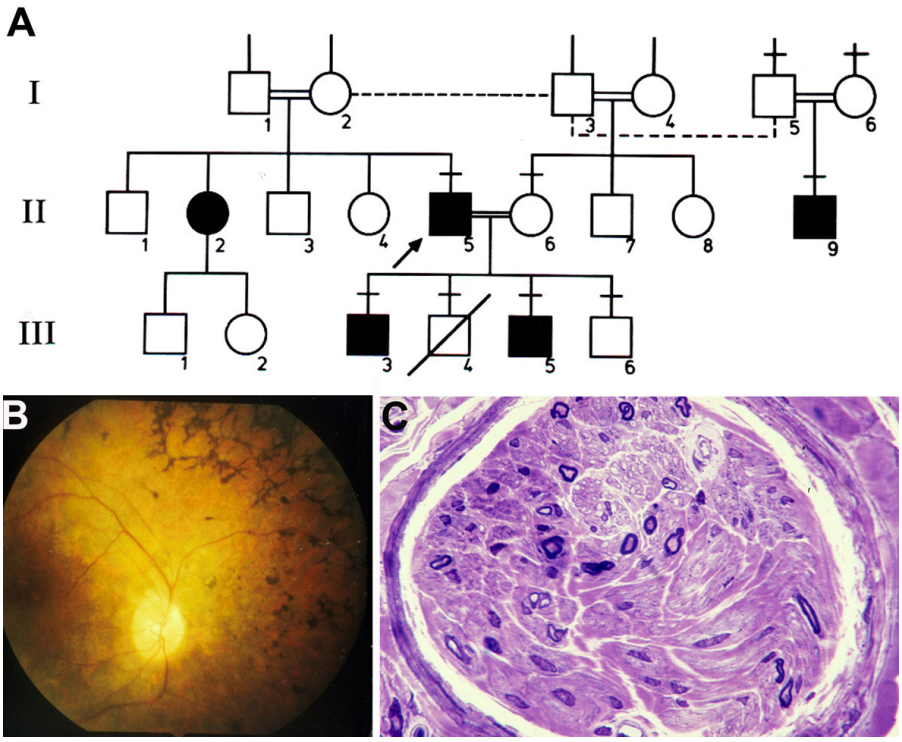


Figure 4. Findings in PCARP. **A**) Pedigree chart showing a pseudo-dominant inheritance pattern.[50] **B**) Eye fundus examination showing retinitis pigmentosa and optic atrophy. **C**) Semithin section of the sural nerve with pronounced decrease in myelinated fibres (850 per mm^2); a complete loss of thick myelinated fibres is observed (≥ 8 μm) (toluidine blue staining).

sulci, diameter and area of the fourth ventricle, brainstem ratio, size of the cerebellopontine cistern, and Evans index. She identified relatively specific patterns of atrophy in patients with suspected OPCA or cortical cerebellar atrophy, and in patients with Friedreich ataxia.

In his doctoral thesis, Dr Polo Esteban performed the first Spanish epidemiological study of ataxias and hereditary spastic paraplegias.[49-51] The series included 48 index cases and 65 secondary cases. Prevalence was calculated at 20.2 cases (95% CI, 16.4-24.3) per 100 000 population; phenotypes with the highest prevalence were the pure form of HSP (9.6) and Friedreich ataxia (4.7). We redefined the phenotype of pure HSP, establishing that it may present with incomplete penetrance and variable clinical manifestations. There are two aspects of this study that merit attention.

In families with Friedreich ataxia, we had identified patients not meeting classic diagnostic criteria, either because they presented preserved reflexes or age of onset older than 25 years, which led us to suggest that there was a need to change those criteria.[49,50] Soon after the identification of the gene causing the disease in chromosome 9,[52] Dr Sue Chamberlain (St. Mary's Hospital, London) contacted us to request information about families including two or more patients with Friedreich ataxia. We informed her that our series included a large family with a pseudo-dominant pattern (see figure 1 in Polo et al.[50]), with patients presenting the mentioned atypical clinical features. This family and another three families from Cantabria were included in a multi-centre study that showed genetic homogeneity at the locus in the total cases studied,[53] which led researchers to review the applicable diagnostic criteria at that time. After cloning the *FXN* causal gene,[54] researchers found that

25% of patients carrying the homozygous GAA expansion in the gene showed atypical clinical symptoms.[55] We subsequently described a family with three siblings presenting late-onset spastic ataxia, whose molecular study revealed a small GAA1 expansion (between 131 and 156 repeats).[56] Neurophysiological studies revealed relative preservation of peripheral sensory conduction parameters with pronounced alteration of somatosensory evoked potentials. This indicates that this late variant may lead to a central sensory axonopathy, with preservation of the somatic afferent fibres, including Ia fibres (see below for more details). Regarding the clinico-molecular correlations in Friedreich ataxia, our group established the possible association between abnormal GAA2 size (not exceeding 800 repeats), and younger age at symptom onset.[57,58] We described the cases of two patients with Friedreich ataxia with pure initial symptoms of tabes, although the molecular study revealed a GAA1 expansion within classical ranges, which supports the variable phenotypic expression of the *FXN* mutation.[59,60] This was subsequently corroborated in a case of late-onset Friedreich ataxia with clinical symptoms similar to those of cerebellar MSA (see the video included as supplementary material of Berciano et al.[61]).

Among our patients with early-onset ataxia other than Friedreich ataxia, there were two families with autosomal recessive or pseudo-dominant inheritance pattern, whose clinical symptoms combined retinitis pigmentosa and sensory neuropathy with a marked proprioceptive deficit (Figure 4).[50] After reviewing the literature, we proposed that this was a novel, well-defined entity and that it should be included in McKusick's Mendelian Inheritance in Man catalogue (OMIM).[62] In 1997, without citing our study, Higgins et al.[63] described a family with a similar condition that was named "autosomal recessive posterior column ataxia and retinitis pigmentosa (PCARP)." We replied,[64] arguing that the findings of Higgins et al.[63] and our own probably corresponded to the same syndrome; in a subsequent reply, Higgins[65] questioned our assertion. The following year, by linkage analysis, Higgins located the PCARP gene on chromosome 1q31-q32,[66] which led us to offer him DNA samples from our patients for him to confirm genetic homogeneity, as he finally observed.[67] This story culminated in 2010 with the identification in our own and in their patients of a homozygous mutation (N121D) in the *FLVCR1* gene[68]; this mutation possibly causes a defect in the regulation or processing of heme in the central nervous system, responsible for neurodegeneration. Currently, PCARP is included in the OMIM catalogue under code number 609033.

Already in the molecular era, Dr Infante Ceberio focused his thesis on the study of dominant ataxias (spinocerebellar ataxias, SCA).[69,70] His series included 30 families, with 65 patients studied. The prevalence of SCA in Cantabria was estimated at 1.6 cases (95% CI, 0.7-3.0) per 100 000 population. The corresponding dynamic causal mutation was detected in 70% of families: SCA2 in 9, SCA3 in 6, SCA7 in 3, and dentatorubral-pallidoluysian atrophy in 1. Clinico-molecular and neurophysiological correlations were established.[69-73] SCA2 is characterised by the triad of areflexia, slow saccades, and reduced vibration sensitivity with abolished jaw reflex; SCA3 by nystagmus, pyramidal signs, or leg areflexia; and SCA7 by retinal degeneration, slow saccades, and pyramidal signs. In this series, two novel semiological variants were observed: SCA2 associated with parkinsonism with good response to levodopa, which ultimately led to motor neuron syndrome,[74] and SCA3 with stiff person syndrome and generalised myokymia (see video in Infante et al.[74]). Autopsy material from our family with Menzel-type OPCA,[17,19] eventually identified as SCA2,[68,69] displayed glial inclusions[75-76] that, unlike in MSA, were not immunoreactive to synuclein.[77] Regarding the familial MSA originally described by Lewis,[78] our critical review suggested that this was not MSA but rather a family with SCA that may perhaps be classified as SCA3.[79]

With the magnificent advances in molecular genetics, the complexity of dominant ataxia has significantly increased, reaching 48 subtypes, mainly caused by dynamic mutations and rarely by conventional mutations (see OMIM, 67 search results). Both Dr Infante Ceberio and I have been part of EUROSCA since its launch 16 years ago. Of the project's fruitful scientific activity,[80-89] I would like to highlight only our contribution to the design of the Scale for Assessment and Rating of Ataxia (SARA).[80] To that end, we performed protocolised, video-recorded examinations of 12 patients with SCA, who were subsequently reassessed by two other members of EUROSCA; the final result, which included a mean of 144 cases between the two trials, was the creation of the SARA scale, which is very frequently used in clinical neurological practice.

SCA38 is a very rare form of dominant ataxia caused by point mutations in the *ELOVL5* gene, which codes for an elongase (ELOVL5) participating in the synthesis of very

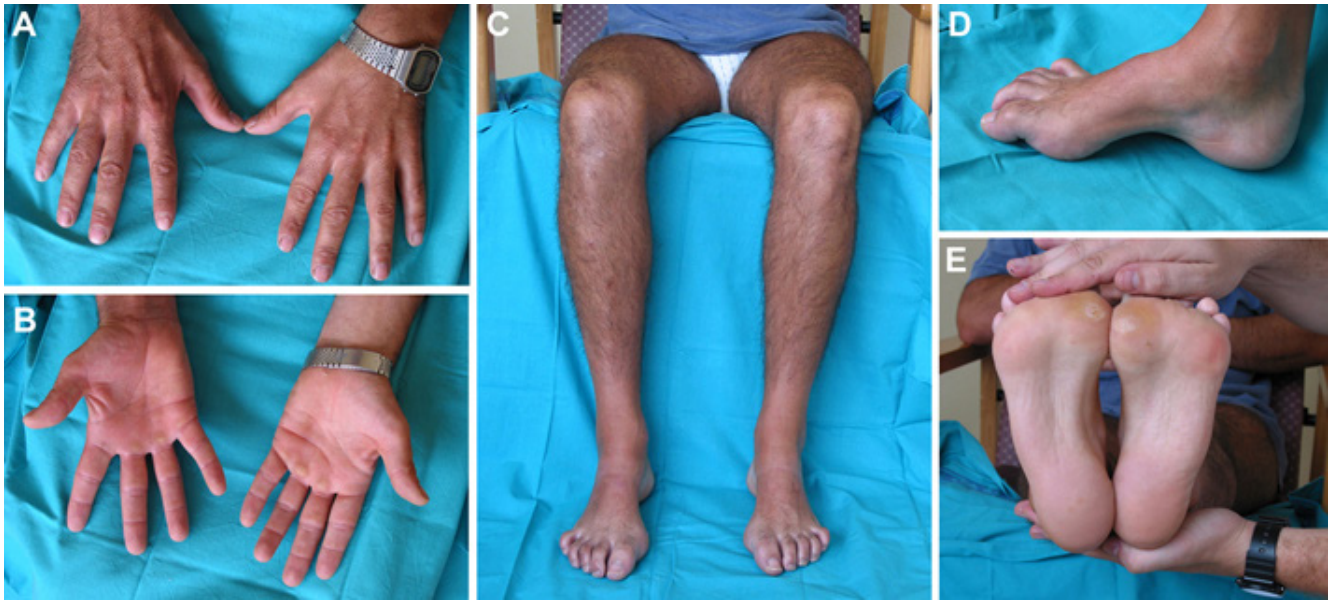


Figure 5. Patient with ARSACS.[96] **A**) and **B**) Close-up of the hands, showing bilateral atrophy of the first interosseous muscle and incipient flattening of the thenar eminences. **C**) and **D**) Presence of pes cavus with hammer toes, pronounced bilateral atrophy of the abductor hallucis, flattening of the anterior plantar arch, and callus on the head of the first metatarsals.

long–chain fatty acids.[90] Collaborating with Dr Gazulla Abío, we described a new family including seven patients with SCA38; all of them presented a heterozygous variant in *ELOVL5*, c.779A>G (p.Tyr260Cys).[91] The phenotype included late symptom onset, ataxia, hearing loss with vestibular dysfunction, intermittent strabismus, and sensory neuronopathy. Baseline levels of docosahexaenoic acid (DHA) were low in four patients; supplementation with DHA restored levels, leading to a clinical improvement according to the SARA scale.

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an early-onset, recessive spastic form of ataxia, with a high prevalence in the Charlevoix-Saguenay area of Quebec (Canada).[92] The causal gene, *SACS*, contains a single exon and encodes the chaperone protein sacsin.[93] The first *SACS* mutation was detected in a European family reported by the Naples group.[94] We had studied a recessive family including two affected individuals, a brother and sister whose symptoms resembled those of ARSACS (Figure 5) (symptoms are illustrated in the video included as supplementary material of Criscuolo et al.[95]). The molecular study performed in the laboratory of Dr Giuseppe De Michele showed a new missense mutation in *SACS*, 7848C>T, which substituted arginine for cysteine at amino acid residue 2556, which is preserved in all species.[95] A particularly interesting aspect of this family was that neurophysiological studies revealed decreased nerve conduction velocity in the intermediate range (this concept is defined below).[96,97] Subsequent studies published in collaboration with Dr Gazulla Abío described the pathophysiological role of hyperplasia of the pontocerebellar fibres in the pyramidal symptoms of the disease, and the mechanisms acting on muscle denervation,[98-100] comparable with those associated with CMT.

Cerebellar ataxia with neuropathy and vestibular areflexia (CANVAS) is a late-onset form of ataxia characterised by the triad of cerebellar, vestibular, and somatosenso-

ry ataxia.[101] Our group described a series of five cases of CANVAS, with some original features that we shall summarise here.[102] We proposed an autosomal recessive inheritance pattern in familial cases, which was corroborated after the discovery that the molecular substrate of the disease is a homozygous, dynamic mutation in the *RFC1* gene.[103-105] Patients may present spasmodic cough (see figure 1 in the supplementary material of Infante et al.[102]), which frequently precedes ataxia even by decades; these symptoms have been related with dysfunction of the sensory C fibres of the upper respiratory tract or oesophagus. Our patients presented highly reduced vibration sensitivity with abolition or pronounced attenuation of somatosensory and distal sensory potentials (see figures 2 and 3 in the supplementary material of Infante et al.[102]), which suggests a sensory neuronopathy with distal and proximal secondary axonopathy. Despite this, stretch reflexes were preserved; in fact, T-reflex testing revealed that the morphology and latency of responses were normal (Figure 6). This led us propose that CANVAS is the first model of severe tabetic neuropathy with preserved Ia fibres.

Let us end this section by making reference to two collaborations with Dr Gazulla Abío, providing new clinico-pathological contributions to the study of hereditary primary lateral sclerosis[106-109] and episodic ataxias.[110,111]

5.2. Charcot-Marie-Tooth disease

Charcot-Marie-Tooth disease (CMT) is the most frequent hereditary neuropathy, and is classically subdivided into five major forms: *i)* CMT1, demyelinating and with an autosomal dominant inheritance pattern; *ii)* CMT2, axonal and with an autosomal dominant inheritance pattern; *iii)* CMT with an autosomal recessive inheritance pattern, whether demyelinating or axonal; *iv)* CMT with an X-linked inheritance pattern; and *v)* intermediate CMT, with a dominant or recessive inheritance pattern. With the recent advances in molecular genetics (panels, WES, and WGS), CMT has become one of the most complex neurological syndromes, with about a hundred pathogenic genes having been cloned (1421 search results in OMIM).

Our studies into CMT started with the doctoral thesis of Dr Combarros Pascual.[112-115] The series included 49 index cases and 95 secondary cases, and we estimated a prevalence of 28.2 cases per 100 000 population in Cantabria. Prevalence rates of demyelinating and axonal forms were similar: 15.3 (95% CI, 12.1-19) and 12.9 (95% CI, 10.6-16.3), respectively. In four families with CMT1, with a total of 26 affected and 21 unaffected individuals, we reached the following conclusions: *i)* peak incidence is in the first decade of life; *ii)* in all age groups, the proportion of affected to unaffected individuals at risk did not significantly differ from the expected 50%; *iii)* there was complete concordance in conduction values between index cases and affected family members; and *iv)* decreased conduction values were detected even in an affected 2.5-year-old family member. Contrary to Bird and Kraft's suggestion that full penetrance of the CMT1 gene would not be reached until the second decade of life,[116] our data suggest that it was already complete since childhood. A few years later, after performing clinico-electrophysiological examinations of 11 families including 73 patients with CMT1 (of 99 individuals examined), we suggested that penetrance was complete since childhood; in fact, from the age of six months, an individual showing normal examination results probably presents zero risk of having inherited the gene causing the disease.[117]

Our pedigree analysis of CMT1, including a considerable number of secondary cases and unaffected subjects at risk, attracted the attention of Dr Harding, who in 1988 requested our collaboration to perform linkage studies. In 1982, Guiloff et al.[118] had reported that the CMT1 locus was linked to the Duffy locus on chromosome 1. This proposal was not confirmed in a large sample of 11 families, including four from Cantabria.[119] In 1989, in a linkage analysis of six families with CMT1, Vance et al.[120] identified the locus of the disease at 17p; this form subsequently came to be known as CMT1A. This finding was immediately corroborated in the 11 families mentioned previously, and even in a family in which the locus had been wrongly identified on chromosome 1.[121] In two independent works published in 1992, the study groups of Raeymakers[122] and Lupski[123] reported that the molecular basis of CMT1A was an allelic trisomy of 1.5 mB at 17p11.2 (CMT1A with duplication; OMIM #118220), now known to include the *PMP22* gene. This finding was corroborated in our families[124]; in fact, we subsequently confirmed the allelic trisomy in all the families with CMT1 that we had previously reported.[113,115] CMT1A with duplication was soon established as the most frequent cause of CMT1.[125]

In the following stage, Dr Antonio García García dedicated his doctoral thesis to the "maturation" of conduc-

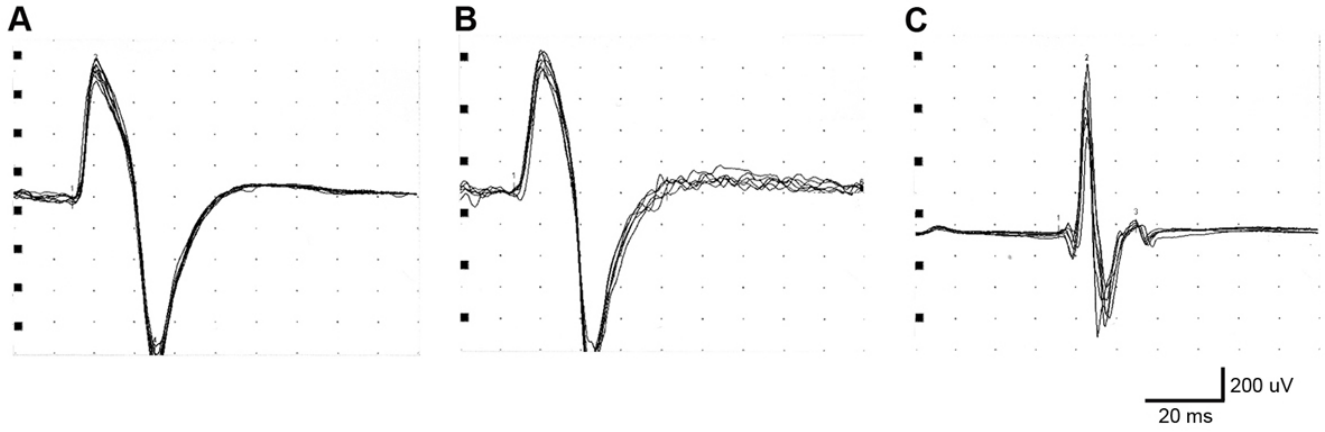
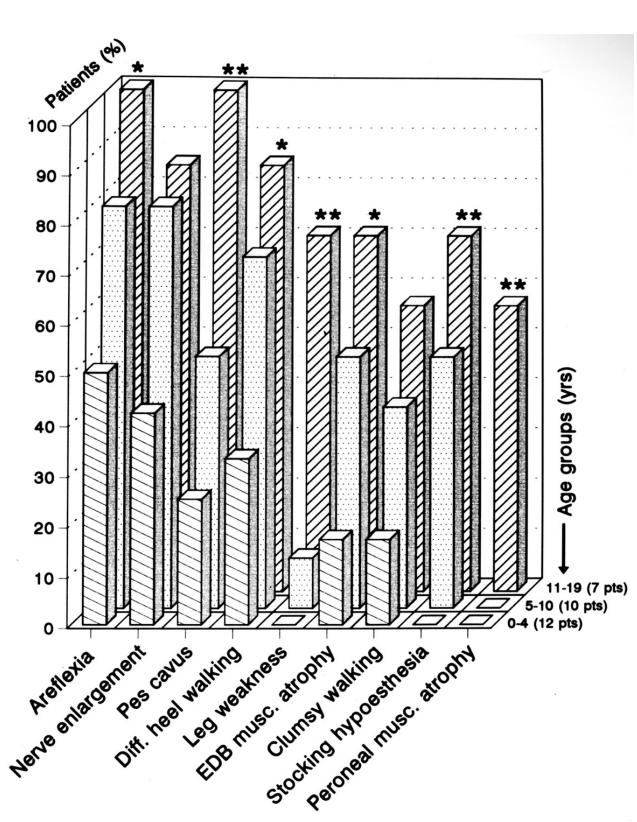


Figure 6. Normal recording of the bicipital T reflex (**A**, **B**) and Achilles reflex (**C**) in two patients with CANVAS, presenting marked reduction in vibration sensation in all four limbs and absence of distal sensory potentials.[102]



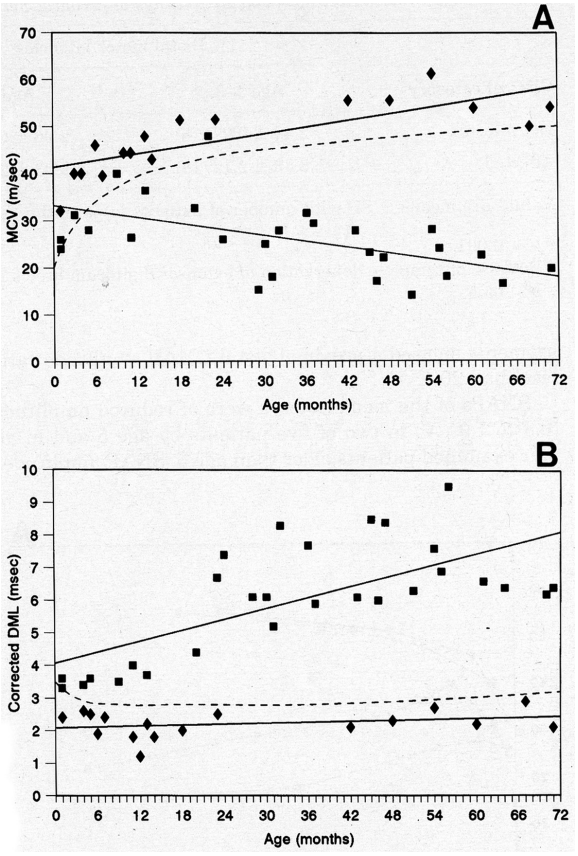


Figure 7. Frequency of signs and symptoms per age group in the 12 children with CMT1A.[125,126]

Figure 8. Measurement of motor conduction velocities (MCV) (**A**) and corrected distal motor latencies (DML) (**B**) in affected (▪) and non-affected children (♦). Continuous lines correspond to regression lines, and dashed lines to the lower limit of normality for MCV, and upper limit of normality for DML. Note how motor conduction alterations are visible in all patients from the age of one year.

tion velocity parameters during the first years of life, dividing the study into two parts, analysed separately: *1)* a cross-sectional study of 92 control children (without neurological disease) divided into six groups: <1 month of life, 2-6 months, 7-12 months, 13-24 months, 25-48 months, and 49-72 months; and *2)* a longitudinal study of 20 children at risk of CMT1A from six unrelated families including one affected parent studied by us. We will detail the findings separately.[126-129]

Physiological maturation of motor and sensory conduction velocities (MCV and SCV) occurs in the first five years of life.[128] The parallel progression of distal motor latencies is explained by applying a correction that considers the distance between the cathode and the recording electrode. Modifications to F-wave latency are explained both by the increase in MCV and by limb growth.

By definition, the 20 children at risk of CMT were assessed within the first five years of life, between one month and four years (mean, 1.5); at the end of the study, ages ranged between four and 19 years (mean of nine).[126,127] Mean follow-up time was 7.7 years. Twelve (seven boys and five girls) of the 20 (60%) individuals at risk were affected. These 12 patients underwent two or more consecutive neurophysiological examinations. Progression is illustrated in Figure 7, showing a clear progression of disease symptoms, although marked peroneal muscular atrophy was only observed in the second decade of life. The percentage of symptomatic patients (essentially, clumsy walking) was 17% in the youngest group (0-4 years) and 42% in the second decade. The frequency of polyneuropathic signs amounted to 50% at the beginning of the study and 83% at the end. From the age of two years, all 12 affected children presented alterations in nerve conduction velocity parameters (Figure 8). There was a perfect concordance with the molecular study of the 17p11.2 duplication. In short: *i)* in the majority of patients with CMT1A, symptoms manifest during adolescence, although signs of peroneal muscular atrophy do not develop until the second decade[130]; *ii)* onset of pes cavus (a cardinal manifestation of CMT) occurs much earlier than peroneal muscular atrophy (Figure 7), which led us to propose that its development depends on weakness not only of peroneal muscles, as reported in the literature, but also of plantar muscles; *iii)* consecutive neuromuscular studies enable identification of carriers of the CMT1A mutation in childhood; and *iv)* confirming our previous findings,[115,117] clinical signs were shown to depend not on the degree of MCV slowing but rather on the degree of attenuation of distal motor potentials, that is, the degree of secondary axonopathy (Figure 9).[126,127,129] More recently, we have shown that carriers of the CMT1A mutation may be identified by studying the T-reflex.[131]

The pathogenic role of amyotrophy of the intrinsic muscles of the foot in the onset of pes cavus in CMT had only been suggested by Sabir and Little,[132] who, during the surgical correction of pes cavus in their patients with CMT, performed a biopsy of the plantar muscles that revealed neurogenic atrophy.

The next step was the MRI study of the muscles of the lower limbs in patients with CMT1A with duplication; this was the focus of the doctoral thesis by Dr Elena Gallardo Agromayor.[133-140] We designed a cross-sectional study of 11 patients with CMT1A, aged between eight and 61 years (median, 24). We applied the Functional Disability Scale (FDS)[141] and the Charcot-Marie-Tooth Neuropathy Score (CMTNS)[142]; six patients with pes cavus presented minimal disability (scores of 0-1 in the FDS and ≤ 10 in the CMTNS), whereas the remaining five presented pes cavus with scores indicating moderate disability. In every patient with mild disease, we detected fatty atrophy of the intrinsic muscles of the feet (Figure 10 C-D), sparing the calf muscles. In the remaining five patients with moderate CMT1A, fatty atrophy of the muscles of the feet was more pronounced (Figure 10 E-F), now associated with fatty atrophy of predominantly peroneal muscles (Figure 11). Therefore, these findings suggest that the denervation process begins in the intrinsic muscles of the foot, particularly in the lumbricals, triggering anterior pes cavus prior to involvement of the peroneal muscles.[143] Areas of oedema were observed in the muscles of the leg (see figure 6 in Gallardo et al.[134]), suggesting that a process of subacute denervation may be in effect in CMT1A; in fact, there are cases of CMT1A with added pathogenic inflammation.[144]

In two large families with CMT1A with duplication, in which 29 subjects were examined and regularly followed up for two or more decades, we observed that the course of the disease is very latent, with minimal or no progression in the majority of cases.[135,138] This is extremely important because the therapeutic trials had been designed to last two years, that is, an insufficient duration considering that the natural history of the disease does not change in that period.[145] This was the basis of the doctoral thesis by Dr Ana L. Pelayo-Negro, who led a 2-year lon-

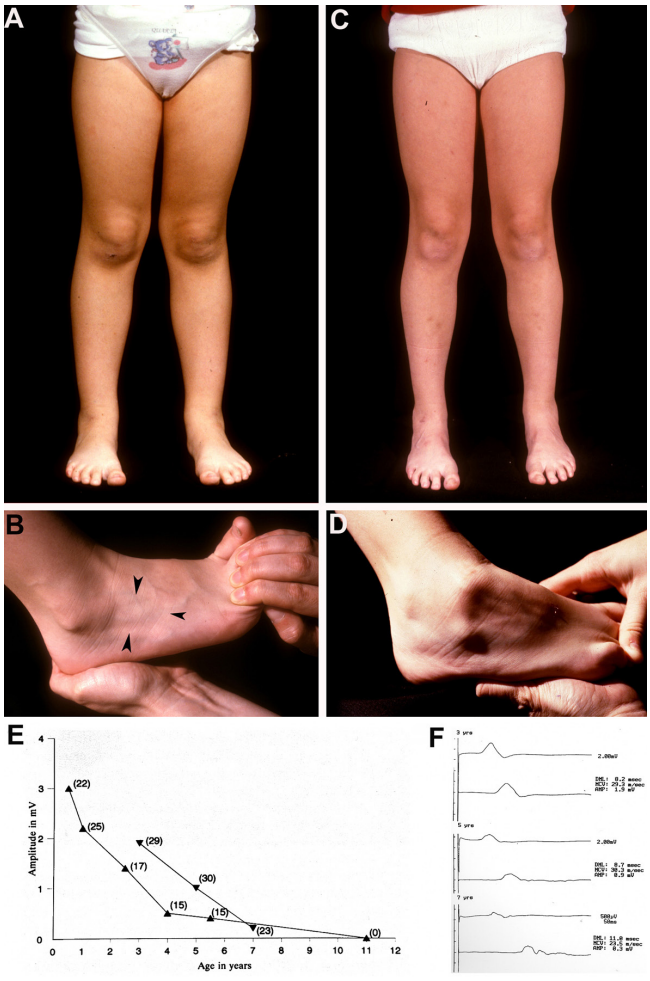


Figure 9. Consecutive images of an asymptomatic patient with CMT1A at the age of four (**A**, **B**) and eight years (**C**, **D**). The extensor digitorum brevis was initially flattened upon palpation, but this sign is barely visible in the close-up image (**B**, arrowheads). Four years later, muscle atrophy was very visible, leaving a pronounced hollow (**D**). No peroneal muscle atrophy is observed (**A**, **C**); therefore, as mentioned in the study, the disease first affects the intrinsic muscles of the foot and later extends to the leg. **E**) CMAP amplitudes of the extensor digitorum brevis in two patients with CMT1A. The connected symbols correspond to the values of consecutive amplitudes (y-axis, expressed in mV) as a function of age (x-axis); numbers in parentheses correspond to the motor conduction velocity of the peroneal nerve. Atrophy of the extensor digitorum brevis was detected between the ages of six and eight years. Drastically reduced amplitudes in motor potentials are observed with relatively preserved conduction velocities, which are only reduced when the amplitude is close to or below 1 mV. **F**) CMAP recording of the extensor digitorum brevis after proximal and distal stimulation of the peroneal nerve in the case represented with inverted triangles in image **E** (right side of the image). Potentials show progressive attenuation, with temporal dispersion only in the last recording (seven years), when amplitude was very reduced (0.3 mV). Total recording time was 50 ms. Vertical calibration was 2 mV in the recordings performed at three and five years of age, and 500 mV at seven years. This consecutive neurophysiological study suggests that onset of amyotrophy of the extensor digitorum brevis does not depend on motor conduction slowing, but rather on the attenuation of motor potentials, that is, sudden axonal degeneration. DML: distal motor latency; MCV: motor conduction velocity. Source: adapted from Berciano et al.[129]

gitudinal study including clinical, neurophysiological, and neuroimaging examination of 14 subjects with CMT1A with duplication and 14 controls.[146,147] Patients presented limited data suggestive of progression, although in the multivariate analysis, none of them helped predict disease progression. To our knowledge, the initial gait disorder, an essential manifestation of CMT1A, depends more on the modification of the foot architecture due to denervation of the intrinsic muscles rather than on peroneal weakness; no pharmacological treatment is expected to correct the symptoms of anterior pes cavus.[139]

Through our active participation in the CMT Consortium, we were able to establish a close collaboration with the Neurogenetics Group of the University of Antwerp (Dr Peter De Jonghe and Dr Albena Jordanova). This resulted in contributions to the nosological definition of CMT2M[146,147] (*DNM2*; OMIM #606482), CMT2J[148] (*MPZ*; OMIM #607736), and CMT2C[149,150] (*TRPV4*; OMIM #606071). We should also mention our two studies on CMT2E[151,152] (*NEFL*; OMIM #607684), which enabled an electrophysiological redefinition of the intermediate form of CMT[153]; Figure 12 summarises this new definition, which essentially consists in the need to examine proximal nerve segments of the arm when the distal potential shows reduced amplitude.

To finish this section, let us consider a large family with CMT2 including ten patients in three generations, displaying male-to-male transmission.[154] In 1986, seven of the ten subjects from the second generation, aged between 22 and 41 years, were affected; however, only one of the ten at risk from the third generation, aged between one and 15 years, was affected. Clinical symptoms included peroneal muscle atrophy with pes cavus and stocking hypoaesthesia, but no signs involving the hands. The findings of the autopsy study of the proband and of the nerves from an amputated leg of his older brother revealed motor and sensory neuronopathy with secondary, length-dependent axonopathy (Figure 13). We regularly followed up patients and individuals at risk. In 2004, in a linkage analysis, we identified the locus at 12q-q13.3 (CMT2G; OMIM #610933).[155] By that time, we suspected that penetrance may be incomplete, even in patients in the second or third decade of life. The scenario changed in the following decade, after consecutive clinical (Figure 14) and neurophysiological examinations, MRI studies of lower limb muscles (Figure 15), and the application of new technologies for mutation analysis (WES/WGS). We detected a pathogenic mutation in the *LRSAM1* gene

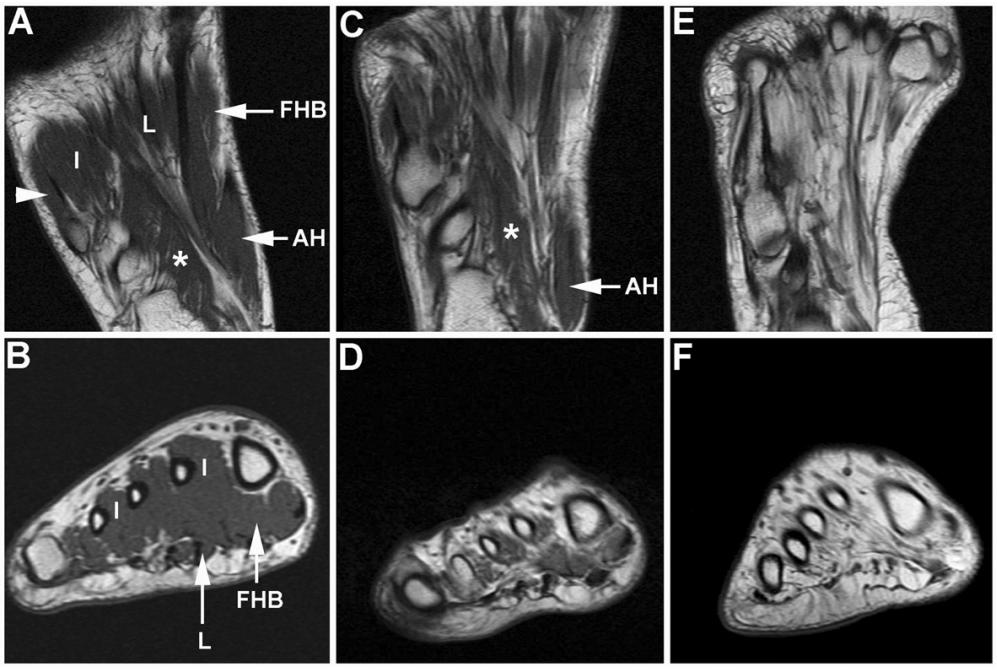


Figure 10. T1-weighted MRI sequences of the muscles of the foot in a control subject (**A**, **B**) and patients with minimal (FDS, 0; CMTNS, 2) (**C** and **D**) or moderate symptoms (FDS, 2; CMTNS, 12) of CMT1A (**E**, **F**); all images were obtained at the same locations on the long and short axes of the foot.[134] **A**) Normal muscles identified in this axial section include the lumbricals (L), interossei (I), flexor hallucis brevis (FHB), abductor hallucis (AH), flexor digitorum accesorius (asterisk), and flexor digiti minimi brevis (arrowhead). **B**) This coronal section shows the lumbricals (L), interossei (I), and the flexor hallucis brevis (FHB). **C**) and **D**) A marked but not total fatty infiltration is observed in the intrinsic muscles of the leg, except for the AH and flexor digitorum accesorius (asterisk), which are preserved; leg muscles (not shown, see figure 4 in Gallardo et al.[134]) were normal. (**E**, **F**) Compared with the previous case, massive fatty infiltration is observed in all the intrinsic muscles of the foot.

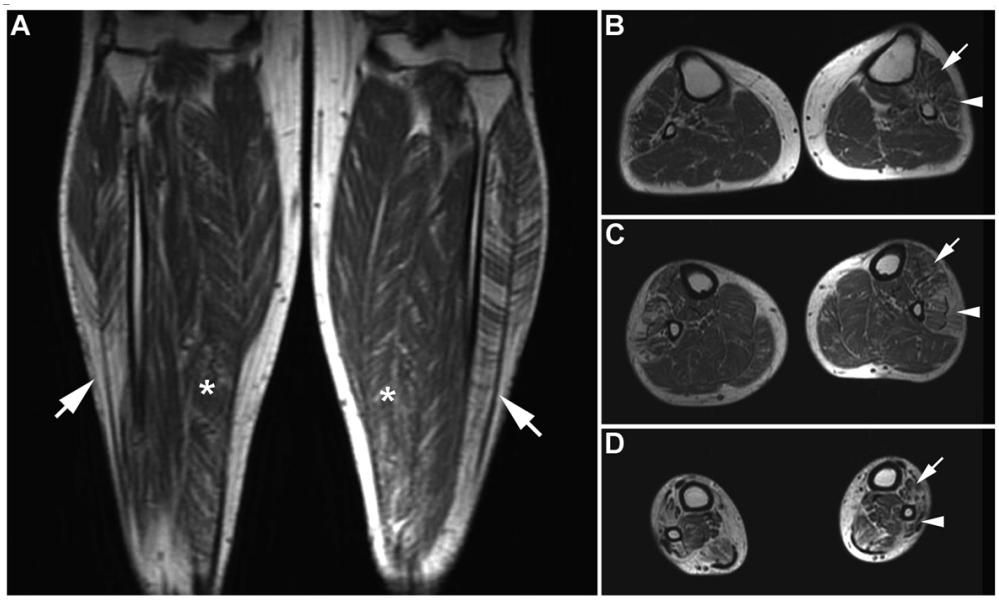


Figure 11. MRI study of the patient described in Figure 10 E-F.[134] **A**) T1-weighted coronal section of the legs showing extensive, striped fatty infiltration of the peroneal muscles, which is more pronounced in distal areas (arrows). The distal portion of the soleus muscles is less affected (asterisks). T1-weighted axial images (**B**, proximal third of the legs; **C**, middle third; **D**, distal third) showing predominantly distal fatty infiltration in the muscles of the anterior (arrows) and lateral (arrowheads) compartments; the posterior compartments are spared.

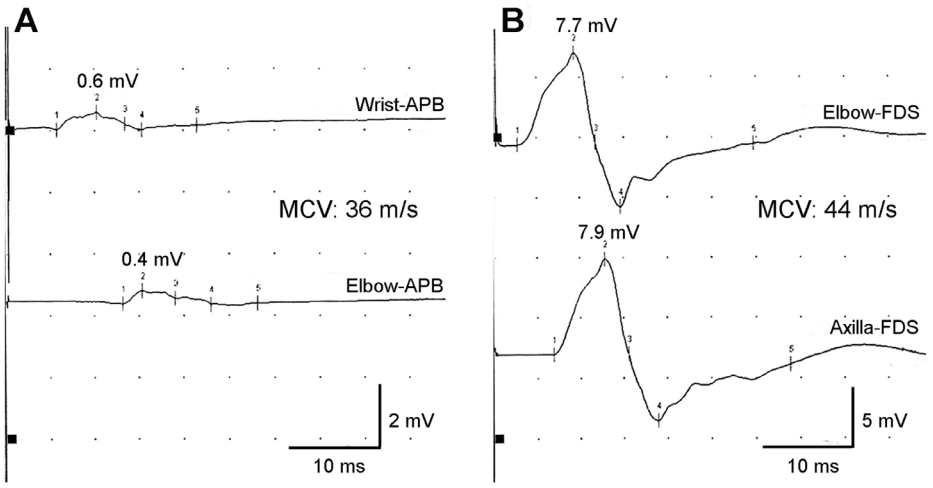


Figure 12. Motor conduction velocity (MCV) of the median nerve in a 59-year-old patient from a family with intermediate, dominant CMT linked to the E396K mutation of the *NEFL* gene.[151,153] **A**) The recorded MCV of 36 m/s (elbow-wrist segment), within the intermediate range (30 to 40 m/s), may be secondary to the pronounced decrease in compound muscle action potential amplitude (15% of the lower limit of normality [≥ 4 mV]), ie, to the loss of thick myelinated fibres. The question is solved by studying the elbow-axilla segment, with stimulation at the axilla and the elbow, and recording in the flexor digitorum sublimis muscle (FDS) (**B**). Motor potential amplitude is then normal, but the velocity recorded (44 m/s) is within the intermediate range for this segment (normal, ≥ 54 m/s).

(p.Cys694Tyr) displaying a perfect clinico-molecular correlation, which led to the reclassification of the disease as CMT2P (OMIM #614436)[156,157]; see Palaima et al.[157] for an analysis of the molecular mechanisms in this *LRSAM1* mutation. Let us only mention that the maximum expression of *LRSAM1* in the foetus affects spinal motor and sensory neurons, this is perfectly consistent with our histopathological findings (see above). It took us almost four decades of follow-up to reliably identify carriers of the *LRSAM1* mutation, a fact duly noted by Dr Michael Shy[158] in the accompanying editorial:

> Peeters and colleagues demonstrate to readers that making a genetic diagnosis still depends on careful clinical neurology, even with modern DNA analysis. The authors needed to go back and re-examine family members thought to be affected, comparing findings over many years, and it was only when several individuals thought to be affected were reclassified that the researchers were able to identify the *LRSAM1* mutation.

5.3. Guillain-Barré syndrome

SGB is an acute, immune-mediated polyradiculoneuropathy with three basic patterns[159]: *i)* demyelinating, or acute inflammatory demyelinating polyneuropathy (AIDP); *ii)* axonal, or acute motor axonal neuropathy (AMAN)/acute motor-sensory axonal neuropathy (AMSAN), frequently associated with antiganglioside reactivity (especially anti-GM1 and anti-Gd1a antibodies); and *iii)* Miller-Fisher syndrome (almost always with anti-GQ1b antibodies).

Dr María José Sedano Tous dedicated her doctoral thesis to the study of GBS in Cantabria in the period 1975-1988.[160,161] Based on the study of 69 patients living in the region, she established annual incidence rate of 0.95 cases per 100 000 population (95% CI, 0.72-1.16). There was a clear predominance of AIDP, with only eight patients presenting other variants: four with the axonal form, two with Miller-Fisher syndrome, and two with the pure sensory variant. At three, six, and 24 months after onset, 70%, 46%, and 12% of patients, respectively, presented poor prognosis. Factors associated with poor prognosis at three months were fast symptom progression, long plateau phase duration, age over 40 years, pronounced weakness during peak severity, electromyography evidence of active denervation, and loss of nerve excitability. These findings were corroborated in another recent study conducted in Valdecilla, in which we observed a

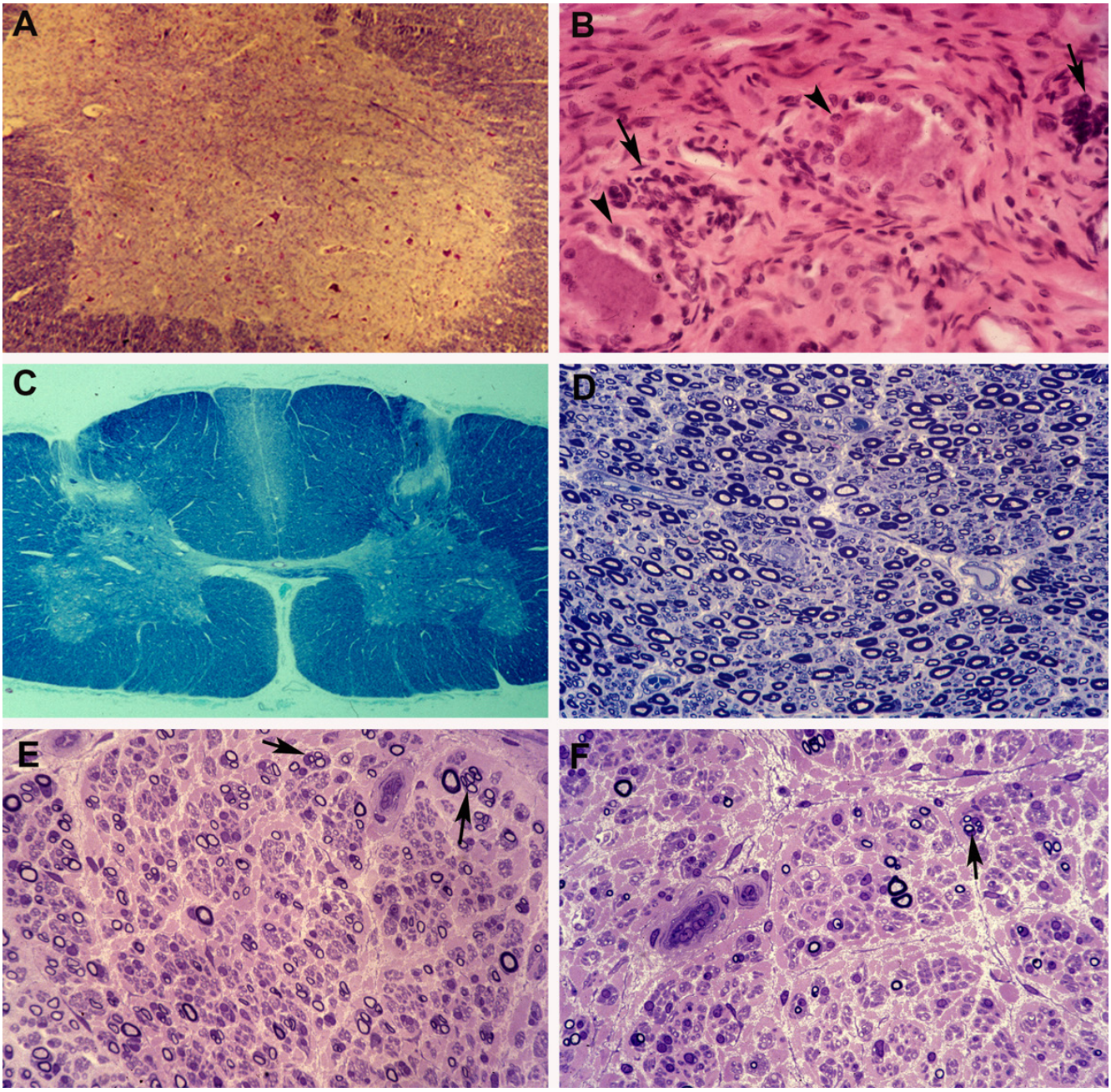


Figure 13. Pathological findings in CMT2P (AC family).[154,156] Autopsy material (**A**-**D**) from the proband (case III-7 in Berciano et al.[154]) and histological study of the tibial nerve (**E**, **F**) dissected from an amputated leg of his older brother (case III-5). **A**) Transverse section of the spinal cord at the S1 level, showing loss of motor neurons and gliosis (Klüver-Barrera staining). **B**) Lumbar spinal ganglion with reduced number of neurons, proliferation of satellite glial cells (arrowheads) and residual Nageotte nodules (arrows) (haematoxylin and eosin staining). **C**) Transverse section of the lower spinal cord at the C5 segment showing demyelination of the column of Goll (Klüver-Barrera staining). **D**) Semithin sections of the posterior L5 root showing a reduction in thick myelinated fibres (≥ 8 µm) and proliferation of thin fibres (see histograms in figure 12 in Berciano et al.[154]) (toluidine blue staining). **E**) and **F**) Semithin transverse sections of the tibial nerve in its upper and lower third, showing pronounced loss of myelinated fibres with a clear proximal-distal gradient (histograms in figure 5 in Berciano et al.[154]) and presence of clusters of regeneration (arrows) (toluidine blue staining).

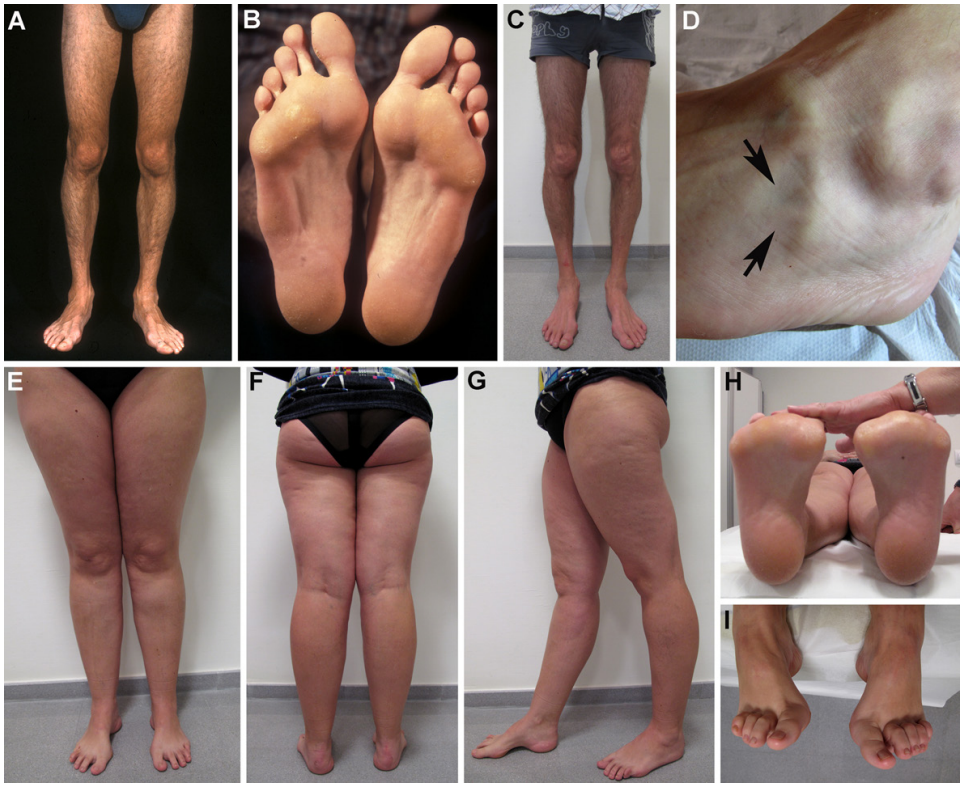


Figure 14. Phenotype of CMT2P.[156] Consecutive pictures of case IV-4 (**A**-**D**) and case IV-11 at the age of 32 years (**E**-**I**). A) At the age of 25 years, the legs appeared normal; particularly, note the absence of peroneal muscle atrophy and claw toes. **B**) Close-up pictures of the soles of the feet showing midfoot hollowing and callosity over the transverse arcus plantaris and external borders of the foot. **C**) At the age of 43 years, amyotrophy is notable mainly in the peroneal muscles; despite this, there was no weakness of the foot flexors/extensors or difficulty in heel walking. **D**) Close-up picture of the left foot showing atrophy of extensor digitorum brevis muscle (arrows). **E**-**G**) There is no lower-leg amyotrophy; pes cavus and clawing of toes are visible even when standing. **H**) and **I**) Close-up pictures of the feet showing marked pes cavovarus deformity and toe clawing.

considerable increase in the frequency of axonal forms (28.5%), which suggests better understanding of the nosology of the syndrome.[162]

Let us now analyse the clinico-pathological studies performed in five fatal cases of GBS reported between 1993 and 2015.[163-168] I would like to mention some other works by the Valdecilla group, whose histopathological findings have modified the nosology of the syndrome.[169-192]

Pure motor GBS was equivalent to its axonal form. In a patient with the motor form, the histological examination revealed a demyelinating disease of the ventral spinal roots with secondary axonal degeneration[163] (Figure 16). In the discussion, we noted the similarity between the lesions we observed and the findings reported by Feasby et al.[193] in axonal GBS. This led to a lively controversy around the nosology of axonal GBS in the "Issues and Opinions" section (June 1994) of the journal *Muscle & Nerve*.[194-196] With the scientific expertise acquired over time, and after analysing in detail figure 1 (semithin section of a lumbar ventral root) of the original publication by Feasby,[193] we had no doubt that we observed both axonal and demyelinating lesions[185,189]; in line with what had previously been reported, this may have been confirmed by a teased-fibre study of the spinal root (Figure 16). In any case, we concluded that in early stages of severe GBS, it remained challenging to confidently establish whether we are dealing with a primary axonal disease or a myelin disease.[189] To determine this, a consecutive neurophysiological study was essential.

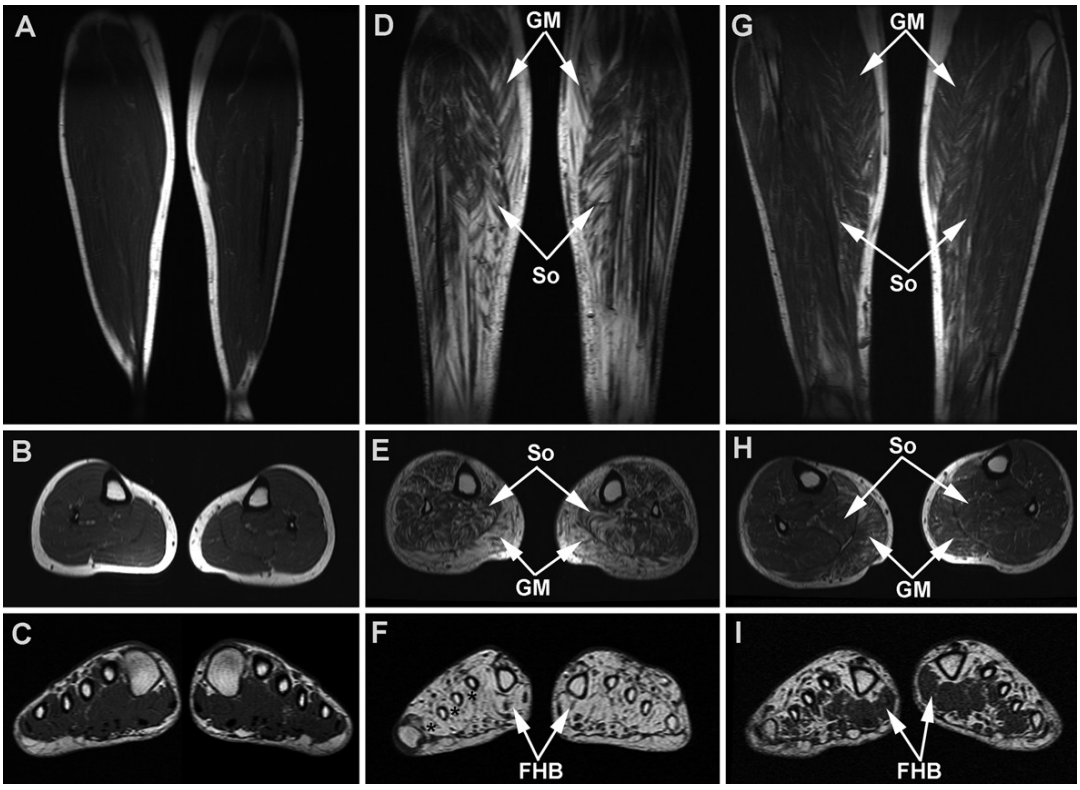


Figure 15. T1-weighted MR images of the legs in the coronal plane from the posterior aspect (top row) and in the axial plane at the mid-calves (middle row), and of the feet at the metatarsal bones (bottom row).[156] **A**-**C**) Case IV-8, showing normal MRI study findings and no *LRSAM1* mutation. **D**-**F**) Case III-10, aged 59 years and with a Charcot-Marie-Tooth neuropathy score (CMTNS) of 9, showing predominantly distal fatty infiltration of all 4 muscle compartments, mainly involving the soleus (So) and gastrocnemius medialis (GM) muscles; massive fatty atrophy of intrinsic foot musculature is shown, especially in the interossei (asterisks) and flexor hallucis brevis (FHB) muscles. **G**-**I**) Case IV-1, aged 41 and with a CMTNS of 3, shows minimal fatty infiltration of soleus (So) and gastrocnemius medialis (GM) muscles; atrophy of the intrinsic foot muscles is more advanced (only FHB are labelled).

Four years later, we studied the case of a patient with fulminant GBS, whose consecutive neurophysiological studies at days 3, 10, and 17 of progression revealed a universal loss of nerve excitability, including the mixed conduction of the median nerve.[164] We reported that this loss was not solely explained by a distal block, but also by a conduction failure in intermediate segments of the nerve trunks. The autopsy study revealed pure inflammatory demyelination of the spinal roots, whereas all the more distal nerve trunks showed predominantly axonal mixed pathology (Figure 17). At this point, we wondered how this histological divergence might be explained. Given the lack of similar pathological findings in humans, we reviewed data on P_2-induced experimental autoimmune neuritis (EAN) in Lewis rats, a recognised model of AIDP.[197-199] Typical immunogen doses cause uniform demyelination of the peripheral nervous system (PNS), whereas with higher doses, the pathological substrate is comparable to what we had observed: pure demyelination of the spinal roots, with mixed pathology (demyelinating and axonal) in more distal nerve trunks. This lesion topography had been associated with a bystander effect, with a more intense inflammatory reaction at higher immunogen doses. We argued that this mechanism did not seem to apply in our material, as the macrophagic inflammatory component was comparable in the roots and at more distal locations (see Figure 17). After studying the microscopic anatomy of the PNS,[200] and after much thought about the pathogenic background of the case, we wondered whether the appear-

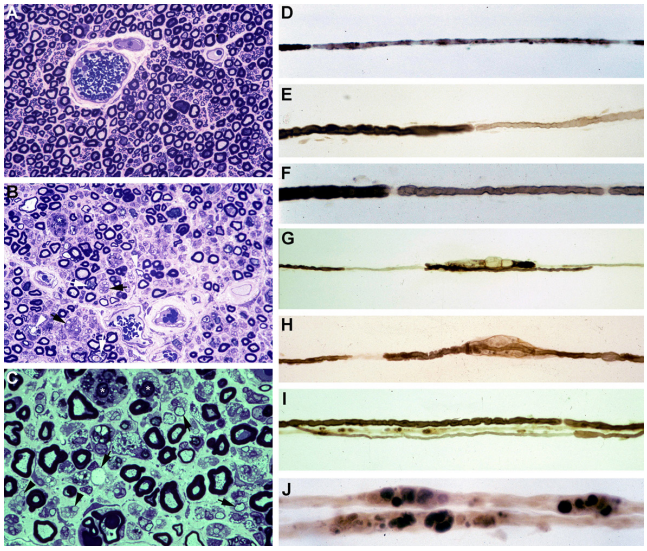


Figure 16. Pathology of pure motor GBS.[163] **A**) Semithin section from the L5 dorsal root showing preserved myelinated fibres (toluidine blue staining). **B**) On the contrary, this semithin section from the L5 ventral root displays a clear reduction in the density of myelinated fibres, presence of lipid-laden macrophages, endoneurial oedema, fibres showing vacuolar myelin dissolution (white arrows), de-/remyelinated fibres (white arrowheads), fibres presenting myelin breakdown, indicating active axonal degeneration (asterisks), and clusters of regeneration (black arrows) (toluidine blue staining). **C**) At greater magnification, this semithin section from the L5 ventral root displays numerous lipid-laden macrophages, de-/remyelinated fibres (black arrows), fibres presenting myelin breakdown (white asterisks), and clusters of regeneration (black arrowheads). Based on these images, it is difficult to establish whether the pathology is primarily axonal or demyelinating. To answer this question, we conducted a teased-fibre study of the L5 ventral root (**D**-**J**), observing the following findings: complete internodal demyelination (**D**); complete internodal remyelination (**E**, **F**); paranodal demyelination with vesiculovacuolar myelin dissolution (**G**, **H**); some groups of fibres of variable morphology (I), including a normal fibre (top), one presenting axonal degeneration (middle), and one presenting de-/remyelination (bottom); and fibres with linear rows of osmiophilic droplets, characteristic of active axonal degeneration (**J**). As 24% of teased fibres presented complete internodal de-/remyelination, we concluded that the patient presented primarily demyelinating disease with secondary axonal degeneration.

ance of epi-perineurium at the subarachnoid angle may play a pathogenic role in early stages of GBS. To verify this hypothesis, we needed to compare the pathology in the nerve roots, with their thin arachnoid covering, and in the spinal nerves with epi-perineurium.

In each case of fatal GBS with neurophysiological evidence of axonal involvement at onset, the post mortem pathology study identified the pathological alterations typical of AIDP, but with a drastic difference in pathology between the spinal roots and the spinal nerves: in the latter structure, inflammatory demyelination was associated with lesions suggestive of endoneurial ischaemia (Figure 18).[165,166] These findings corroborated the first description by Haymaker and Kernohan[201] locating the initial predominant lesions at the convergence of the anterior and posterior spinal roots to form the spinal nerves; furthermore, these authors very accurately suggested that the initial histological alteration was oedema. Years later, Izumo et al.[197] described the chronology of symptoms and lesions in EAN in Lewy rats as follows: *i)* disease initially manifests with flaccid tail and hindlimb paralysis at day 3.5-4 post-inoculation of the immunogen (T cells sensitised against myelin P_2 protein); *ii)* the first histological alteration is visible at day 4 post-inoculation and is characterised by endoneurial inflammatory oedema; and *iii)* between days 7 and 9 post-inoculation, demyelination and axonal degeneration appear. By then, it was established that oedema in EAN may be pathogenic when it critically increases endoneurial pressure, as it constrains transperineurial blood vessels leading to ischaemic conduction failure, and eventually endoneurial ischaemia with the subsequent active axonal degeneration (Figure 18B).[202]

Persuaded by the pathogenic value of endoneurial oedema in early stages of GBS, we designed a prospective study of the early stage (≤ 10 days after onset) using ultrasound mapping of peripheral nerve trunks, including the ventral rami of the fifth to seventh cervical nerves.[167] The study included six patients with classical and severe GBS: four classified as AIDP and two as AMSAN. When compared with controls, the most relevant ultrasound finding, though not constant, was a significant increase in the cross-sectional area of the cervical nerves, with blurring of perineurial rims (Figure 19). The autopsy study of one of the deceased patients, who died at day 9, showed that the fundamental lesion was inflammatory endoneurial oedema, with clear predominance of the ventral rami of the cervical and lumbar nerves (Figure 20).

As explained in the section on CMT, muscle MRI is a sensitive technique for detecting muscle denervation from the acute to the chronic stage.[203] For us, this technique has been of inestimable value in studying the progression of alteration to the muscles of the pelvis and the lower limbs in two specific situations: *i)* in a patient with GBS and prolonged nerve excitability, indicative of poor prognosis, the consecutive MRI study revealed absence of signs of subacute denervation, which suggests unaffected muscles and good progression, as subsequently

occurred in prolonged follow-up[204]; and *ii)* in a patient with AMAN with severe paresis of the legs and thighs, the MRI study reliably revealed chronic muscle denervation, which subsequently helped in the functional diagnosis and to guide rehabilitation.[205] MRI studies with fat-suppression sequences (STIR or fat-suppressed T2-weighted sequences) may be extremely helpful to delimit the location of endoneurial oedema in the early stages of GBS, and particularly to show that spinal nerves are a hotspot for every form of GBS.[167,182,183,185,188-190,206]

Also persuaded by the pathogenic role of endoneurial oedema in very early stages of GBS (up to four days after onset), we performed two retrospective studies including 22 patients with consecutive neurophysiological studies, with the first being performed within the first four days after onset.[187,191] In the first neurophysiological examination, only 20% of cases could be classified as axonal or demyelinating forms, with alteration of the F-wave and distal compound muscle action potential attenuation being the most frequent neurophysiological findings. Again, the first study corroborated that early ultrasound alterations affect the spinal nerves.[187] We concluded that endoneurial oedema in the spinal nerves and pre-terminal nerve segments is an essential pathogenic element in the first days of the disease, when demyelination and axonal degeneration have not yet manifested. Figure 21 depicts the microscopic anatomy of the PNS from its origin at the spinal root to the formation of the spinal nerve, with its dorsal and ventral rami, followed by a subsidiary, more distal nerve trunk. With this, we aim to illustrate that the location of the initial inflammatory oedema differs between preforaminal and postforaminal nerve trunks (see caption to Figure 21), which in very early stages of GBS gives rise to other additional considerations: *i)* abrupt endoneurial ischaemia explains the increase in levels of neurofilament light protein (NfL) in the serum, even in primarily demyelinating forms[207]; *ii)* the probable pathogenic role of oedema is the rational basis to add intravenous methylprednisolone pulse therapy to conventional immunotherapy[189,192,208,209]; and *iii)* proximal motor conduction block, whether in AMAN or AIDP, may manifest as reversible conduction failure.[191]

We noted previously that in CANVAS, afferent fibres may be preserved despite the presence of severe somatosensory deficit.[102] For instance, in a 36-year-old patient with classical GBS (tetraparesis scoring 3-4/5 on the MRC scale) and generalised areflexia, we observed abolished Achilles T-reflex at day 7, whereas findings in the motor and sensory conduction studies were normal.[186] Treatment with intravenous immunoglobulins achieved a fast response with total recovery. At day 33, study of the Achilles T-reflex revealed normal amplitude and latency. Based on these data, we proposed that recording of T-reflex enables detection of reversible conduction failure, which probably indicates selective dysfunction of Ia fibres. Ia fibres are the fastest (conduction velocity, 80-120 m/s) and thickest (diameter, 12-21 μm) of the PNS,[210] and therefore, as our findings suggest, probably present selective vulnerability to the causes of the different neuropathic syndromes.[211]

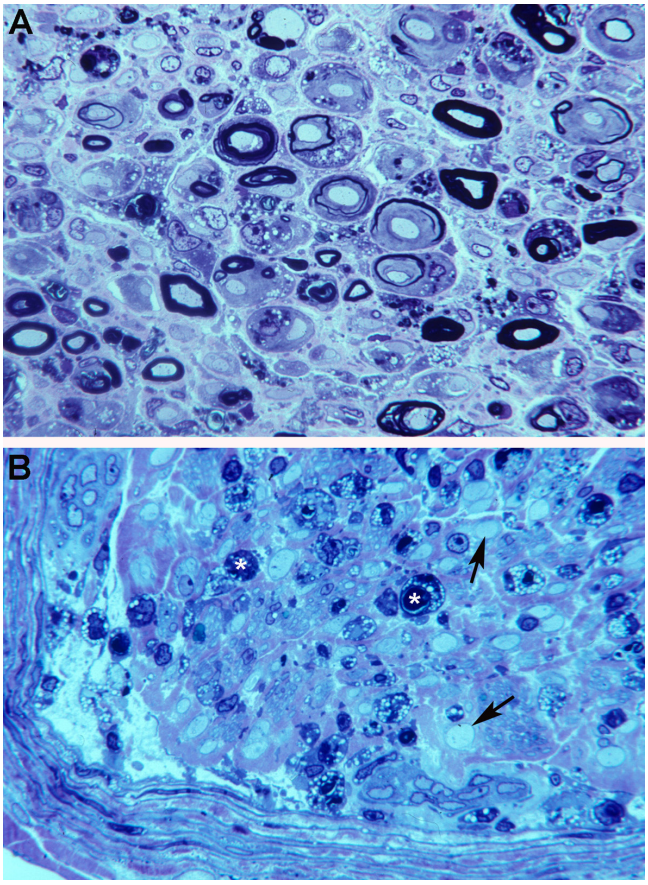


Figure 17. Guillain-Barré syndrome with early loss of excitability of the nerve trunks. **A**) Semithin section from the L5 ventral root, displaying massive demyelination, numerous lipid-laden macrophages, and interstitial oedema (toluidine blue staining). **B**) Semithin section from the crural nerve, presenting numerous fibres with myelin breakdown (asterisks), indicating active axonal degeneration. Note also the presence of denuded axons (arrows) and inflammatory endoneurial and subperineurial oedema (toluidine blue staining). Adapted from Berciano et al.[164]

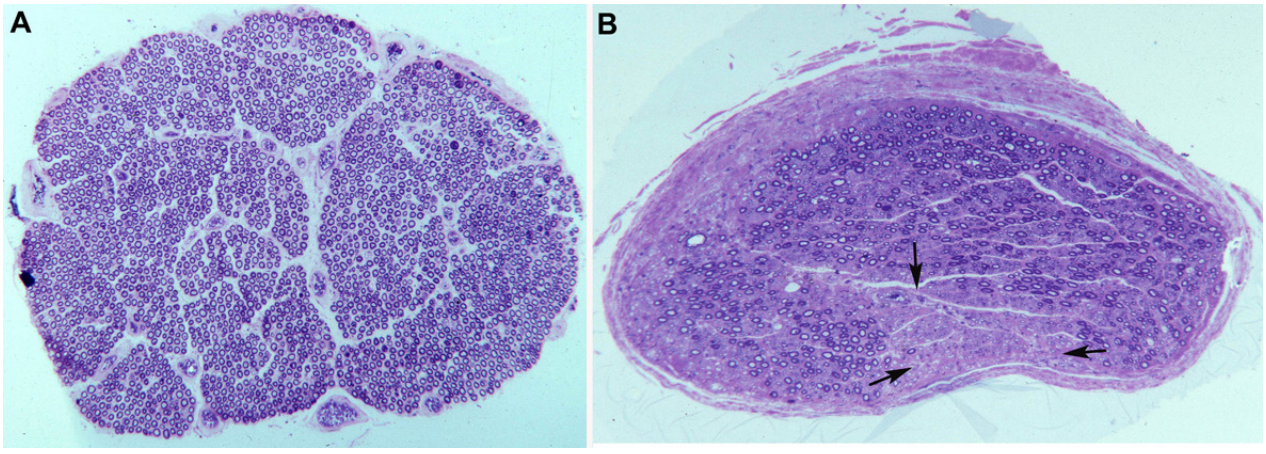


Figure 18. Pathological findings from a patient with fulminant Guillain-Barré syndrome who died 60 days after onset.[165] Neurophysiological studies on days four, seven, and 50 initially detected normal MCV, with subsequent slowing, progressive attenuation of CMAP, and diffuse muscle denervation. **A**) Semithin section from the L5 ventral root showing preserved myelinated fibre density; note the lack of perineurium (toluidine blue staining). **B**) Complete semithin section of the ventral ramus of the L3 nerve showing a generalised reduction of myelinated fibre density, particularly in the subperineurial region; note also the presence of a wedge-shaped area (arrows) displaying complete loss of myelinated fibres, a characteristic finding in endoneurial ischaemia (toluidine blue staining).

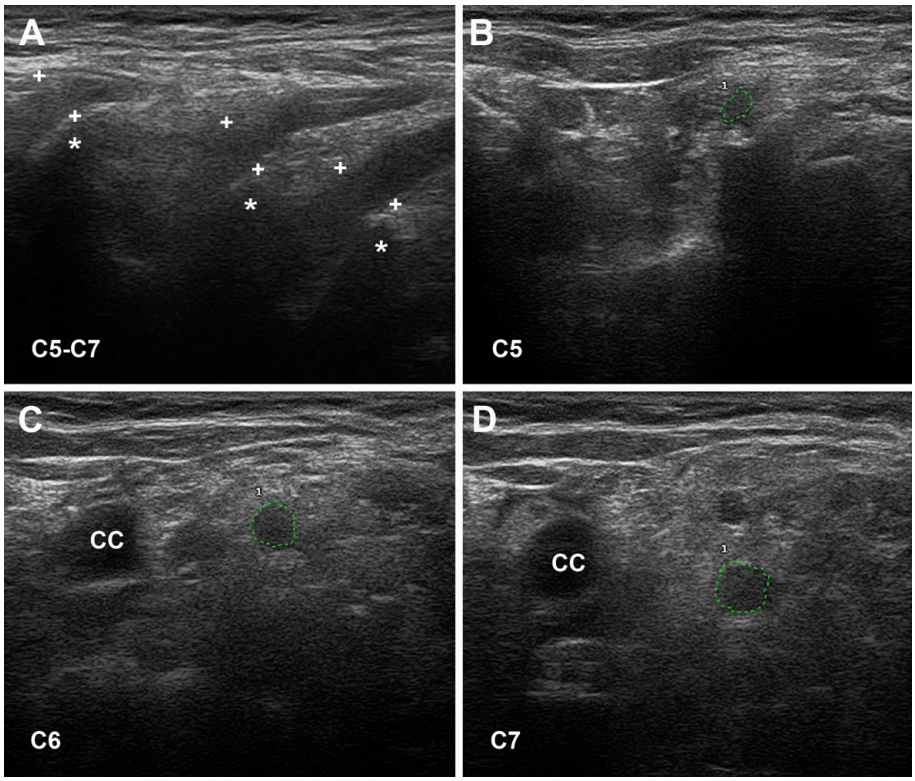


Figure 19. Ultrasound study of the cervical nerves in a patient with fatal AIDP, who died at 9 days of onset (case 1 from Gallardo et al.[167]). **A**) Sagittal ultrasound study showing blurring of the outline of the three scanned cervical nerves (crosses indicate calibration points; asterisks indicate transverse vertebral process). **B-D**) Short-axis ultrasound showing transverse fascicular areas, which are visibly enlarged in C6 and C7 (see values in Gallardo et al.[167]); blurred outlines are delimited by a green dashed line. Blurring of perineurial hyperechoic rings also indicates the presence of epi-perineurial inflammatory oedema. CC: common carotid artery.

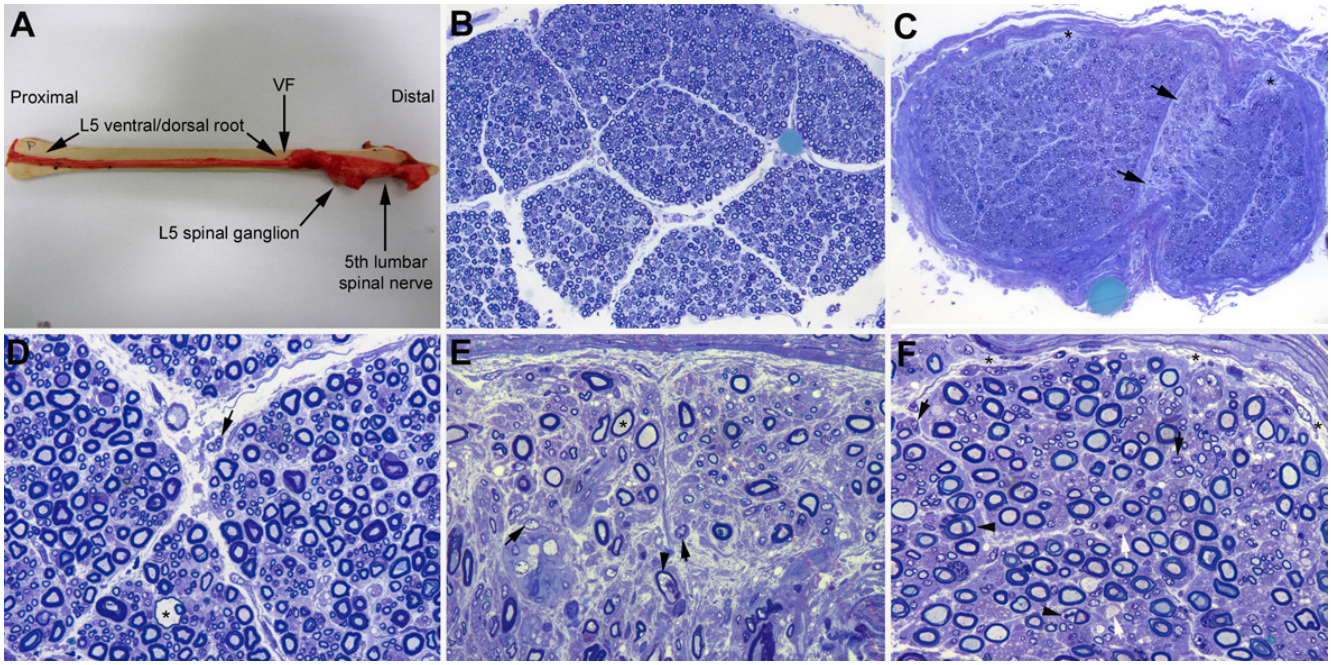


Figure 20. Histological findings of a patient with fatal AIDP, whose nerve ultrasound study is shown in Figure 19. **A**) Macroscopic view of the L5 nerve from the proximal end to its entry into the vertebral foramen (VF). The dissection continues to show the spinal ganglion and the fifth lumbar nerve. The nerve thickens after passing through the VF. **B**) In this semithin section of the L5 ventral root, taken 1 cm beyond its passage through the VF, myelin fibre density is preserved (toluidine blue staining). **C**) In this semithin transverse section of the ventral ramus of the fifth lumbar nerve, at the level of its emergence from the VF, we observe diffuse endoneurial oedema, which is more marked in certain subperineurial areas (asterisks) and in one of the areas adjacent to the perineurial septum (arrow). Oedema spaces out the myelinated fibres, hence their apparent reduced density as compared to the previous images (toluidine blue staining). **D**) At greater magnification, this semithin section from the L5 ventral root displays preserved density of myelinated fibres and occasional presence of mononuclear cells (arrow) and an isolated fibre with myelin vacuolation (asterisk) (toluidine blue staining). **E**) Detailed image of the area adjacent to the septum, labelled by the arrows in **C**). Inflammatory oedema is apparent, with numerous mononuclear cells (arrow), isolated fibres with inappropriately thin myelin sheaths (asterisk), and fibres presenting vacuolar myelin degeneration (arrowhead) (toluidine blue staining). **F**) Semithin section from the sciatic nerve, showing isolated demyelinated axons (white arrow), fibres with vacuolar dissolution of myelin (arrowheads), and discrete but disperse endoneurial oedema that was more visible in subperineurial regions (asterisks) with presence of mononuclear cells (black arrow); as a consequence of this, spacing of myelinated fibres was barely visible (toluidine blue). In short, the predominant lesion at the ninth day after symptom onset is endoneurial inflammatory oedema, which was more pronounced in the ventral branch of the fifth lumbar nerve.

In short, our epidemiological, clinical, electrophysiological, imaging, and histopathological studies have helped to provide a new vision of the nosology of GBS, questioning some strongly held dogmas in the literature.

5.4. Other contributions

We include a series of publications, according to their time of publication on PubMed.[212-412] These publications include original articles, editorials, reviews, clinical notes, letters to the Editor, or commentaries in which I participated as lead author or main co-author. Some of these works are related to the three previous sections; therefore, no additional comments will be made. In the interests of brevity, this section will focus on some works that are particularly meaningful.

5.4.1. Sneddon syndrome

In 1971, as a resident in neurology, I attended a 40-year-old woman who had been referred to our outpatient clinic due to recurrent transient ischaemic attacks. The patient reported many episodes of alternating hemiparesis or amaurosis fugax in one eye or the other, followed by a rapid, complete recovery. Such episodes had occurred several times per year during the previous 10

years. She reported no headache or constitutional symptoms; blood pressure values, monitored by her physician, had always remained normal. During the examination, the only positive finding was livedo racemosa generalisata (LRG), which the patient reported she had presented since adolescence. We were very surprised, as no previous neurology article had mentioned LRG at the time. After a search of Index Medicus, we found the work by Sneddon, who for the first time associated LRG with stroke.[413] In line with the recommendations of Sneddon himself, we considered polyarteritis nodosa, lupus erythematosus, Takayasu arteritis, and thrombocytopenia as possible aetiological causes. Analytical studies and skin and muscle biopsies did not support any of these possibilities. Despite this, a diagnosis of suspected polyarteritis nodosa was established, and recommended treatment with prednisone for several months with subsequent tapering. To my knowledge, it was easier to rule out the causes not present for the exceptional syndrome combining LRG and stroke. The long clinical course (30 years for LRG) and benign progression, as well as the absence of constitutional symptoms, seemed to constitute strong arguments against any systemic vasculitis.

At Valdecilla, between January 1977 and December 1981, we gathered eight cases of Sneddon syndrome that constituted the basis of the doctoral thesis of Dr Rebollo Álvarez-Amandi.[223,229,414] In this five-year period, stroke (ICD-8, 430-438) was diagnosed in 3006 patients; therefore, the eight cases of Sneddon syndrome represented 0.26% of the total. After a clinical study, laboratory analysis, angiography study (head and hand), head CT scan, and histological study of the digital arteries, we concluded that Sneddon syndrome was a new progressive, occlusive, non-inflammatory disease affecting medium-calibre arteries. Based on the hereditary component in three of the eight cases, we proposed that the syndrome may have a genetic basis with an autosomal dominant inheritance pattern. This question was neglected in a subsequent review of the Mendelian aetiologies of stroke,[415] which led us to write a reply,[254] after which Sneddon syndrome was included in the OMIM catalogue (#182410). Figure 22 illustrates the autopsy studies in case 4 of the series by Rebollo.[223,407] In this patient, who presented an angiographic pattern of collateral supply resembling moyamoya syndrome, the autopsy study revealed a universal, obstructive, non-inflammatory arteriopathy, with profuse compensatory proliferation of cortical vessels that should not be misinterpreted as angiomatosis; it was a pseudo-angiomatosis, a term that is probably also applicable to many patients diagnosed with Divry-Bogaert syndrome.[243] As an interesting cultural and historical note, LRG has been depicted in paintings.[411]

5.4.2. Craniocervical junction abnormalities and type I Chiari malformation

During my time as a neurology resident (1971-1973), I established a special relationship with Dr Zaragozá, who at the time was immersed in his doctoral thesis on craniocervical junction abnormalities (CJA) and its correlation with type I Chiari malformation (CM1) and syringomyelia.[416] With him, I learnt the art of performing myelography studies with pantopaque to show ectopic cerebellar tonsils and stenosis in the vallecula, without contrast passing to the supratentorial cisterns. At the time, the neural anomaly was considered the primary pathogenic phenomenon. In 1980, I was studying a large family with nine affected members from three generations, three of whom presented spastic ataxia (Figure 23A). Imaging studies revealed occipital dysplasia of varying severity (Figure 23B, C) and CM1 (see figures 3 and 4 in Coria et al.[224]), although the only feature shared by all three generations was occipital dysplasia. We were mired in doubt regarding the pathophysiological mechanisms at work in this family, when Dr Jesús Flórez Beledo (chair of Pharmacology, UC) called to tell us that Dr Miguel Marín-Padilla, with whom he coincided at the Dartmouth College (USA), was going to give a lecture on the morphogenesis of Chiari malformation, which would surely be of interest for neurologists. He was right: it was an unforgettable experience. Dr Marín-Padilla presented his anatomical studies of anencephalic fetuses and experimental studies on mesodermal alterations induced by hypervitaminosis A, reporting that from anencephaly to Chiari malformation, the basic defect would be poor development of the paraxial mesoderm, which in the case of Chiari malformation mainly affect the basioccipital bone.[417-419] This defect results in a posterior fossa of insufficient size to contain the cerebellum during postnatal growth. With these data in mind and after reviewing the literature, we concluded that CJA may be familial, with an autosomal dominant inheritance pattern (OMIM #118420), whose pathogenic sequence may be the following[224,231]: *i)* bone malformation (occipital and suboccipital) as the primary malformation; *ii)* caudal displacement of cerebellar tonsils (CM1) as secondary to stenosis of the posterior fossa due to occipital dysplasia;

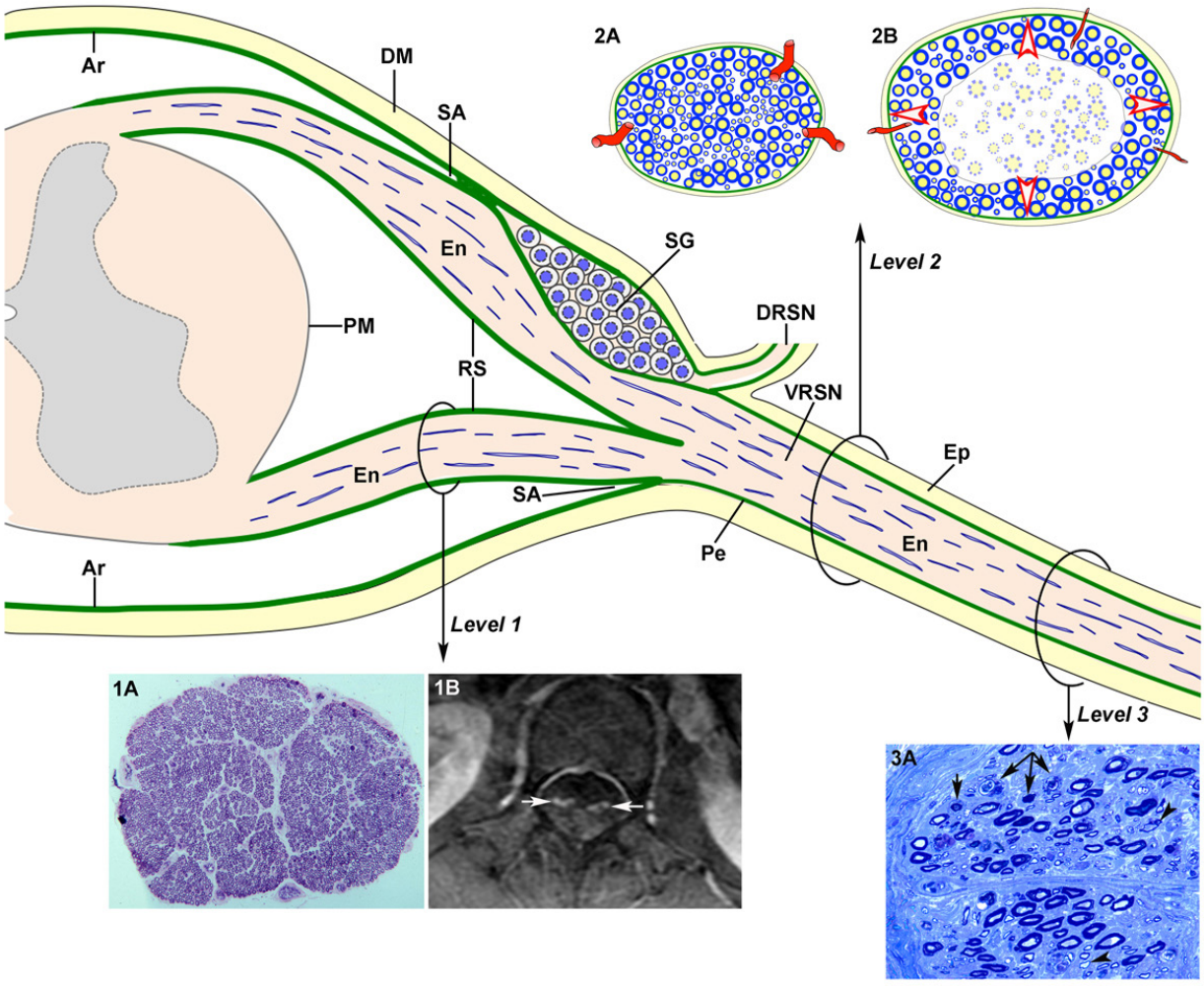


Figure 21. Diagram of the microscopic anatomy of the spinal cord, spinal roots, and spinal nerves, taken from Berciano et al.[182] From the subarachnoid angle (SA), the epineurium (Ep) is in continuity with the dura mater (DM). The endoneurium (En) of the peripheral nerve trunks extends through the spinal roots until their junction with the spinal cord. At the SA, most of the perineurium (Pe) joins the subdural arachnoid (Ar), with some layers forming the root sheath. The Ar of the spinal roots is continuous with the pia mater (PM) at their emergence from the spinal cord. Immediately after the spinal ganglion (SG), in the SA, the ventral and dorsal roots join to form the spinal nerve, which emerges from the vertebral foramen and splits into the dorsal and the ventral rami (DRSN and VRSN, respectively). Therefore, the intrathecal spinal roots possess an elastic sheath derived from the arachnoid mater, whereas the spinal nerves and more distal nerve trunks are ensheathed in epi-perineurium, which is relatively inelastic. The proximo-distal inflammatory lesions observed in early GBS are illustrated for a lumbar ventral root (Level 1), a spinal nerve (Level 2), and the sciatic nerve (Level 3). The image for Level 1 shows a complete semithin transverse section of the L5 root of a patient with fatal GBS. The density of myelinated fibres is preserved (1A), although the inflammatory lesions visible at greater magnification (not shown) may explain the increased cross-sectional area, enlargement, and the contrast enhancement on MRI sequences (1B, arrows). The diagrams for Level 2 depict the following: *a)* normal spinal nerve anatomy, usually monofascicular, with transperineurial vessels and epi-perineurial covering (2A), explaining the normal appearance in ultrasound studies, with a round or oval hypoechoic structure surrounded by a hyperechoic rim; and *b)* in early GBS, endoneurial inflammatory oedema may cause a critical increase in endoneurial pressure in the spinal nerves, stretching the epi-perineurium beyond the limit of its compliance and constricting the transperineurial vessels (arrowheads); this would result in endoneurial ischaemia, here involving the centre of the fascicle (2B). The image for Level 3 shows a semithin section of the sciatic nerve from a patient with fatal AIDP, with several fibres displaying axonal degeneration (myelin breakdown, arrows), which in this case is secondary to more proximal inflammatory demyelinating lesions. Note also the presence of remyelinated fibres (arrowheads) and lipid-laden macrophages. Had we not been aware of the proximal demyelination, it would have been very difficult to accurately interpret the pathogenic role of the florid axonal degeneration observed. This diagram is inspired by figures 2-6 of Berthold et al.[200]

and *iii)* syringomyelia as a possible complication of impaired CSF flow when *i)* and *ii)* are present.

A few years later, Dr Alfonso Vega Bolívar dedicated his doctoral thesis to the volumetric study of the posterior fossa in 42 patients with CM1 and 46 controls, revealing that the poor development of the basichondrocranium is an integral aspect of this complex malformation.[271,420] Among others, our contributions represented the basis for the design of a new surgical strategy for symptomatic CM1, seeking to reconstruct rather than to decompress the posterior fossa.[421] A well-known headache expert,[259,261,262,269,276,292,300,306,312,320,322,330,332] Dr Pascual Gómez analysed the incidence of headache in a series of 50 patients with CM1, observing that 14 (28%) presented a specific pattern of headache: prolonged, suboccipital, of variable pain characteristics, aggravated by Valsalva manoeuvres (effort, cough, or postural changes), sometimes alleviated by craniectomy, and correlated with the degree of ectopia of the cerebellar tonsils.[287]

5.4.3. Stroke in young adults

Dr Leno Camarero performed the first Spanish prospective study of stroke in young adults (≤ 50 years) during the period 1 April 1986 to 31 March 1988.[249,275,284,286,293,305,422] Of the 81 patients studied, the incidence in Cantabria for both sexes was established at 13.9 cases per 100 000 population (95% CI, 9.6-18.2). The distribution of nosological entities was as follows: 24 patients (30%) with non-embolic stroke, 14 (17%) with embolic stroke, 20 (25%) with subarachnoid haemorrhage, 22 (27%) with spontaneous cerebral haemorrhage, and one (1%) with cerebral venous thrombosis. Eighteen patients (22%) died within 30 days after onset, and another two during follow-up; 79% of survivors achieved satisfactory recovery. In short, the aetiological complexity of stroke in young adults was corroborated.

5.4.4. Multiple sclerosis

As discussed elsewhere,[2] Dr Julio Miró Jornet developed a specific programme for patients with multiple sclerosis (MS) at the HUMV. Dr Miró initially became interested in such patients as a resident in internal medicine (1978-1982). In 1983, he presented his bachelor's thesis, based on the study of 30 cases of MS gathered between 1976 and 1980; incidence was preliminarily estimated at 1.21 cases/100 000 person-years, and prevalence at 56 cases per 100 000 population, making Cantabria a medium-risk area.[230,423] Having completed his residency, Dr Miró joined the emergency department of a public healthcare centre in Torrelavega, where he remained in contact with us, selflessly attending patients with MS and designing diagnostic and treatment protocols; above all, he conducted exemplary clinical follow-up of each patient. In these conditions, the manager of HUVM (Dr Julio Baro Calle) accepted our proposal, dated 22 January 1986, for the creation of a specific programme to care for patients with MS. The MS clinic was initially integrated into the daily activities of the general neurology department. After joining the El Astillero healthcare centre, which provided care during the whole morning shift, Dr Miró decided to attend patients with MS in the afternoon, two days per week. Considering the growing healthcare demand, I requested that the administration create a special programme to release him partially from his activity at the healthcare centre; this request was unfortunately denied. By the end of 1997, Dr Miró was forced to stop attending patients with MS due to the impossibility of combining this care with the high healthcare demand at his hospital. By that time, the MS programme included 170 patients and held 450 consultations per year (including new patients, relapses, and follow-up visits). Chronologically, the scientific contributions of Dr Miró may be summarised as follows[247,265,268,282,359,424]: *i)* the description of pelvic pain as a new paroxysmal manifestation of MS; *ii)* the demonstration, based on a protocolised, prospective study of 64 consecutive patients with MS, that the association of the disease with primary Sjögren syndrome is coincidental, which as shown by an accompanying letter,[425] dispelled the dogma on the presumed pathogenic relationship between both processes; *iii)* the demonstration that the hypothalamic-pituitary-adrenal axis is preserved after steroid therapy for MS relapses, whether with oral prednisone or pulses of intravenous methylprednisolone, making compensatory steroid therapy unnecessary; *iv)* the demonstration, with unquestionable diagnostic repercussions, of the inhibitory effect of corticosteroids on quantitative CSF IgG synthesis (estimated using formulae), with no effect on qualitative synthesis (oligoclonal bands); *v)* the demonstration, based on long-term longitudinal follow-up (≥ 10 years) since symptom onset, that 48% of patients present benign MS, which may help when considering implementation of immunotherapy; and *iv)* the relevance of the psychopathology associated with the disease (54%), with a prevalence of depression of 22%.

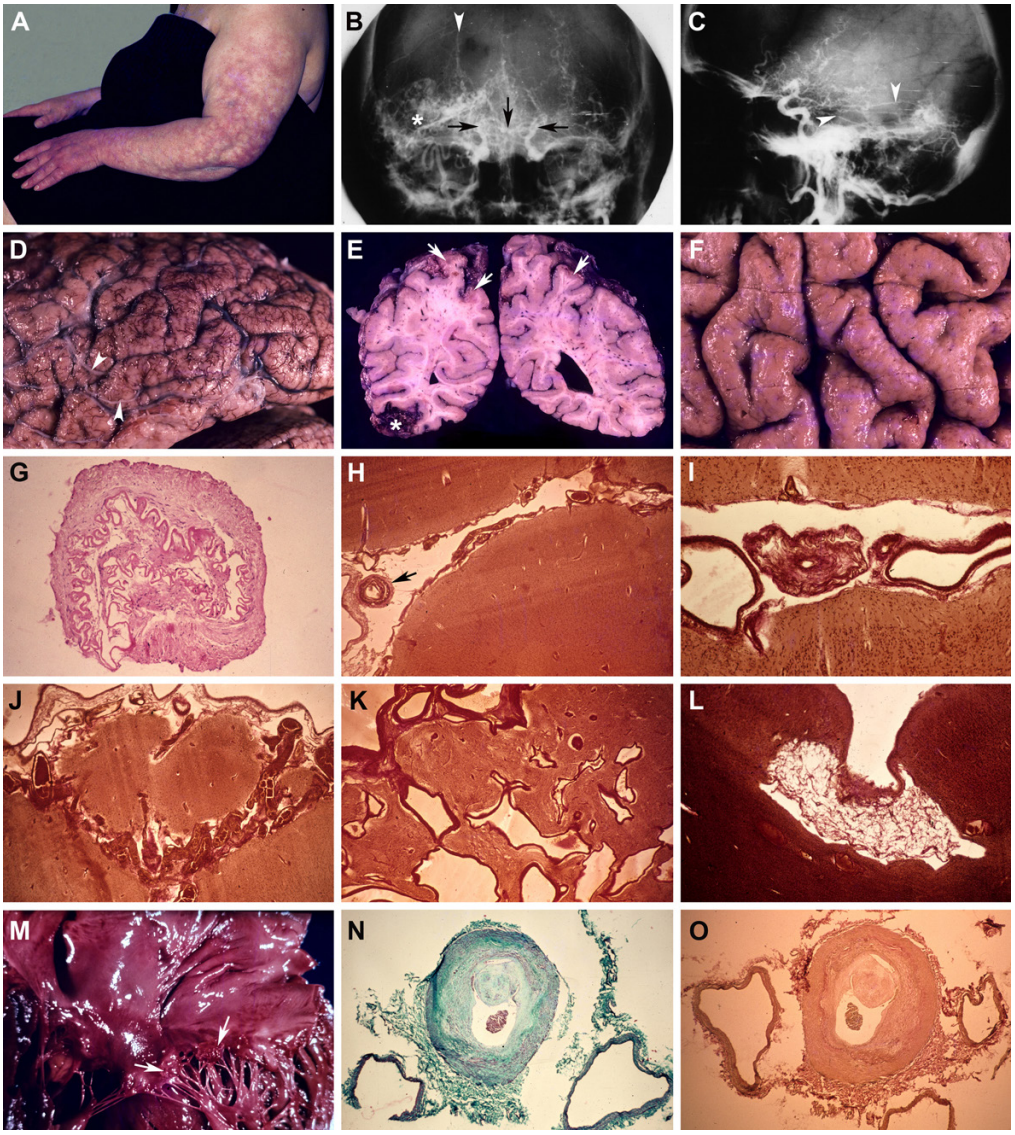


Figure 22. Clinico-pathological findings in Sneddon syndrome.[407] **A**) Extensive livedo racemosa of the left arm, which also affected the chest, abdomen, buttocks, and thighs. **B**) and **C**) Bilateral brain angiography study (carotid and brachial arteries) showing complete occlusion of both middle and anterior cerebral arteries (black arrows) and a right occipital arteriovenous malformation (asterisk) supplied by a tentorial branch of the carotid artery and meningeal arteries (arrowhead); note the presence of a collateral supply system in the base of the brain (similar to moyamoya syndrome). **D**) Close-up image of the brain convexity, illustrating a vast subarachnoid supply system; note the presence of whitish bloodless vessels corresponding to occluded arterioles (arrowheads). **E**) Coronal sections of the brain at the level of the posterior ventricular horns, revealing ventricular dilation, brain atrophy, prominent subcortical vascular profiles, small intracortical infarcts (arrows), and occipital vascular malformation (asterisk). **F**) After dissecting the meninges, pronounced granular atrophy was observed. **G**) Transverse section of the middle cerebral artery, whose lumen was occupied by a recanalised thrombus; note also the hyperplasia of the tunica intima with preserved internal elastic lamina and absence of inflammation (haematoxylin and eosin staining). **H**) At low magnification, this cerebral sulcus displays an arteriole with hypertrophy of the internal elastic lamina (arrow), as well as hyperplasia of sulcus vessels (orcein stain). **I**) At higher magnification, note the presence in the sulcus of an arteriole with hypertrophy of the tunica intima and reduplication of the internal elastic lamina, delimited by two large venules (orcein stain). **J**) In some areas, hyperplasia of subarachnoid vessels is so intense that it acquires a pseudo-angiomatous appearance (orcein stain). **K**) The characteristic texture of occipital arteriovenous malformation, characterised by vascular clusters with interposed brain parenchyma, but without an intermediate capillary network (orcein staining). **L**) Small cortico-subcortical infarct (orcein staining); similar lesions (not shown) were observed in deep subcortical areas. **M**) Libman-Sacks endocarditis in the mitral valve (arrows). **N**) and **O**) Transverse sections of the subclavian artery, showing a greatly enlarged tunica intima displacing the internal elastic lamina, which is in turn reduplicated; a large thrombus is adhered to the wall; and again, no inflammatory infiltrates are observed (Masson's trichrome and orcein staining).

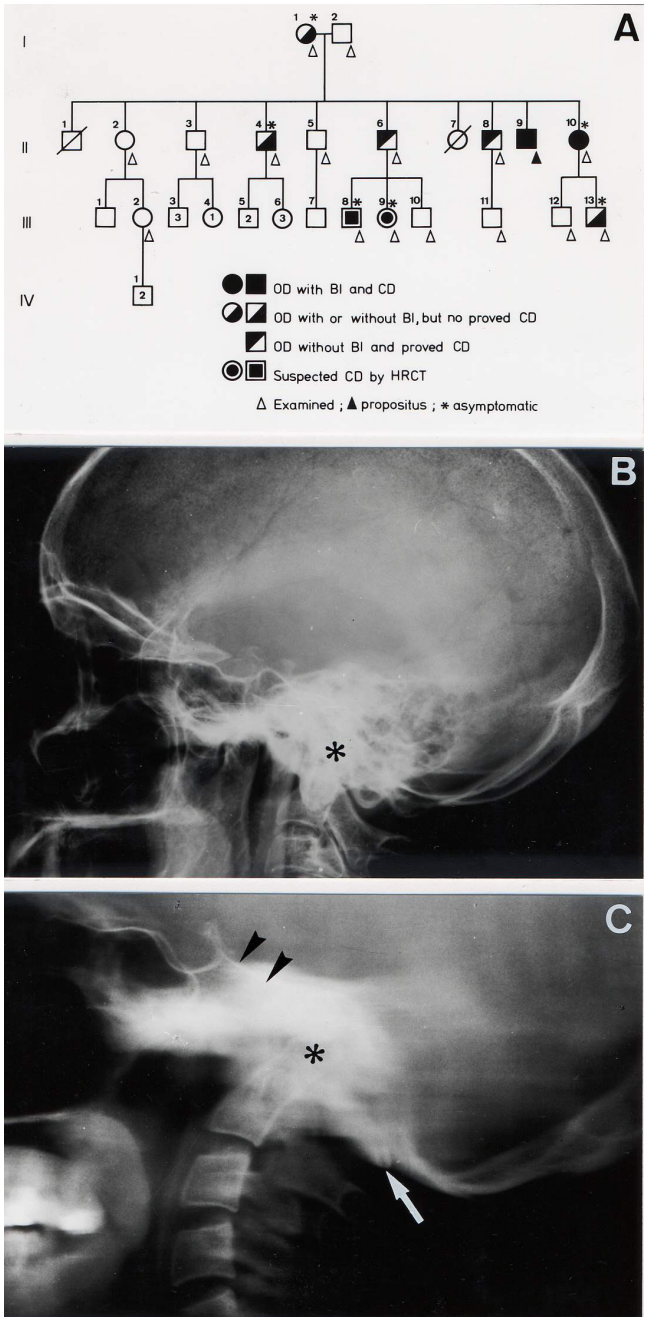


Figure 23. A) Pedigree chart of the family with familial occipital dysplasia described by Coria et al.[224] BI: basilar invagination; CD: type I Chiari malformation; HRCT: high-resolution CT scan; OD: occipital dysplasia. **B**) Lateral radiography of the head from case I-1, showing clear basilar invagination (the asterisk marks the tip of the odontoid process). **C**) Lateral tomography of the head in case II-9 showing a short, lordotic clivus (arrowhead), occipitalisation of the posterior arch of the atlas (arrow), and very pronounced basilar invagination (the asterisk marks the tip of the odontoid process).

5.4.5. Motor neuron disease

In 1985, during the last year of his medical studies, Dr José Manuel López-Vega told me that he was interested in reviewing the medical records of patients with motor neuron disease diagnosed at the neurology department (1974-1985). I provided him with the files with the corresponding codes (ICD-8 codes 348.0 to 348.9) from our archive. At the end of the academic year, he drafted his bachelor's thesis based on those files.[247,426] The series included 62 patients, of whom 33 (53.2%) were diagnosed with amyotrophic lateral sclerosis, 22 (35.5%) with progressive bulbar palsy, and seven (11.3%) with progressive muscular atrophy. This was the first study to provide epidemiological data for the disease in Spain, and estimated incidence at 1.01 and prevalence at 3.52 cases per 100 000 population in Cantabria. This study included a detailed semiological analysis. Decades later, a new epidemiological study analysing patients with motor neuron disease during the period 2003-2013, with 53 patients identified in the Santander healthcare district, showed a slight increase in incidence (1.7/100 000) and prevalence (4/100 000), although clinical patterns remained the same.[402]

Dr Javier Riancho Zarrabeitia dedicated his doctoral thesis to the possible neuroprotective effect of bexarotene in an experimental ALS-SOD1 transgenic mouse model (B6SJLTg [SOD1-G93A] 1Gur/J).[397-402,427] Experimental findings suggested that the drug has a beneficial effect in this devastating disease, which currently lacks an aetiological therapy. Histological illustrations, including conventional microscopy, immunohistochemistry, and confocal microscopy images, and semithin and ultrathin sections (material from the Cell Biology and Anatomy department, UC), represent a highly valuable document to understand the course of the lesion in this neurodegenerative syndrome; in this sense, it is worth mentioning the pathogenic role of alterations to the perisynaptic glia, both in the anterior horn and spinal ganglia.

5.4.6. Three final considerations

Among my contributions to the study of Creutzfeldt-Jakob disease (CJD),[260,263,273,274,291,303,313,317] I would like to underscore only the clinico-pathological and imaging study of a patient with the ataxic and panencephalopathic type of CJD.[263,274] The study of the cerebellum showed the disappearance of the granule cell layer, associated with massive loss of parallel fibres and the consequent

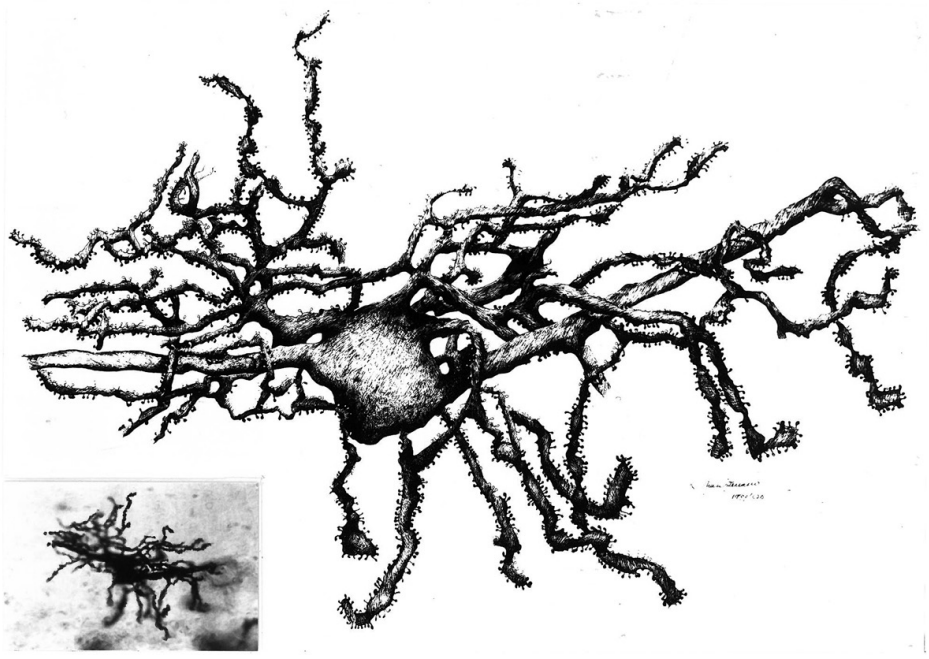


Figure 24. Camera lucida drawing of the Purkinje cell in the inset image.[263] Note the multipolar cell body with thick horizontal dendrites and descending dendritic branches (resembling the branches of a weeping willow). The dendritic tree of the molecular layer is absent, and dendrites with segmental loss of spines or with polymorphic spines are observed (Golgi-Hortega staining).

deafferentation of Purkinje cells. As shown in Figure 24, Purkinje cells were preserved in number, although their dendritic trees were composed of a hypertrophic supraganglionic plexus; this demonstrates their plasticity to avoid anterograde trans-synaptic atrophy. The pattern of posterior fossa atrophy, with significant progressive dilation of the fourth ventricle, is very characteristic of this variant of CJD (see figure 1 in Berciano et al.[274]).

In neurological practice, lesion localisation in patients with infrequent symptoms is an everyday exercise. One extreme case was a 54-year-old woman with hypertension and a small thalamic infarct, who suddenly developed contralateral cheiro-oral syndrome.[281] The patient reported burning paraesthesias (as if stung by nettles) in the tongue, mouth, lips, and tips of the index finger and thumb of the left side; the sense of taste was preserved. The MRI study revealed a lacunar infarct in the right inferolateral part of the optic thalamus (Figure 25A), which corresponds to its posterior ventral nucleus. The particular topography of the sensory deficit is explained by the representation of the surface of the human body in the posterior ventral nucleus, as observed with electrode mapping techniques during stereotactic thalamotomy for the treatment of movement disorders.[428] As illustrated in Figure 25B, the tongue is extruded medially, adjacent to the index finger and thumb, which explains the peculiarities of the lacunar syndrome described here.

Our last observation is interesting in the congress and historical context, and is something that neither Dr Polo Esteban nor myself will ever forget. A 37-year-old woman at week 23 of gestation was admitted due to blurred vision and generalised weakness. Examination revealed external ophthalmoplegia and bilateral facial weakness, nasal voice, dysarthria, and tetraparesis.[314] Results of the obstetric examination were normal. The patient's mother was also affected; the outbreak of botulism was triggered by a home-made green bean preserve; another relevant fact was that all the hens in the family's hen-

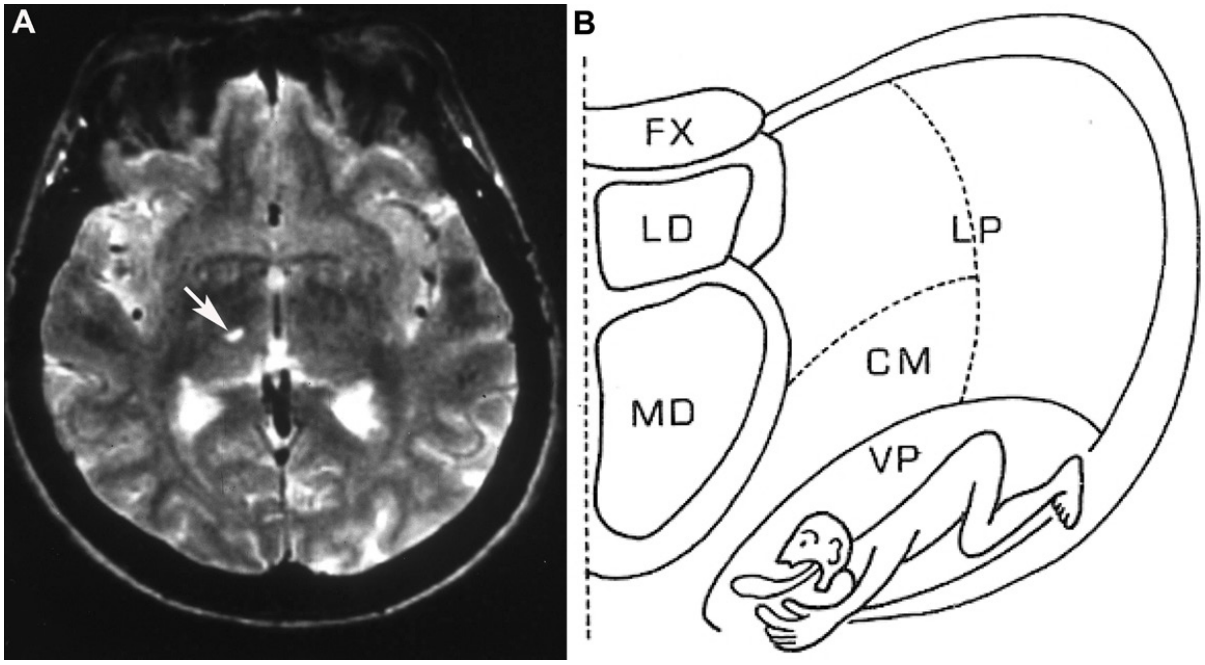


Figure 25. A) T2-weighted MRI sequence showing a lacunar infarct in the area corresponding to the right posterior ventral nucleus (arrow). **B**) Homunculus diagram of a coronal section of the posterior ventral nucleus. Adapted from Ohye.[428] CM: central middle nucleus; FX: fornix; LD: lateral dorsal nucleus; MD: middle dorsal nucleus; VP: posterior ventral nucleus.

house that had been fed with the contaminated beans had died. The type of *Clostridium botulinum* was not identified. Repetitive nerve stimulation at 50 Hz showed a 70% potentiation. Five vials of AB botulism antitoxin were administered. Weakness progressed to tetraplegia, with the patient requiring ventilatory support; the only visible movement was that of the fetus. In this period, successive abdominal ultrasound studies showed that fetal development was normal. The patient was discharged at three months of symptom onset with minimal residual weakness. A healthy child was born by vaginal delivery. Thus, botulism in this patient had no negative repercussion on the pregnancy, which supports the decision to treat pregnant women with BoNTA when necessary, at least in the second half of pregnancy. This study was published as a Letter to the Editor in *The Lancet* on 20 July 1996.[314] A month earlier, we presented it as a poster at the European Neurological Society Meeting in The Hague.[429] As was customary, Dr Polo Esteban and I went to hang our poster very early in the morning (around 7:30). In a huge, almost empty room, a few metres behind us, we saw the silhouette of a woman who was patiently waiting to talk with the leading author, Dr Polo Esteban. She was none other than Dr Angela Vincent, a very well-known neuroimmunologist from the University of Oxford (UK), who began a relaxed conversation to which I was a silent witness. As she thanked us for the study, she stated "this goes against what we had been thinking to date."

6. Postscript: in recognition of Dr Onofre Combarros Pascual

As mentioned above, in 1994, Dr Combarros Pascual launched the Neurogenetics Laboratory in a space attached to the Molecular Genetics Laboratory at HUMV, directed by Dr José Luis Fernández Luna. In its almost thirty years of existence, it has changed location on three occasions: first to basement of the School of Nursing, then to the sixth floor of that building, and finally to the Faculty of Medicine. Dr Combarros Pascual focused his research on the analysis of associations be-

tween different genetic risk loci and sporadic Alzheimer disease; subsequently, and within an international programme, he led several epistatic studies of this disease. His research activity was exceptional, with 103 studies indexed in PubMed (search terms: "Combarros O" and "Alzheimer disease"). Furthermore, Dr Combarros Pascual created a centre that attracted many young researchers, where many consultants and specialists with grants from IDIVAL and ISCIII have worked; this has been an essential pillar for the research activity of the neurology department. He was the principal investigator of our neurodegenerative diseases study group, both at CIBERNED and at IDIVAL. After his retirement, he was replaced by Dr Jon Infante Ceberio, with considerable support from Dr Pascual Sánchez-Juan.

Conclusions

My career has spanned almost five decades of uninterrupted neurological research, largely derived from my solid post-graduate training and the inestimable help of my colleagues. This research activity soon received international recognition, which unquestionably served as great encouragement.

Acknowledgements

I would like to express my deepest gratitude to all those who have collaborated with the neurology department at HUMV, and especially those not mentioned in the text. Special mention should be made of Marta de la Fuente (secretary of the neurology department) for her invaluable help in the typing of our studies, and Mario Corral (in charge of Marquesa de Pelayo Library) for his help in the literature search.

I would like to dedicate this historical review to two people. To my wife, May, who has been always by my side encouraging me to keep going during our 48 years together. And to Prof Juan Martínez López de Letona (1937-2012), thanks to whom I reached my maturity as a physician in the widest sense of the term; when I think of him, I always recall the last paragraph of his obituary by Ignacio Sotelo (*El País*, 17 January 2013):

> He never made the slightest effort to receive honours; entirely to the contrary, he would make it difficult to anyone who tried, remaining in the weak shadow of a Spain where only the tinsel shines and we hear only echoes instead of voices, and the best of us are ultimately ignored.

Conflicts of interest

The author has no conflicts of interest to declare. This study has received no public or private funding.

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