Charcot-Marie-Tooth disease with optic atrophy: an early observation

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ABSTRACT

Charcot-Marie-Tooth disease (CMT) became known in Spain through the observations made by Barraquer Roviralta just two years after the disease was first described in 1886. In 1962, Alberto Rábano and Justiniano Campa studied a family in which three siblings had CMT associated with optic atrophy, in one of the first observations of this combination to be reported in the literature. The detection of asymptomatic optic atrophy in the youngest patient led them to travel to her home town to examine her brothers, both of whom were found to be in a very advanced stage of the disease, with optic atrophy causing severe visual impairment. The family described probably had CMT type 2A, which is characterised by early onset and severe progression, and is associated with mutations of the gene encoding mitofusin 2. This confirms the importance of performing eye fundus examinations in all patients with axonal CMT.

KEYWORDS

Alberto Rábano, Charcot-Marie-Tooth disease, CMT2A, Justiniano Campa, optic atrophy

Introduction

The first description in Spain of Charcot-Marie-Tooth disease (CMT) was published by Barraquer Roviralta, who in 1882 created an electrotherapy clinic (later the Department of Neurology and Electrotherapy) at Hospital de la Santa Creu, Barcelona.[1]

In 1888, Barraquer Roviralta described two brothers with the disease, one of whom was a well-known banker in Barcelona's social and financial circles.[2,3] The disease had been described only two years earlier by Jean-Martin Charcot (1825-1893) and Pierre Marie in France[4] and by Howard Henry Tooth[5] in England.[6] Years earlier, Paul Broca had described two cases clearly identifiable as CMT, although his observations were based on post mortem examinations.[7] In 1882, Charcot and Marie had presented five cases, including two siblings, assuming that the disease in question was some kind of myelopathy; it was for this reason that both Barraquer Roviralta and his son Barraquer Ferré[2,8] referred to the disease as "Charcot-Marie amyotrophy" instead of "peroneal muscular atrophy," the term proposed by Tooth.[5]

When the wealthy banker travelled to Paris to visit Charcot, the latter is said to have responded that "there was no need for you to come to me; there is a man in your own country who is all too familiar with your disease."[9] The Museo Archivo Histórico of the Spanish Society of Neurology holds handwritten correspondence between Jean-Martin Charcot and Barraquer Roviralta (Appendix; Figure 1), in which Charcot refers to an article received for publication in *Archives de Neurologie*

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Received: 10 June 2017/ Accepted: 30 November 2017

(Appendix, Letter 1), notes that he is awaiting an anatomical piece for a study (Appendix, Letter 2), states his intention to visit a patient in Barcelona, and mentions the fees received for his (apparently frequent) trips to San Sebastián (Appendix, Letter 3).

In the present study, we review an article by Alberto Rábano (1923-1975) and Justiniano Campa, pioneers of neurology in post–Civil War Madrid, entitled "Charcot-Marie-Tooth neural atrophy with optic atrophy."[10] Besides the interest of this association, no other publication related to CMT was listed among the 992 bibliographical citations of Spanish works in the field of neurology in the period 1882-1936, collected by Izquierdo Rojo.[11]

Material and methods

We analysed the original 1962 publication by Rábano and Campa. Rábano's bibliographical data were obtained from Fundación Romanillos (www.fundacionromanillos.es). Justiniano Campa's data were obtained online (at www.neurostaff.com) and from the author himself (personal correspondence, 30 May 2017). We reviewed the literature pertaining to the history of CMT type 2A (CMT2A), associated with a mutation of the gene encoding mitofusin 2 (*MFN2*), and optic atrophy linked to a mutation of *OPA1*.

Results

The article

Rábano and Campa's article, published in 1962 in the journal *Hospital General*, is just two pages long and lacks an introduction or bibliography. The journal, founded in 1960, was as an outlet for the research work of physicians at the Hospital Provincial de Madrid until it was discontinued in 1975. The journal was highly influential among physicians at the time.

The patients described in Rábano and Campa's brief communication were members of the Contreras Hurtado family of Villanueva de los Infantes, in the province of Ciudad Real. Three of the five siblings (a woman and two men), then aged 19, 31, and 33, were all affected by the same disease; according to the authors, "the chronology was similar in all three patients." The first patient was admitted to the Hospital Provincial de Madrid, with the following clinical history:

> Clinical symptoms manifested when the patient was five years old, with symmetrical amyotrophy of the peroneal muscles causing progressive bilateral pes cavus. Symptoms rapidly spread to involve almost all muscles of the lower legs, but barely affected those of the thigh and pelvic girdle, causing pronounced clubfoot. Between the ages of 12 and 15, amyotrophy began to involve the intrinsic muscles of the hands and all forearm muscles, but not the upper arms or the shoulder girdle.

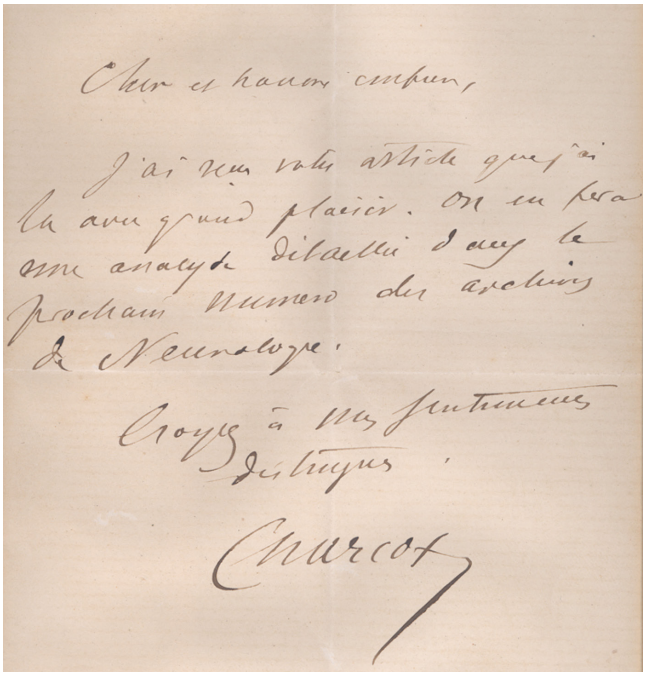

Figure 1. A fragment of one of the letters sent by Charcot to Barraquer Roviralta

The photographs accompanying the article show marked atrophy of the distal part of the patient's legs and the distal third of her thighs (Figure 2A). Although her vision was preserved, the authors note bilateral temporal optic disc atrophy. At the age of 14, the patient had received surgical treatment for the clubfoot from Dr Sanchís Olmos, "with a very favourable functional outcome"; the deformity did not resurface. However, the lower limb amyotrophy and weakness continued to progress; by the time the authors examined her, at the age of 19, she struggled to walk with the aid of crutches. The article makes no mention of hearing loss, sensory alterations, or lancinating pain.

Campa recalls travelling with Rábano to Villanueva de los Infantes in the latter's modest Seat 600 to examine the

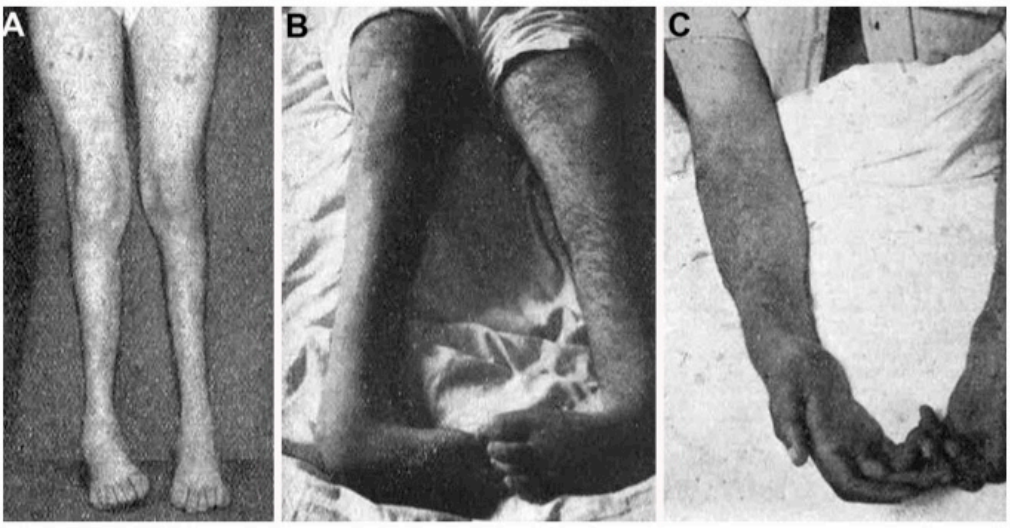

Figure 2. A) Severe muscle atrophy involving the legs and the distal third of the thighs, and the incipient right-sided clubfoot in the youngest of the three siblings (age 19). B) Severe deformity of the feet in one of the older brothers, at a very advanced stage of the disease. C) Severe muscle atrophy of the hands and the distal third of the forearms in one of the older brothers (not identified in the original publication)

patient's two older brothers. For two years, they had lived in a local, church-run refuge for elderly and disabled people. The authors report severe deformity of the feet (Figure 2B) and atrophy of the muscles of the hands (Figure 2C) (the article does not specify which brother was photographed). They emphasise "underdevelopment of the affected areas of the limbs, which are of reduced length in comparison to the proximal sections." This underdevelopment, together with the low skin temperature, pallor, and distal cyanosis, were attributed to involvement of the autonomic nervous system.

The older of the two brothers, aged 33 at the time, displayed considerable visual impairment, which had manifested several years before. The other brother, aged 31, also had visual impairment, although it was less severe. All three siblings displayed pronounced atrophy of both optic discs, particularly in the temporal segment.

The authors created a pedigree of the family, collecting data on three generations. The parents were not consanguineous and presented no symptoms; the disease manifested only in the three siblings described. It is unclear whether the other, apparently unaffected, family members underwent neurological examination. The authors assert that the interest of their publication lies firstly in their having examined all affected members of the family, and secondly in the highly advanced stage of the disease. They did not deem it "helpful" to perform a differential diagnosis considering Déjerine-Sottas disease or to consider the association between optic atrophy and demyelinating disease. The authors conclude their article with a discussion of future developments, predicting that "neurochemistry and biochemistry will lead to considerable change in the mentality and approach of the modern clinical neurologist."

The authors

Alberto Rábano Navas (Figure 3A) was one of the pioneers of neurology in Madrid after the Spanish Civil War. His biography is fascinating and merits an extensive study. It should be noted that he had his early experiences with neurological disease during an internship at the Hospital Provincial de Madrid, where

he worked alongside Lafora, recently returned from exile in Mexico. In 1941, the surgeon-in-chief Eugenio Díaz Gómez (1890-1970) was practising neurosurgery in addition to general surgery. Showing great generosity and bonhomie, he permitted Rábano to open a neurology clinic and to admit his own patients.[12] Although he had taken a state exam to become a *facultativo* (an equivalent role to chief clinician today) at the Hospital Provincial, this position did not at the time require dedication to a single specialty. The situation changed when Díaz retired in 1963 (information from SGR) and was replaced by a new head of teaching: the same wards were now officially denominated the department of neurosurgery. Rábano was forced to leave the hospital, and took charge of a neurology clinic at a small Red Cross hospital on Calle Pozas, as well as working as a consultant at Hospital del Rey, a centre specialising in infectious diseases.[13]

Rábano left an enormous scientific legacy and fond memories among his many students. Fundación Romanillos preserves his memory, awarding an annual prize in recognition of the best doctoral thesis published the previous year representing an advance in neuroscience.

Figure 3A. Alberto Rábano Navas

Justiniano Campa (Figure 3B) was Rábano's first student around 1959, shortly before he completed his medical studies. Campa recounts his personal memories with evident emotion; for example, he recalls sitting with Rábano opposite Atocha railway station after a difficult morning's work, and sharing a calamari sandwich, a typical meal in Madrid, before his mentor drove him home. In those days, Spain was no place for a young person who had discovered a passion for neurology; in 1962, Campa emigrated to the United States, where he remains today. He specialised at the University of Virginia (1963-1968), and later studied electromyography and neuromuscular diseases in Copenhagen and Bethesda, making significant contributions in these fields. He has spent his career in Charlottesville, Virginia, and is currently (2017) working on the prevention of cognitive impairment.

Remarks

Despite the absence of auxiliary diagnostic tests, Rábano and Campa's publication is an example of great clinical precision. The detection of asymptomatic optic atrophy in the propositus, a 19-year-old woman with severe, aggressive, early-onset CMT, led the physicians to make what at the time would have been a long journey with the sole purpose of examining the patient's two brothers, at a charitable institution for disabled adults. These cases enabled them to determine that the optic atrophy progressed slowly, from an initial asymptomatic stage to severe vision loss in advanced phases. The pedigree of the Contreras Hurtado family did not include other affected family members. The disease may have been caused by a *de novo* mutation, or may equally constitute a recessive form of CMT.[14] However, it is also possible that sub-clinical cases may have been identified had more family members been examined.

The protein mitofusin 2 (MFN2) is a GTPase in the dynamin family of proteins and is involved in mitochondrial membrane fusion. Mutations in the gene encoding this protein are observed in 20%-30% of patients with axonal CMT; some of these patients also display optic atrophy. This combination of conditions is denominated subtype CMT2A.[14] The *MFN2* mutation is not necessarily associated with optic atrophy[15] or with childhood-onset forms with severe progression.[16] Dominant optic atrophy and CMT2 are inherited neurodegenerative diseases often caused by mutations of the mitochondrial fusion genes *OPA1* and *MFN2*

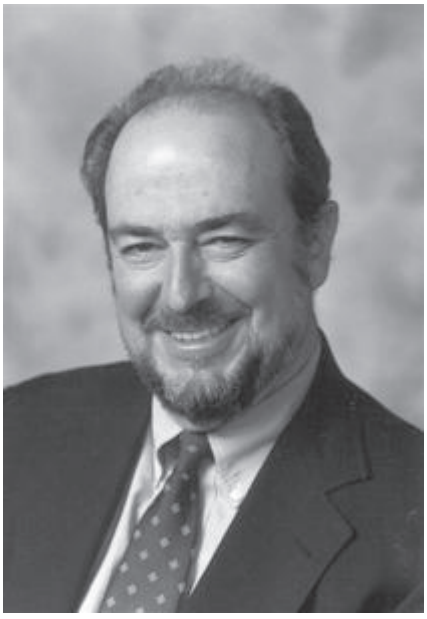

Figure 3B. Justiniano Campa

(related to the fission and fusion of the inner and outer mitochondrial membranes, respectively). Mutation of the mitochondrial gene *SLC25A46* has been reported to cause the clinical combination of optic atrophy and CMT2 in some families.[17]

In 1962, the year that Rábano and Campa published their paper, CMT co-presenting with optic atrophy was an extremely rare observation. In an important classification published in 1975, Dyck bases his description of this association (denominated hereditary motor and sensory neuropathy type VI) on a total of seven cases from the literature (Vizioli, 1879; Davidenkov, 1927; and Milhorat, 1943).[18] There have since been excellent studies into Spanish families carrying the *MFN2* mutation.[19-21] Banchs et al.[21] emphasise the importance of eye fundus examinations to identify subclinical optic atrophy in patients with CMT2,[20] as Rábano and Campa predicted 55 years ago.

Appendix

The three handwritten letters from Charcot to Barraquer Roviralta, held at the Museo Archivo Histórico of the Spanish Society of Neurology, from a total of 4 documents. They are translated as follows:

1) Dear, honourable colleague,
I received your article, which was a great pleasure to read. We will include a detailed analysis in the next edition of *Archives de Neurologie*.
My warmest regards ("*Croyez à mes fructueuses distinguées*"),
Charcot

2) My most honourable colleague,
I have received the highly interesting details that you were so kind as to send me regarding spinal lesions. However, I am yet to receive the other pieces you mention; I do hope that they have not been misdirected.
Sincerely yours,
Charcot

3) My dear colleague,
I write from Brighton, where I am enjoying a change of scenery, and will remain here for the next few days. We are on holiday, and there is no reason I should not travel to Barcelona in late August or early September. The fees are a more difficult matter, as I am not familiar with the patient's situation. I have been to San Sebastián several times, and asked 9000 to 12 000 francs. I think it best to leave the matter for your consideration, dear colleague.
Warm regards,
Charcot

Acknowledgements

We are grateful to the Museo Archivo Histórico of the Spanish Society of Neurology (V. Cisteré) for kindly providing us with copies of the letters sent by J.M. Charcot to L. Barraquer Roviralta. We would also like to thank Mr Giménez Utiel for his excellent French to Spanish translation of these letters.

Conflicts of interest

The authors have no conflicts of interest to declare.

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