Received: 28 October 2012 / Accepted: 12 December 2012

Original

Neurosciences and History 2013; 1(2): 71-79

The history of Huntington disease in Spain: first observations

S. Giménez-Roldán

Former head of Neurology, Hospital General Universitario Gregorio Marañón, Madrid, Spain.

ABSTRACT

Introduction. As occurred in other countries, doctors in Spain became aware of Huntington disease a relatively long time after its initial description. One factor contributing to the delay was confusion about features described by the term 'chorea'.

Material and Methods. We searched a variety of bibliographic sources to identify all Spanish-language articles that might be related to Huntington disease within a defined 75-year period (1900-1975).

Results Two articles dated 1910 and 1911 mention Huntington disease, but the entities they describe do not meet current diagnostic criteria for HD. In 1923, Sanchís Banús presented the first clear description of HD in a study of a geographical case cluster in Berlanga de Duero in Soria (Spain). He highlights the co-presence of muscle rigidity and disordered movement that evolved over a 16-year period in his index case. In a detailed post-mortem study of that case, Del Río-Hortega described atrophy of the globus pallidus, oligodendrocyte changes, and numerous neurodegenerative phenomena in the lenticular nucleus and frontal cortex. We have also included a few biographical notes about some of the most relevant authors.

Conclusions The observational study by Sanchís Banús promoted the search for new geographical clusters of HD in Spain. Significant concentrations were discovered in the Region of Valencia.

KEYWORDS

Huntington disease, History of Neurology, J. Sanchís Banús, E. Fernández Sanz, B. Rodríguez Arias, P. del Río Hortega.

Introduction

No one would have believed that the short article written by a 22-year-old graduate, the son and grandson of modest rural doctors from the small town of East Hampton (Long Island, NY), would go down in history. By 1872, however, researchers' interest in the role of heredity had grown. George Huntington's paper had the good fortune to be cited by Nothnagel and Kussmaul, two eminent internists.[1,2] Nevertheless, many years would pass before his study was recognised in Spain, Europe, or even in the United States.

The purpose of this study is to review Spanish articles published between 1900 and 1975 that mention Huntington disease. This 75-year period was chosen because it coincides with the emergence of the field of neurology in almost every region of Spain. In addition to evaluating the significance of these contributions from a modern perspective, the article includes information about the private lives and professional careers of some of the most important early researchers in HD.

Material and methods

Searches of multiple sources identified a number of Spanish-language articles that could be related to Huntington disease, including descriptions of entities named chronic chorea, acute chorea,[3] hemichorea,[4] and idiopathic double athetosis.[5] References were obtained from the literature on the history of the neurosciences, the history of neurology in Spain, and publications on general history. We consulted the articles mentioned above in their original sources, which are kept in different libraries in Madrid and the author's personal collection.

Corresponding author: Santiago Giménez-Roldán
Fuencarral, 126
28010 – Madrid, Spain

Email:sgimenezroldan@gmail.com

Results

The vague concept of chorea

"In the whole range of medical terminology there is no such 'olla podrida' as Chorea, which for a century has served as a sort of nosological pot". (William Osler, 1894).[6]

To this day, it comes as a surprise that acute onset hemichorea was identified in Spain many years before Huntington disease.[4] It began with the case of a 47-year-old man who was admitted to Hospital de la Princesa, Madrid, on 12 December 1875, two days after having suffered a severe attack of right-sided chorea. The description of violent, continuous, involuntary movements with rotation and elevation of the arm and cessation of movement during sleep unequivocally corresponds to acute hemiballismus. The patient recovered 18 days later after being treated with potassium bromide.

Published by Miguel Gayarre y Espinal (1866-1936), the first article in Spain to mention Huntington disease dates back to 1910 (Figure 1).[7] Nevertheless, it is unlikely that the 36-year-old patient described in the article actually suffered from HD, and Gayarre himself expressed uncertainty as to that diagnosis. The patient had no family history of Huntington disease and symptom onset was relatively acute following mild head trauma two years before. According to the author, the patient's mental abilities remained intact. The photograph illustrating the doctor's observations suggests torsion dystonia (Figure 2).

A year later, in 1911, Fernández Sanz described three cases of chronic chorea.[8] Given the absence of family history in all three cases, he ruled out the possibility of Huntington chorea. Interestingly, he considered variable chorea of Brissaud as an alternative diagnosis for case 1 (I should mention that Jiménez Díaz presented this supposed syndrome in his classes into the 1960s). According to Fernández Sanz, variable chorea of Brissaud was the third most common cause of chronic chorea, followed by Sydenham's chorea and Huntington disease. The patient was a 40-year-old woman who suffered severe parkinsonism with resting tremors and violent action tremors. Case 2 was a former member of the Spanish civil guard who at the age of 34 suffered sudden-onset complex and bizarre movements and abrupt muscular jerking which may have been psychogenic in origin. The third case was a woman aged 61 who suffered severe and continuous buccolingual movements and other more moderate movements in different areas of the body. Fernández Sanz concluded that his three patients might be displaying chronic forms of meningoencephalitis.

Little is known about Dr Miguel Gayarre y Espinal of Pamplona (1866-1936) except that he studied under Achúcarro in Hospital General de Madrid and Oppenheim in Berlin.[9] A well-known painting by Joaquín Sorolla shows Simarro working with a microscope while a small group of men look over his shoulder. Gayarre is the figure on the far right (private letter from Ana de la Quadra Salcedo, Gayarre's granddaughter). His doctoral exam booklet, dated June 1895, was incidentally discovered among the pages of the well-known *Lehrbuch* published by Hermann Oppenheim in 1894.[10] This discovery allows us to make some interesting conjectures about Gayarre's relationship with the prestigious German neurologist. We believe that Gayarre returned to Madrid in 1895 to sit the doctoral exam, taking the book with him

Figure 1. Portrait of Miguel Gayarre y Espinal showing him older than he is depicted standing on the far right in Sorolla's famous painting An investigation.

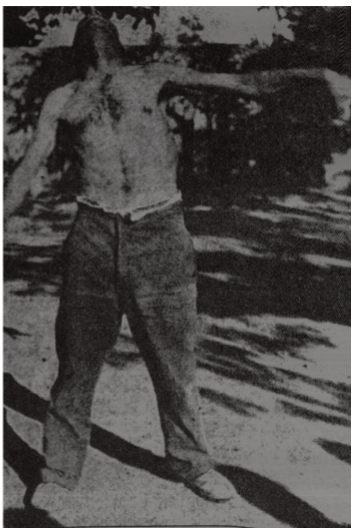

Figure 2. Image of the patient described in 1910. Note the pronounced opisthotonos, an infrequent clinical sign in Huntington disease.

and forgetting that he had tucked his personal papers between its pages.

Charité University Hospital in Berlin employed the most prestigious German neuropsychiatrists of those early years.[11] However, Gayarre had to endure a somewhat hostile work environment. After Westphal, the head of Charité-Nervenklinik, fell ill, Oppenheim became the interim department head and would retain that post for four years. Upon Westphal's death in 1890, local authorities made the unexpected decision to ban Oppenheim's candidature because he was Jewish. He was forced to leave the hospital and university and was only able to continue his research in a single, albeit successful, private outpatient clinic.[12] Gayarre probably felt the effect of these strained circumstances during his stay in Berlin. Gayarre made a hasty departure from Madrid at the outbreak of the Spanish Civil War. His house was confiscated, but at the very end of the war, his family was able to recover a few belongings that had been stored in the Italian Embassy.

Enrique Fernández Sanz (1872-1950) was a prolific writer who left behind some 350 articles and 5 short monographs (Figure 3). He gained clinical experience in the Santa Isabel insane asylum in Madrid, where he was awarded a permanent position in 1919. He was the asylum's director in the 1930s during the time of the Second Spanish Republic[9] and left the institution shortly after the Spanish Civil War began. Neurologists have much to thank him for. In 1933, when authorities at Hospital General de Madrid were making plans to build a large annex exclusively dedicated to mental patients, someone asked what was to be done with the neurological patients who were largely scattered in different general wards. Fernández Sanz staunchly supported the creation of a specific department for neurological patients,[13] but he was ignored. Neurological patients were treated by doctors of all types, especially internists, psychiatrists, and later, neurosurgeons; no such department would be constituted until 1981.

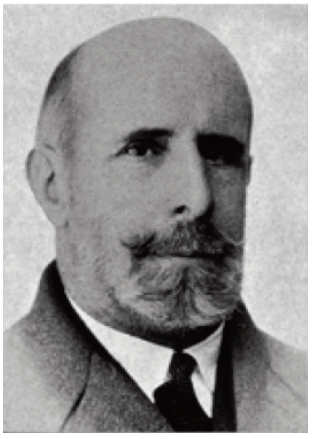

Figure 3. Dr Enrique Fernández Sanz, taken from the historical figures archive maintained by the Spanish Royal Academy of Medicine.

Sanchís Banús and the family from Berlanga de Duero

We believe that the first documented case of a family with Huntington disease in Spain was the one reported by José Sanchís Banús (1893-1932). While the case was published in 1923, a preliminary note also appeared in 1922.[14,15]

Pedro S., a 53-year-old man with severe symptoms of agitation and aggressiveness, was admitted to a department called Mental Patient Observation at Hospital General in Madrid on 18 July 1921. The department was directed by Dr Huertas. Unlike his father, he was not held in high esteem by his colleagues, who called him 'Paquito Huertas', (personal correspondence, Dionisio Nieto). Mental Patient Observation was a separate unit from the neuropsychiatry department, founded by Nicolás Achúcarro; Sanchís Banús became head of neuropsychiatry upon Achúcarro's death. Sanchís Banús did not notice any involuntary movements during his initial examination of the patient. He did learn, however, that the patient's mother and several siblings had a similar disease. From the age of 37, Pedro S. did indeed suffer a progressive illness that caused abnormal movements and marked irritability. His four young sons remained healthy.

A few days after being admitted, the patient became less agitated and his mental state could be assessed using tests developed by Masselon, Ebbinghaus, Henneberg, and Heilbronner. This speaks volumes about his doctor's cultivation, thoroughness, and his German influence in particular. In any case, he concluded that the patient's working memory, attention, and time orientation were impaired. He then noticed generalised abnormal movements and identified them as choreic. He was surprised by the "marked hypertonia" accompanying these abnormal movements. The patient remained hospitalised during five months with severe depression before dying of bronchopneumonia.

Domingo Manrique, who worked with Sanchís Banús, travelled to the patient's hometown of Berlanga de Duero in the province of Soria. In addition to contacting the Pedro S. family, he got in touch with another two families. In the space of three generations, seven cases had appeared in "Family U", as well as three cases in three generations in "Family M". If truth be told, the data collected by Dr Manrique were quite deficient. His report

omitted age at onset of the disease and whether the affected patients were still alive. He even excluded the sex of the patients. He did take the time to highlight that none of the deceased patients had committed suicide.

One symptom which struck Sanchís Banús as peculiar was the patient's rigidity rather than the more typical hypotonia. R. Alberca Lorente, in his 1932 obituary for Sanchís Banús which mentioned his works, stated that "the presence of associated parkinsonism could in fact indicate a new type of degenerative chorea".[16,17] Dr Pío del Río-Hortega, aware of the special interest of the Pedro S. case, travelled to Hospital General upon the patient's death in order to personally conduct the autopsy.

Sanchís Banús could be called a prototypical representative of the Madrid school of neuropsychiatry (Figure 4)

Figure 4. José Sanchís Banús, neuropsychiatrist at Hospital General in Madrid, who described the first family with Huntington disease to be documented in Spain.

which developed around Hospital General and the teachings of Santiago Ramón y Cajal. Gregorio Marañón's gifted pen[18] describes the school as consisting of "rigorous and idealistic men", who included José María Esquerdo, Jaime Vera, Luis Simarro, Pérez Valdés and Nicolás Achúcarro, the true founding fathers of neuropsychiatry. Marañón also described Sanchís Banús as "generous with both time and money, an avid reader with a thirst for knowledge". In his old age, the beloved family doctor Valentín Otaño described Banús's power of speech as he had heard it as a young man. This compelling speaking ability must have been useful to Banús during his stint as a delegate for the Socialist Party. A true Renaissance man, he spoke brilliantly on psychosocial subjects, such as delinquency; purely psychiatric topics, such as "the paranoid delusion of the blind", and naturally, complex neurological studies as well.[19]

Figure 5. Majorcan psychiatrist Joan Alzina i Melis.

We should also mention the Catalan-language study published in 1913 by the Majorcan doctor Alzina i Melis (Figure 5) under the thought-provoking title *Nota sobre'l metabolisme nutritiu en dos casos de corea familiar* [20] [Description of nutritional metabolism in two cases of familial chorea]. Although these patients were studied in Germany, they may constitute a topic for an interesting article in the future.

Del Río-Hortega and neuropathology of Huntington disease

The brain of Pedro S. was meticulously studied by Dr Del Río-Hortega. In addition to dyeing methods used by the Spanish school, such as Ramon y Cajal's chrome silver staining method for studying nerve cell structures and gold sublimate for protoplasmic astroglia and oligodendrocytes, he used his own methods, such as silver carbonate for studying microglia and myelin. He modified this technique from one developed by his mentor Achúcarro.

Del Río-Hortega discovered altered cell morphology in two different locations. Neurons in the frontal cortex were smaller than one might have expected, with particularly marked atrophic changes in the molecular and small pyramidal cell layers. He also found neuronophagia, nuclear pyknosis, neuronal chromatolysis, astroglial proliferation, and microglia mobilisation phenomena, all of which are indicative of degenerative illness. He was especially interested in nerve cells with few branches (oligodendrocytes) which he himself had discovered, and therefore meticulously described the changes he observed in them. "They were swollen, with a balloon-like appearance and found near affected neurons, where they seemed to engage in the improperly-named phenomenon of

neuronophagia". With commendable caution, he suggested the possibility of their being post-mortem artefacts. Apart from the degenerative changes in areas typically affected by the disease, the pathologist clearly highlighted the unusual feature of the similar degrees of degeneration in the putamen and the globus pallidus.[16]

Office politics, and possibly professional jealousy as well, drove Del Río-Hortega to leave the Histopathology Laboratory which was adjacent to Ramón y Cajal's Biological Research Laboratory in a wing of the National Museum of Anthropology in Madrid. (Figure 6). When Del Río-Hortega moved his laboratory to the Student Residence

Figure 6. Dr Pio del Río-Hortega, who performed the neuropathology study on the patient described by Sanchís Banús in 1923. This constitutes one of the first cases in the literature in which the onset of rigidity was associated with globus pallidus degeneration.

building in late October 1920, he also changed its name to the Nervous System Histopathology Laboratory. By doing so, he established that his focus would include both nervous system histology and neuropathology –a decision which might reflect nostalgia for the brain tumours he analysed for his doctoral thesis– and he began studying pathological cases referred by Hospital General. The doctor thus began a new chapter of his life in a small, cold, poorly lit office on the ground floor of the residence.

Belarmino Rodríguez Arias and the search for geographical clusters

It was no mere coincidence that all three families studied by the Barcelona Neurological Institute came from the region of Valencia, and more specifically from the towns of Denia, Elda, Alicante, and Requena.[21] In an oral presentation of the study by Rodríguez Arias, J.J. Barcia Goyanes mentioned six families studied at Hospital Provincial in Valencia. In particularly florid terms ("Spanish provinces, the chrysalis of racial admixture,

Figure 7. Dr José Espín Herrero, author of the first epidemiology study of Huntington disease in Spain. The discovery of the "eastern Mediterranean cluster" gave rise to important subsequent studies. Portrait from his youth.

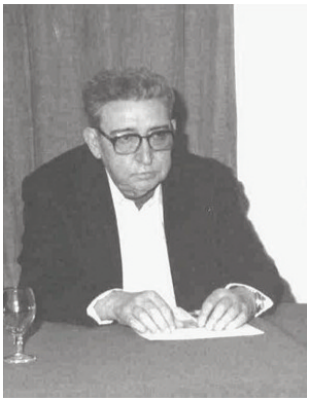

Figure 8. Portrait dating to when the author of this article, then stationed in Valencia as a medical officer, met him at Hospital Provincial. Photography courtesy of Dr J. A. Burguera.

confluence of endless migrations"), Rodríguez Arias proposed a method that we today would consider primitive, with the grand goal of compiling "a census of lunatics throughout the entire country".

Spain's eastern Mediterranean coast has been known for its high concentrations of Huntington disease since 1948 when José Espín Herrero (Figures 7 and 8) published his detailed study.[22] Espín collected data from five generations of the same family, in which 16 of the ancestral couple's 77 descendants were affected. Mean age at onset ranged from 25 to 55 years, whereas mean age at death was 60 (range, 35-75). He was surprised by the presence of four cases of "psychopathic personality" without chorea. Although the author discreetly omits the patients' places of residence, we now know that they lived in the towns of Manuel and Énova in the Region of Valencia (J.A. Burguera, in a private letter dated December 1981).

The Spanish Society of Neurology was founded in Barcelona on 19 December 1949. Rodríguez Arias, one of its three founding members,[23] steadily supported the study of what he termed "casuistics of hereditary or familial neuropathies". This may have had to do with his experience as the director of the psychiatric hospital in San Baudilio de Llobregat.[24] In short, he proposed tracking the origins of hereditary nervous system diseases throughout the length and breadth of Spain.

Research on specific facets of the illness

For many years, doctors believed that Huntington disease was rarely seen in Spain (Figures 9-10). When one publi-

Figure 9. First case of Huntington disease encountered by the author in 1966. This patient and his sister were included in a series of 29 patients with different movement disorders who were treated with diazepam in 1968.[28] Patients were monitored by the neurology department at Gran Hospital de la Beneficencia General del Estado in Madrid, headed by Dr Gonzalo Moya Juan-Cervera. One of this department's innovative features was a medical photography laboratory with a full-time photographer (note the lateral spotlights and the black backdrop).

cation cited a case of severe chorea in about 1933, doctors assumed that it referred to a severe form of Sydenham's chorea.[3] However, by the 1960s, we begin to identify isolated cases examining psychopathological aspects,[25] pneumoencephalography images,[26] treatment with haloperidol[27] and diazepam,[28] uncommon presentations such as severe dysphagia,[29] and the first attempt at preclinical disease detection by studying the blink reflex.[30]

Remarks

Chorea: a vague definition of a clinical phenomenon

The articles referring to Huntington disease which were published in 1910 and 1911 in Spain[7,8] are proof that chorea was poorly defined as a clinical phenomenon; this concurs with Osler's description of the term 'chorea' as a catch-all or *olla podrida*.[6] Even with the help of photographs, such as those that illustrate Gayarre's case (1910), it is hard to determine what type of movement disorder may have affected the patient. In rare cases, we find film recordings of patients who were diagnosed with chorea at the time, but who would receive very different diagnoses today.[31] The situation becomes increasingly complex given the considerable variety of movement disorders among survivors of encephalitis lethargica.[32]

Detection of the first geographical clusters

When Sanchís Banús identified affected families in 1923 in Berlanga de Duero, this was the first time a geographical cluster had been detected in Spain. Upon investigating the birthplace of the index case, he detected some 20 additional cases in three apparently unrelated families, all of them living in the same town in the province of Soria.[15,16] The importance of the founder effect would later be illustrated by Espín Herrero[22] in his study of a couple who gave rise to no fewer than 16 cases in the course of eight generations. Years before, De la Vega and Serra[33] had also described three cases in unrelated families, all residing in Villena in the province of Alicante. The aggregation in the Region of Valencia has been studied repeatedly[34] and we now know that it is the product of two different mutations that arose 4700 and 10 000 years ago. Today, these mutations are expressed by families living in two different geographical locations: Marina Alta and La Safor, near the coast, and the inland region near l'Alcoià.[35]

Between 1965 and 1985, neuropsychiatrist Faustino Díaz Beunza of Granada (Figure 2B), detected a total of 107 patients representing 17 families in the Balearic Islands. This followed an initial study of five siblings at the Mallorca Psychiatric Hospital.[36] We do not know if he published any findings, but he did cooperate in early research aimed at detecting the gene involved in the disease. Another noteworthy study was carried out by Calcedo Ordóñez, the chair of the Psychiatry Department in Cádiz, in and around 1970.[37-40] After 1975, the endpoint chosen for our historical review, doctors were also aware of the geographical clusters in Salamanca, Badajoz and Zaragoza, and possibly others.

One of the most enigmatic and fascinating articles on Huntington disease clusters was published in 1947 by the veterinarian Gil Fortún.[41] Preoccupied by the disease's hereditary nature, its link to suicidal tendencies, and the belief that "adenoidal speech" was an early symptom, Gil Fortún mapped out one of the most detailed family trees ever to have been completed in Spain (34 patients in six generations). Although he names the location of the family cluster only as "site Z", it was probably located in the province of Jaén in Andalusia. The fact that Gil Fortún mentions Morcillo Hervás,[42] who had described a similar case in the provincial asylum in Jaén a few years before, and states that the doctor had been working in a town near "site Z", supports this hypothesis.

Del Río-Hortega's neuropathological study

It is likely that neuropsychiatrists at Hospital General in Madrid would have been particularly aware of chorea as a clinical phenomenon thanks to experimental studies by Rodríguez Lafora.[43] Most of these doctors had worked with Ramón y Cajal; furthermore, Sanchís Banús did not

pass up the opportunity of collaborating with the great Pío del Río-Hortega, a histologist who was also well-informed about human neuropathology.

Sanchís Banús was surprised to find hypertonia along with involuntary movements in his patient Pedro S. The doctor noted that, according to Lhermitte, the latter symptom would clearly justify ruling out Huntington disease. He then wondered if a patient might develop a new extrapyramidal syndrome that might be called "chronic chorea with hypertonia". Autopsy data cited by Del Río-Hortega's report show the typical changes in the striatum and the frontal lobe with the added feature of atrophy of the globus pallidus. This last feature also surprised the pathologist, who had an excellent understanding of normal anatomical pathology in Huntington's disease.[44, 45] Pedro S., who had then been under observation for 16 years, was in a very late stage of the disease, whose mean survival time is 17 years according to current calculations.[46] Atrophy of the globus pallidus is a late-onset event occurring in stages 3 and 4 of HD.[47] It is possible that the abnormal movements which Sanchís Banús observed during very late stages were more reflective of dystonia than chorea.[48]

Another atypical feature which Del Río-Hortega points to in the Pedro S. autopsy was alteration of the oligodendrocytes, described as "swollen and globular, especially near neuronophagic nodules". Soon after having left Cajal's laboratory, Del Río-Hortega published his initial study on oligodendroglia. In 1928, in the process of gathering his material and his ideas, he wrote *Tercera aportación al conocimiento morfológico e interpretación funcional de la oligodendroglía*[49] [Third contribution to the morphological knowledge and functional understanding of oligodendroglia]. One section of his book (VII) was dedicated to abnormal variations of oligodendrocytes and it included chorea in a long list of diseases. Demonstrating scientific rigour, Del Río-Hortega concedes that he does not know whether the increased volume of protoplasm indicates "the effect of post-mortem autolysis, or if it is due to artefacts caused by reactants". Gómez-Tortosa et al.[50] have observed higher oligodendrocyte density among bearers of the mutation, with particularly high densities at the level of the tail of the caudate nucleus.

In summary, the Pedro S. case represents one of the first observations of Huntington disease to highlight the development of rigidity in advanced stages of the process and a correlation with atrophy of the globus pallidus.

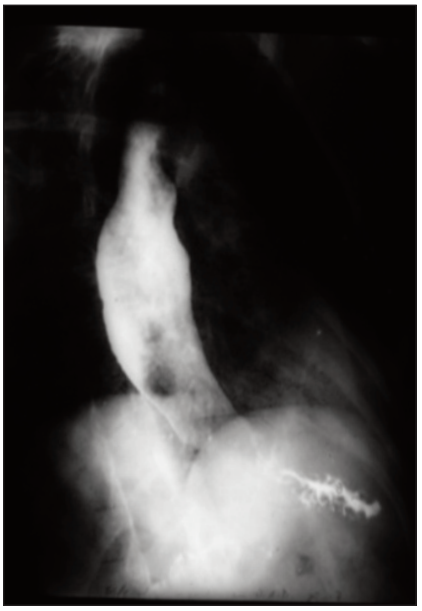

Figure 10. Oesophageal transit study in a 59-year-old patient whose clinical symptoms included severe progressive dysphagia. The study revealed the cause to be progressive systemic sclerosis and not Huntington disease.[29] This case is described by Bruynen in his Handbook of Clinical Neurology.[48]

Unfortunately, the detailed post-mortem report drawn up by Del Río-Hortega did not include any images, which would have provided important information.

Prevalence

We know today that Huntington disease is relatively frequent in Spain. However, it is important to recall that records at Hospital Psiquiátrico Nacional in Leganés corresponding to the period between 1931 and 1952 do not list any cases of HD.[51]

There is no doubt that the technique, available since 1993, of locating mutation IT15 on chromosome 4p16.3 to diagnose Huntington disease has had a major influence on our understanding of HD prevalence in Spain. We now know this prevalence to be considerably higher than the figures suggested by older studies.[52] In fact, mortalities due to HD have been increasing by 4% yearly, with prevalence figures between 5.4 and 8.4 per 100 000 inhabitants, in recent years.[53]

Acknowledgements

I would like to thank Dr Juan Andrés Burguera for the photo of Dr Espín Herrero, and Dr Miguel Marco Igual for his help in finding the article by Alzina i Melis. Original studies were obtained from the following libraries: Ateneo Científico, Literario y Artístico de Madrid; Universidad Complutense; Hospital General Universitario Gregorio Marañón; and Biblioteca Nacional de España. I also thank library staff for their invaluable assistance.

References

1. Lanska DJ. George Huntington (1850-1916) and hereditary chorea. J Hist Neurosci. 2000;9:76-89.
2. Neylan TC. Neurodegenerative disorders: George Huntington's description of hereditary chorea. J Neurpsychiatr Clin Neurosci. 2003;15:108.
3. López Albo W. Tratamiento de la corea grave por el sulfato de magnesio. Arch Neurobiol (Madr). 1933;2:307-13.
4. Salazar M. Un caso de hemicorea. Anales de Ciencias Médicas. 1876;1:61-6.
5. Vázquez Helbrun S. Atetosis doble idiopática. Arch Med Cir y Esp. 1936;39:178.
6. Osler W. On chorea and choreiform affections. Londres: H.K. Lewis; 1894.
7. Gayarre M. Un caso de corea de Huntington. Revista Clínica de Madrid. 1910;1:137-41.
8. Fernández Sanz E. Tres casos de corea crónico. Rev Med Cir Pract. 1911;91:161-72
9. Izquierdo Rojo JM. Historia de la Neurología clínica española (1882-1936) [doctoral thesis]. Madrid: Universidad Complutense; 1978
10. Giménez-Roldán S. Miguel Gayarre (1866-1936) y la neurología madrileña: contribución a su biografía. Neurología. 2002;17:324-7.
11. Holdorff B. Founding years of clinical Neurology in Berlin until 1933. J Hist Neurosci. 2004;13:223-38.
12. Van Gijn J. Hermann Oppenheim (1858-1919) J Neurol. 2004;1028-9.
13. Fernández Sanz E. La instalación de departamentos neuropsiquiátricos en los Hospitales Generales. Arch Med Cir y Esp. 1933;24:181-96.
14. Sanchís Banús J. Contribución al estudio del "corea crónico hereditario" de Huntington. Resumen general con motivo de los primeros casos españoles. Los Progresos de la Clínica. 1923;25:221-42.
15. Sanchís Banús J. Contribución al estudio del "Corea crónico hereditario" de Huntington. An Acad Med Quir Esp. 1922;9:294.
16. Alberca R. Necrología. In memoriam. José Sanchís Banús. Arch Neurobiol (Madr). 1932;12:808-13.
17. Codina Castellví. En memoria de Sanchís Banús. Gac Med Esp. 1932;7:72.
18. Marañón G. Obras completas. Vol. 9. Madrid: Dossat; 1973. p. 73-6.
19. Pérez Salmón C. La obra psicológica de José Sanchís Banús (1893-1932) [doctoral thesis]. Madrid: Universidad Complutense de Madrid; 2009.
20. Alzina i Melis J. Nota sobre'l metabolisme nutritiu en dos casos de corea familiar. Treballs de la Societat de Biologia. 1913;6:49-52.
21. Rodríguez-Arias B, Pons-Clotet A. Una gran cepa familiar y un doble foco geográfico de corea de Huntington en el Levante español. Rev Esp Otoneurooftalmol Neurocir. 1952;19:154-7.
22. Espín Herrero J. Contribución al conocimiento de la demencia en la corea de Huntington. Rev Esp Otoneurooftalmol Neurocir.1948;5:304-14.
23. Barraquer Bordas L. Dr. Belarmino Rodríguez Arias (1895-1997). Neurología.1997;12:375-9.
24. Rodríguez Arias B. Pequeña crónica, en glosa, de mi transitoria vinculación al Hospital Psiquiátrico de San Baudilio de Llobregat. Arch Neurobiol (Madr). 1971;34:161-68.
25. Gimeno Álava A, Calcedo Ordoñez A. Estudio psicopatológico de un caso de corea de Huntington. Clin Lab (Zaragoza). 1956;57:358-63.
26. López García E, López Zanón A, Martínez Pastor E, Ramírez Guedas. Corea crónica progresiva de Huntington. Rev Clin Esp. 1957;56:259-60.
27. López de Lerma J. Tratamiento del corea de Huntington con haloperidol. Medicamenta. 1961;35:348-50.
28. Moya G, Giménez-Roldán S. Ensayo terapéutico con diazepan en enfermos con movimientos involuntarios. Medicina Clínica (Barc). 1968;51:595-606.
29. Giménez-Roldán S, Esteban A, Ballesteros R. Disfagia grave en un corea de Huntington con esclerodermia asociada. Rev Clin Esp. 1971;120:165-70.
30. Esteban A, Giménez-Roldán S. Blink reflex in Huntington's chorea and Parkinson's disease. Acta Neurol Scand. 1975;52:145-57
31. Giménez-Roldán S, Aubert G. Hysterical chorea: Report of an outbreak and movie documentation by Arthur Van Gehuchten (1861-1914). Mov Disord. 2007;22:1071-6.
32. Corral-Corral I, Quereda Rodríguez-Navarro C. Síndromes postencefalíticos en la literatura médica española. Rev Neurol. 2007;44:499-506.
33. De la Vega P, Serra F. Tres casos de enfermedad de Huntington. Rev Esp Otoneurooftalmol Neurocir.1948;1:213-23.
34. Burguera JA, Solís P, Salazar A. Estimación de la prevalencia de la enfermedad de Huntington en la Comunidad Valenciana mediante el método de captura-recaptura. Rev Neurol. 1997;25:1845-47.
35. García-Planells J, Solís P, Millan JM et al. Ancient origin of the CAG expanse causing Huntington disease in Spanish population. Hum Mut. 2005;25:453-9.
36. Fernández S. El legado mallorquín de la enfermedad de Huntington. [Internet].
[Updated 14 June 2011; accessed 10 Oct 2012]. Available at: http://susanafernandez.wordpress.com/2011/06/14/el-legado-mallorquin-de-la-enfermedad-de-huntington/
37. Calcedo Ordoñez A. Enfermedad de Huntington. Estudio familiar (A propósito de un caso tardío). Rev Fac Med Sevilla. 1970;2:421-34.
38. Calcedo Ordoñez A. Enfermedad de Huntington. Revisión histórica y etiopatogénica. Rev Esp Otoneurooftalmol Neurocir.1948;28:135-41.
39. Calcedo Ordoñez A. Enfermedad de Huntington en la provincia de Cádiz. Estudio epidemiológico y familiar. Rev Clin Esp. 1970;119:333-44.
40. Calcedo Ordoñez A. Corea de Huntington. Una investigación epidemiológica en la provincia de Cádiz. Murcia: Asociación Española de Neuropsiquiatría; 1971.
41. Gil Fortún F. La forma en que se hereda la corea de Huntington y su posible relación con la demencia suicida. Rev Clin Esp. 1947;27:104-11.
42. Morcillo Hervás C. Tres casos de enfermedad de Huntington. Rev Clin Esp. 1943;10:260-5.

43. Rodríguez Lafora G. Corea y atetosis experimental. Nota preliminar. El Siglo Médico. 1922;70:463-4.
44. Solé Sagarra J. Hallazgos anatomopatológicos en la corea de Huntington. Rev Clin Esp. 1945;18:329-37.
45. Martínez A, Rábano A. Anatomía patológica de la enfermedad de Huntington. Rev Esp Patol. 2002; 35: 517-28.
46. Martin JB. Huntington's disease: new approaches to an old problem. Neurology. 1984;34:1059-72.
47. Vonsattel JP, Myers RH, Stevens T, Ferrente RJ, Bird ED, Richardson EP. Neuropathological classification of Huntington's disease. J Neuropathol Exp Neurol. 1985;44:6.559-77.
48. Bruyn GW. Huntington's chorea: historical, clinical and laboratory sinapsis. In: Vinken PJ, Bruyn GW. Handbook of Clinical Neurology, diseases of the basal ganglia. Editores. Amsterdam: North Holland; 1968.
49. López Piñero JM. Pío Del Río Hortega. Madrid: Biblioteca de la Ciencia Española; 1990. p. 234-53.
50. Gómez-Tortosa E, MacDonald ME, Friend JC, Tylor SAM, Weiler LJ, Cupples A et al. Quantitative neuropathological changes in presymptomatic Huntington's disease. Ann Neurol. 2001;49:29-34.
51. Vázquez de la Torre P. Nosografía psiquiátrica en el Manicomio Nacional de Santa Isabel (1931-1952). Frenia. 2008;8:69-96.
52. Burguera JA, Láinez GM, Blasco R, Catalá J. Casanova B. Mortalidad por enfermedad de Huntington en España, 1975-79. Rev Neurol. 1990;18:13-6.
53. Ramalle-Gómara E, González MA, Perucha M et al. Mortalidad por la enfermedad de Huntington en España en el periodo 1981-2004. Rev Neurol 2007;45:88-90.