

Américo Negrette and Huntington's disease

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ABSTRACT

The authors present a historical review of the seminal clinical contribution of Professor Américo Negrette, a Venezuelan neurologist, to the evolution of scientific knowledge about Huntington's disease.

Key words: Américo Negrette, Huntington's disease, chorea, huntingtin, CAG.

Américo Negrette e a doença de Huntington

RESUMO

Os autores apresentam uma revisão histórica sobre a magistral contribuição clínica do Professor Américo Negrette, neurologista venezuelano, na evolução do conhecimento científico sobre a doença de Huntington.

Palavras-chave: Américo Negrette, doença de Huntington, coréia, Huntingtina, CAG.

Huntington's disease (HD) is a neurodegenerative disorder with an autosomal dominant inheritance pattern, resulting from an expanded and unstable trinucleotide repeat in the IT15 gene on chromosome 4 that encodes a protein called huntingtin^{1,2}.

The prevalence of HD in the Caucasian population ranges from 0.5-1 in 10,000. Mean age at onset is between 35 and 50 years, and the main manifestations are involuntary movements, especially chorea, behavioral and psychiatric disturbances, and dementia. The disease progresses inexorably and has a mean duration of 17-20 years. No effective treatment is currently available¹⁻³.

Among the great strides made in the search for greater understanding of HD was the discovery of the gene in 1993 in a cooperative research effort in Venezuela known as the Huntington's Disease Collaborative Research Group⁴. This effort was influenced by the pioneering work of

a Venezuelan physician, Dr. Américo Negrette, who is the subject of this review.

Américo Negrette

Américo Negrette (1924-2003), a Venezuelan physician, biochemist, artist and poet (Fig 1 and 2), was born in La Cañada, Venezuela⁵.

Negrette graduated in medicine in 1949 at the Central University of Venezuela.



(Extracted from Google Images: vitae.ucv.ve)

Fig 1. Professor Américo Negrette (1924-2003).

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While working as a rural practitioner in San Francisco, Maracaibo, in 1952, he was instructor in clinical medicine in the Faculty of Medicine at the University of Zulia. During his stay in San Francisco, Negrette found patients in the streets with a peculiar gait disorder and involuntary movements known by the local people as "Sanviteros". In fact, these patients had a hereditary disease, known locally as "el mal de San Vito", later known as HD^{3,5-7}.

In 1955 Negrette presented the study "Huntington chorea: a first communication" during the 6th Medical Sciences Congress in Venezuela. In 1963 he published the book "Huntington's chorea", containing clinical descriptions of several patients⁶.

Later, Negrette received graduate training in neurology at the Institute for Clinical and Medical Research in Madrid. Following this, he was appointed professor of clinical neurology in the Department of Medicine at the University of Zulia and became founding director of the Clinical Research Institute at the same university⁵.

Negrette's book on Huntington's disease

Negrette's book on HD, published in 1963, has 226 pages and eight chapters, covering clinical description of several cases, their semiology, pathophysiology of choreas, basic genetics, diagnosis, additional tests and hereditary aspects, as well as social, economic and environmental aspects and bibliographical references⁶.

The two most important chapters are "Clinical histories" and "a compendium of clinical histories" in which the author discusses the clinical manifestations of HD⁶.

The chapter "Clinical histories" describes the anamnesis and general and neurological examination of 39 chorea patients (17 male and 22 female). The clinical histories of a further 29 at-risk individuals without chorea (13 male and 16 female) are also discussed⁶.

In the chapter "A compendium of clinical histories" Negrette summarizes the main abnormalities found on examination. The chapter is illustrated with figures, tables and photographs, and emphasis is placed on the main abnormalities observed on neurological examination, particularly involuntary movements (chorea and ataxia), muscle hypotonia, abnormal deep tendon reflexes, language disturbances, and behavioral/cognitive disturbances⁶.

Overall, Negrette's book on HD provides an extensive basic clinical assessment of the cases he studied, which served as the basis for further international genetic studies⁶.

The connection between Negrette's work and Dr. Wexler from the USA

At the Centennial Symposium on HD in Ohio, USA, in 1972, a former student of Negrette, Dr. Ávila-Girón,



Personal archive of Roberto Weiser.

Fig 2. Professor Américo Negrette during the celebration of the opening of AVEHUN (Asociación Venezolana de Huntington) in 2000.



(Extracted from Google Images).

Fig 3. Venezuela Map and Maracaibo Island.

presented a series of cases of patients with HD in the Maracaibo region of Venezuela (Fig 3). Ávila-Girón's data were published in 1973 in a book edited by Barbeau et al.⁸. In fact it was Barbeau himself who visited Venezuela and confirmed the diagnosis. Because of the large number of cases in areas close to Lake Maracaibo, where there were families in which both parents were HD sufferers, it was agreed that a study would be carried out to evaluate possible homozygotes^{7,8}.

However, there can be no doubt that the main interest in studying Venezuelan patients with HD came from the Hereditary Disease Foundation, an organization coordinated by Dr. Milton Wexler after his wife, Alice Wexler, developed confirmed HD. Dr. Nancy Wexler, Alice Wexler's daughter, played a major role in research into HD⁷.

With the support of the United States National Institute of Mental Health, Dr Nancy Wexler started a genetic study of HD patients in Maracaibo, which culminated in the discovery of the HD gene^{3,7,9}.

Discovery of the gene for Huntington's disease

The Venezuelan HD kindreds were first described by Negrette and represented the largest and best characterized HD population in the world. Most of the families live in the Lake Maracaibo region in the state of Zulia, Venezuela. The Venezuelan kindreds were highly heterogeneous. While the majority were Hispanic, their genetic and phenotypic heterogeneity was the result of miscegenation with European sailors and traders, with some Native American admixture^{3,5-8}.

In 1979 Nancy Wexler visited Venezuela for the first time, originally with the intention of finding a homozygote. Once she began fieldwork in 1981, the recombinant DNA revolution had begun and she and other researchers changed their plans, deciding instead to carry out genetic linkage studies in these families. The group collected extensive pedigrees - who is related to whom - which were essential for mapping the HD gene to a chromosome. The Venezuelan Pedigree proved to be of great value, not only for research on HD, but also for understanding inheritance in general. These family trees were perfectly structured for use in genetic linkage studies^{3-5,7,9}. The research effort culminated in 1983 with the mapping of the HD gene to chromosome 4p16.3, by Gusella et al.¹⁰.

The Huntington's Disease Collaborative Research Group, which involved six research groups (four from the USA, two from the UK) and more than 150 investigators, found the defective HD gene in 1993. This finding was published in the seminal paper "A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes" in the prestigious journal *Cell*⁴.

The huntingtin mutation is an unstable trinucleotide (CAG) repeat expansion in the ORF of exon 1 of the gene

and is related to the expression of an expanded polyglutamine repeat in the huntingtin protein^{1-3,7,9}.

Since the discovery of the gene, HD has been defined as an autosomal dominant neurodegenerative disease caused by a CAG repeat expansion mutation, i.e., a polyglutamine disease^{1,2,7,9,10}.

Conclusion

The enormous progress in HD research in recent years with the mapping of the gene, the identification of the mutation and the current definition of the condition as a polyglutamine disease, owes much to the masterly clinical study carried out by professor Américo Negrette in Venezuela in the 1950s.

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