Article Title: George Huntington's "On chorea" after 150 years: how a "few words" changed the history of a disease.

Author's Name: Sergio A. Castillo-Torres[1,2]

Author ID: https://orcid.org/0000-0002-4727-2535

Email: sact.md@gmail.com

Social media contact. Twitter: twitter.com/sacastillot

Institutional Affiliations:
1. Servicio de Movimientos Anormales, Departamento de Neurología, Fleni. Buenos Aires, Argentina.
2. Servicio de Neurología, Hospital Universitario "Dr. José Eleuterio González", Universidad Autónoma de Nuevo León. Monterrey, NL, México.

Corresponding Author:
Sergio Andrés Castillo Torres
Servicio de Movimientos Anormales
Departamento de Neurología, Fleni
Montañeses 2325, Capital Federal, C1428AQK
Buenos Aires, Argentina.
Telephone: +5491157773200
Email: sact.md@gmail.com

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"In the whole range of descriptive nosology there is not, to my knowledge, an instance in which a disease has been so accurately and fully delineated in so few words were given."

- Sir William Osler, On Chorea and Choreiform Affections (1894)

Huntington's disease (HD, OMIM #143100) is an autosomal dominant neurodegenerative disorder caused by a repeat expansion of the CAG trinucleotide in the Huntingtin gene (*Htt*) located in chromosome 4 (4p16.3). Clinically, it is widely known for chorea: an involuntary hyperkinetic movement disorder with movements apparently flowing from one body site to another in a random, non-rhythmic, and non-patterned fashion.[1]

Chorea comes from the Greek χορεία (*khoreía*) meaning "a round dance", and was proposed by Paracelsus in the XVI century to describe the main symptom of St. Vitus' dance (the dancing disease);[2] which he suggested to rename *chorea lasciva* (unrestrained dance) which arose from the sufferer's imagination since neither "God or the Saint inflict it". In contraposition to *chorea naturalis*, or of natural ("organic") origin, which required medicines to be treated.[2]

Before Paracelsus' treatise, interest in chorea as a disorder appears to be scarce, as demonstrated by reports on chorea being practically absent until the early seventeenth century, when only few German and several English physicians

wrote about it. Among them, the most remarkable is Thomas Sydenham, who in 1686 described the infantile form of chorea that today bears his name, even though he confused it with the religious procession and named it *Chorea Sancti Viti*. Later, Osler would reclassify Sydenham's chorea under the term *chorea minor*, reserving the term *Chorea Sancti Viti* dance for the religious dance.[3]

Although today adult chorea is almost synonymous with Huntington's disease (HD), there is even less evidence of hereditary chorea cases prior to Huntington's observations in the XIX century. This might be explained by the fact that adult-onset or hereditary cases were considered infrequent or even non-existent. But it has also been attributed to the lower life expectancy during and prior to the XIX century meant that patients with hereditary chorea died before they could manifest chorea or have descendants carrying the disease.[4] Also, prevailing views of hereditary chorea as a curse may have prevented afflicted families from openly discussing the matter.

George Huntington published "On chorea" on April 13th, 1872 in *The Medical and Surgical Reporter*.[5] The article begins emphasizing the essential features of chorea: motor impersistence ("tongue is protruded and suddenly withdrawn") and the random nature ("The contortions are never localized to one muscle or set of muscles, but the whole muscular system seems to be involved") of the movements.[5] Followed by a review of the

post-infectious form of chorea (Sydenham's chorea) and its association with rheumatism, highlighting the importance of cardiac examination.[5] Afterwards, Huntington laments the scarce evidence on the underlying pathological changes of patients with chorea, hoping one day this would be "laid open to the light of day".[5] Concluding with a brief review about the therapeutic agents used in those days, from purgatives to electricity, with varying degrees of success.[5]

After this general perspective of chorea, he brings forward the case for *hereditary chorea*. Although at the time of writing he was 22 years-old and had been licensed as a physician for only one year, the conception of the article had been lingering in his mind for nearly 14 years. Huntington considered his interest on hereditary chorea began at the same time that his medical education, when he was 8 years old, while accompanying his father on his rounds and witnessing a mother and daughter afflicted with "that disorder", as the families usually referred to hereditary chorea.[6, 7] Thus, his observations also relied upon the experience of his father and grandfather (also physicians) who had already registered cases of hereditary chorea since the early eighteenth century.[7, 8]

Huntington highlighted three features of the disease: (1) its hereditary nature; (2) the proclivity towards cognitive decline and suicide; and (3) the manifestation of severe disease only in adults, without cases before the age of 30.[5] Of these,

only the third did not endure the test of time, since today we know that young adults and even children can manifest HD from an early age, particularly as a rigid-akinetic syndrome known as the Westphal variant. Huntington concludes by declaring that he considered hereditary chorea "merely as a medical curiosity". Unknowingly, he would help to make visible a disease that had remained ignored by the medical profession and less than a decade after its publication, hereditary chorea was renamed as "Huntington's chorea" (Browning, 1908 as cited by Lanska[7]).

Nevertheless, this eponym was not universally accepted, and figures like Jean-Martin Charcot argued against it, considering hereditary chorea as originating from infantile chorea.[9] However, other seminal figures of medicine like William Osler and William Gowers argued for it, recognizing the value of Huntington's observations.[10] Although there are at least three reports on hereditary chorea prior to Huntington's (thoroughly analyzed by Lanska[7]), these did not received widespread attention. Nevertheless,they were acknowledged by Huntington himself shortly after his report received attention from the medical community and turned the medical profession's gaze towards hereditary chorea.

Huntington's report provides a noteworthy example of the power of observation, and its relevance as one of the indispensable qualities of the practicing neurologist.[11] Like James Parkinson's essay on the shaking palsy, Neither

Huntington's report (or the ones prior to his) include detailed information about specific patients.[12] As stated by the opening quote from Sir William Osler, the history of a disease can be shaped with only a "few words". Thus reminding us that minute clinical observation and accurate description of findings remain relevant even in the presence of advanced medical technologies.

In 1984, British neurologist McDonald Critchley reviewed the history of Huntington's chorea and lamented the absence of "clinical, anthropomorphic, electroencephalographic, biochemical, or pharmacological" markers to recognize premanifest HD carriers.[13] Nevertheless, in the 150 years since George Huntington's seminal description, most of these features have been "laid open to the light of day",[5] allowing for the detection of premanifest carriers and for the research on potential disease-modifying therapies. Contrary to Crichtley's opinion, that "the end is not yet in sight",[13] we are closer than ever to witnessing the beginning of the end of HD.

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