

## Huntington disease: a journey through history

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### ABSTRACT

The story of Huntington disease takes us on a fascinating journey through history. Initially, the Ancient Greek word *choreia* was used to describe a functional movement disorder, a strange dance observed in people gripped by hysteria at the height of the bubonic plague epidemic in medieval Europe. The first descriptions of this hereditary neurodegenerative disease were formulated in the 19th century, with the causal gene being identified in 1993. Neurologists including Charcot, Gowers, Lund, and, finally, George Huntington made highly valuable contributions in the description of the disease. The contribution of the Venezuelan neurologist Américo Negrette, who drew attention to a community in Maracaibo which had an unusually high prevalence of Huntington disease, was crucial in sparking scientific interest in the condition. Cases of Huntington disease have now been described worldwide, due to its migration first across Europe and subsequently across other continents. No cure has been found to date, but the recent advancements in biotechnology mean that silencing the affected gene could become a reality in the near future.

### KEYWORDS

Huntington disease, chorea, Américo Negrette, dancing mania, *HTT* gene

### Introduction

The term chorea comes from the Greek word *choreia*, meaning “dance”. Choreia, or “dancing mania”, as it was then called, was first described in the Middle Ages, at the time of the bubonic plague epidemic which devastated central Europe. The first reports of this “dancing mania” date it to Christmas 1021, when 18 people congregated in a church doorway in the now disappeared Saxon village of Kölbigk, and began to dance obscenely. The parish priest cursed them, and they did not regain control of their limbs until a year later. Similar episodes took place in 1247, 1374, and 1518. The cause of “dancing mania” was attributed to sin, with the only possible cure being pilgrimage to hermitages consecrated to particular saints offering protection. It was common to invoke Saints John and Anthony, but above all Saint Vitus, an adolescent martyr from Sicily and the patron saint of dancers; Vitus was the most popular saint among the German and Slavic peoples.<sup>1</sup>

Saint Vitus was martyred in 303 after being tortured with boiling oil; in some theories, he is attributed with “mira-

culously” healing Diocletian’s son of epilepsy. In 1418, Saint Vitus (sometimes also called Saint Guy) was called upon to cure people affected by chorea; from that time he has been appointed the specific saint for that disease.<sup>2,3</sup> The disease was thought to be cured by making patients touch the walls of churches containing relics of Saint Vitus.<sup>4</sup> Since then, the name Saint Vitus’ dance was used to describe people who had the condition and who were cured at the chapel of Saint Vitus in Zabern, a small village in Alsace.

However, it was in the early 16th century that the term Saint Vitus chorea or chorea Sancti Viti was first coined, by the Swiss physician and alchemist Philippus Aureolus Theophrastus Bombastus von Hohenheim (Paracelsus, 1493-1541). Paracelsus distinguished three separate types of chorea: chorea lasciva, chorea imaginativa, and chorea naturalis. The latter type was the only one caused by a physical pathology, while the other two were psychological disorders.<sup>5,6</sup>

The term chorea was not used to describe neurological syndromes until the 19th century, in the work of Jean-

Martin Charcot (1825-1893), Silas Weir Mitchell (1829-1914), William Osler (1849-1919), and William Richard Gowers (1845-1915).<sup>7</sup> Charcot made a hugely important contribution to the description and differential diagnosis of chorea, although he failed to differentiate Sydenham chorea, of autoimmune aetiology, from Huntington disease (HD).<sup>6,8</sup> Charcot assigned chorea the name “ordinary chorea” and attributed its varying clinical characteristics to the condition’s hereditary transmission and the influence of environmental factors, rejecting the hypothesis that there were two types of chorea. According to Charcot’s initial description, chorea was not a severe condition, although he did acknowledge the progressive course of the disease, which affected both “mind” and body in certain patient groups. Charcot stressed the hereditary nature of the disease. Huntington later described this as follows: “When either or both the parents have shown manifestations of the disease, (...) one or more of the offspring almost invariably suffer from the disease (...) it never skips a generation ...”<sup>9</sup>

It was Gowers who established the different types and aetiologies of chorea: senile chorea, vascular chorea (possibly late-onset HD), maniacal chorea with psychosis (probably related to systemic lupus erythematosus or HD), tetanoid chorea with dystonia (probably Wilson disease), functional chorea (a possible psychogenic movement disorder), and Sydenham chorea, with or without paralysis.<sup>6</sup> Gowers was also the first to note behavioural abnormalities and decreased verbal fluency in patients with chorea.<sup>10</sup>

Migration from Europe, where the disease is thought to have originated, is responsible for the spread of HD to every other continent. Genealogical studies performed in North America have associated HD to England, Germany, Ireland, and Norway.<sup>11</sup> There are published references to the first cases of the disease in Europe and its migration to North America. Vessie<sup>12</sup> carried out a familial study of 1000 cases of HD in the United States, concluding that HD was transmitted by two brothers who emigrated from Suffolk, England, in 1630 and settled in New England. Descendants of these families were accused of witchcraft; the witch of Groton is an example of this.

Although HD continues to be considered a rare disease, it is thought that population ageing and improved diagnostic techniques have resulted in a worldwide rise in prevalence. Global prevalence of HD is currently esti-

ated at 2.71 cases per 100 000 population.<sup>13,14</sup> This figure would appear to have increased in the last 50 years, with prevalence being higher in Australia, Western Europe, and North America (5.70 cases per 100 000 population) and lower in the Asian population.<sup>14</sup>

## Development

The pre-Huntington disease era

In 1832, the English physician Elliotson observed that chorea was associated with presence of paralysis, idiocy, incurability, and a family history of the condition.<sup>15</sup> A letter written in 1841 by Dr Charles Oscar Waters of New York describes a disorder popularly known as the “magrums” (a common name for HD), a Dutch word to describe a twisting movement.<sup>16</sup> Waters observed that the disease involved both motor and cognitive degeneration and that it was transmitted by heredity. The first edition of Dr Robley Dunglison’s *The practice of medicine*, published in 1842, also describes patients displaying chorea, who most probably would have had HD.<sup>17</sup> Dr Charles Rollins Gorman also contributed, describing the condition in similar terms in the third edition of Dunglison’s book, although he failed to recognise HD as being hereditary.<sup>18</sup> In 1846, Dr Charles Foreman presented a doctoral thesis entitled “On a form of chorea, vulgarly called ‘magrums’” at the Jefferson medical college (Philadelphia).<sup>6</sup> Unfortunately, there are no extant copies of this thesis. The first full description of HD was made in 1860 by Norwegian physician Christian Lund and included the associated cognitive impairment. Unfortunately, this paper had minimal impact: as it was published in Norwegian in a journal of limited circulation, its existence was not known beyond Norway until its translation into English a century later.<sup>6</sup>

George Huntington

George Huntington (1850-1916) was born in East Hampton (New York) and graduated from the University of Columbia in 1871. In 1872,<sup>19</sup> he published a description of adult-onset hereditary chorea, entitled “On chorea”, in the *Medical and Surgical Reporter*, after presenting the paper to the Meigs and Mason Academy of Medicine in Middleport (Ohio) at 22 years old.<sup>6</sup> Although he was not the first to discover this hereditary chorea, George Huntington’s description of the condition was so brilliant that the only subsequent attempt to alter the name was the change from Huntington chorea to Huntington disease.<sup>20</sup> In a display of brilliance, Huntington recognised the par-

ent-child transmission of the disease, its onset during adulthood, the progression to disability, the association between chorea and dementia, inappropriate and uninhibited behaviour, frequent suicide, unresponsiveness to treatment, and early death.<sup>18</sup> George Huntington's contact with chorea patients was through his clinical practice assisting his father and grandfather in his native city, and from observing patients during his horseback journeys to make house calls. *On chorea*, one of three treatises he published on HD over the course of his career, drew the attention of the most highly regarded neurologists of the time.<sup>21</sup>

#### Américo Negrette: diagnosing Huntington disease in Venezuela

In 1955, Américo Negrette published a book describing a community with an unusually high number of patients with chorea, in the village of San Luis, on the outskirts of Maracaibo (Zulia state, Venezuela).<sup>22</sup> At the time, Negrette was practising as a rural physician and as an instructor of clinical medicine in the Faculty of Medicine of the Universidad de Zulia. The community Negrette described were known as "sanviteros", and were famously lawless and dangerous; they lacked access to healthcare and were completely excluded from society. When Américo Negrette began to visit the community, he concluded that they were affected by an autosomal dominant familial disease with various clinical manifestations, including chorea and dementia. His first publication, studying 68 patients with Huntington chorea,<sup>23</sup> was largely rejected by Venezuelan healthcare professionals, who accused him of insanity, dishonesty, and of seeking celebrity with falsified research. He was dismissed from his position at the university; however, he later returned to his academic career thanks to the vice-chancellor, Dr José Domingo Leonardi, who allowed him back on account of the lack of evidence against him. Negrette later published the book *Huntington chorea*, describing the clinical manifestations of the disease, including psychological manifestations and its hereditary nature.<sup>24</sup>

The local population told Américo Negrette that HD came to Venezuela with a Spanish sailor, Antonio Justo Doria, who in the 18th century married a local woman, Petronila González, and passed the disease to their many children. Nonetheless, Alice Wexler<sup>25</sup> carried out a genealogical study using thousands of birth and death certificates, and found no conclusive data confirming this theory; it therefore remains unclear who brought HD to Venezuela.

#### The discovery of the Huntington gene

It was in the 1960s when HD began to have reverberations in American society, with the creation of foundations by Alice Pratt, Marjorie Guthrie, and Milton Wexler. Marjorie Guthrie's foundation, dedicated to the fight against HD, was created by the wife of the prolific singer-songwriter and political activist Woody Guthrie, who died of HD aged 55.<sup>26</sup> This foundation was the precursor to the Huntington's Disease Society of America (HDSA). Years later, Europe and Canada witnessed a similar phenomenon, with HD patient associations being founded in various countries, including the Netherlands, the United Kingdom, Canada, Germany, France, and Belgium; subsequently, associations also started in Australia and many other countries.

HD research underwent radical change in 1972, when a student of Américo Negrette's, Ramón Ávila-Girón, presented footage of chorea patients from Maracaibo at the Centennial Symposium on HD, held in Ohio. The footage was controversial and provoked scepticism, but two neurologists, Dr André Barbeau and Dr Loe Went, visited Maracaibo to confirm the cases.<sup>27</sup> The evidence was so impressive that the Milton Wexler foundation in New York, a research organisation for hereditary diseases created by Milton Wexler, husband of Leonore Wexler (who had HD), appointed a commission, led by his daughter Nancy Wexler, to study patients and relatives at risk. Nancy Wexler, trained as a neuropsychologist, organised expeditions to Maracaibo from 1979 to 2002. Prevalence of HD in Maracaibo was so extraordinarily high (1 in every 10 people) that the research work led by Nancy Wexler and the thousands of blood samples donated enabled the identification of the first locus in 1983, and subsequently, in 1993, the causal gene on chromosome 4p16.3.<sup>25</sup> This work identified the *HTT* gene, which causes HD, with the CAG sequence on exon 1.<sup>28</sup>

Efforts from the various patient and scientific associations led to the creation in 2003 of the European Huntington's Disease Network (EHDN), which has 26 member countries and aims to create an observational registry of the disease. The organisation has served as a launchpad for a range of research projects and is currently funded by CHDI, a New York-based scientific foundation created to study the cause and treatment of HD. Cohort, Track-HD, and Enroll, the longitudinal studies sponsored by EHDN and CHDI, have included thousands of patients with HD, at-risk family members, and controls.<sup>29-</sup>

<sup>31</sup> These studies are improving knowledge about HD and

its clinical manifestations and phenotype variability, and supporting the development of new clinical trials for pharmacological and non-pharmacological treatments. There can be no doubt that the great hope for HD, as with other monogenic neurodegenerative diseases, lies in the silencing of the affected gene. Clinical trials into gene silencing for HD are already underway. Progress in biotechnology will certainly make curing genetic diseases such as HD a real possibility in the coming years.

### Conflicts of interest

The author has no conflicts of interest to declare.

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