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Tremor and Other Hyperkinetic Movements

Reviews

Chorea: A Journey through History

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Abstract

The original descriptions of chorea date from the Middle Ages, when an epidemic of "dancing mania" swept throughout Europe. The condition was initially considered a curse sent by a saint, but was named "Saint Vitus's dance" because afflicted individuals were cured if they touched churches storing Saint Vitus's relics. Paracelsus coined the term chorea Sancti Viti and recognized different forms of chorea (imaginativa, lasciva, and naturalis). In the 17th century, Thomas Sydenham provided an accurate description of what he termed chorea minor. He also described rheumatic fever but did not associate it with chorea. It was only in 1850 that See established a relationship between chorea and rheumatic disease. A connection with cardiac involvement was soon recognized and in 1866 Roger postulated that chorea, arthritis, and heart disease had a common cause. The last quarter of the 19th century is marked by the works of Jean-Martin Charcot, Silas Weir Mitchell, William Osler, and William Richard Gowers, all of paramount importance in the refinement of the definition of chorea, its causes, and differential diagnosis. In 1841, Charles Oscar Waters gave a concise account of a syndrome, likely to be Huntington's disease (HD), later described further by George Huntington and named after him. In 1955, the Venezuelan physician Americo Negrette published a book describing communities in the State of Zulia in Venezuela, with unusual numbers of individuals with chorea. Negrette's works culminated in the creation of the Venezuela project and the subsequent discovery of seminal findings in HD. We review the historical facts and outstanding physicians that mark both HD and Sydenham's chorea's history in various sections.

Keywords: Chorea, Sydenham's chorea, Huntington's chorea, history

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Saint Vitus's and chorea

The term "chorea" derives from the Ancient Greek word "choreia", which means dance. The original descriptions of chorea date from the Middle Ages, coincident with the Black Death, when many epidemics of both infectious and psychogenic (previously labeled as hysterical) chorea swept through Europe. Afflicted individuals with the hysterical "dancing mania" would dance wildly in circles for hours until they dropped from exhaustion.[1] The Middle Ages saw a virtual explosion of cults devoted to all kinds of saints. The first descriptions of dancing mania related this disease either to St John or to St Vitus. However, during a dancing mania outbreak in 1418 in Strasbourg, Saint Vitus (sometimes called Saint Guy) was called upon to intercede and became the specific saint of this disease.[2,3] Saint Vitus was the son of a pagan Sicilian senator called Hylas and was martyred in 303 AD during Diocletian's persecution of Christians.[4] The reason he is associated with the dancing mania is because individuals reportedly afflicted with chorea were cured if they touched churches storing his relics.[5,6] Saint Vitus's dance or chorea Sancti Viti was the eponym used to describe those afflicted; they were kept isolated from Strasbourg inhabitants at the chapel of Saint Vitus in Zabern, a small village in Alsace.[7]

Philippus Aureolus Theophrastus Paracelsus Bombastus von Hohenheim (1493–1541) first coined the term Chorea Sancti Viti at the beginning of the 16th century to describe the dancing mania. The majority of those diagnosed with Saint Vitus's dance or chorea Sancti Viti were likely affected by the mass hysteria provoked by contemporary religious beliefs.[8,9] Paracelsus also differentiated various forms of dancing manias and named them "choreas".[10] He recognized three forms of chorea: chorea imaginativa (arising from imagination, such as Chorea Sancti Viti), chorea lasciva (arising from sexual desire and associated with passionate excitement), and chorea naturalis (arising from physical or corporeal causes). The last one was named after Paracelsus' belief that "the saints have nothing to do with this

disease". Paracelsus associated chorea naturalis with anxiety and described involuntary laughter without howling or screaming with an urge to dance as additional features.[11,12]

The distinction of different etiologies of chorea found in the Middle Ages is essentially derived from Paracelsus' view of the issue. Subsequent authors have subscribed to this opinion. In summary, the dancing mania was regarded as a psychogenic movement disorder roughly equivalent to what 19th century authors would call "mass hysteria". This was the cause of most cases of the movement disorder relieved by touching churches storing relics of Saint Vitus. It is also assumed that some of the cases were related to Sydenham's chorea (SC) as currently defined. Finally, this movement disorder was not causally related to the Plague with which there was just a temporal coincidence.

Thomas Sydenham and chorea

Thomas Sydenham (1624–1689) was a conscientious and keen physician interested in epidemic illnesses and known as the British Hippocrates.[13] Recently, there have been criticisms of his career, suggesting that the promotion by his friend John Locke rather than his own merits accounts for part of his reputation.[14] Nevertheless, in 1686, in chapter XVI, "On Saint Vitus' dance", of his last book *Schedula Monitoria de Novae Febris Ingressa*, Sydenham provided an accurate clinical description of acute chorea, named chorea minor, which subsequently became known as SC:

> There is a kind of convulsion, which attacks boys and girls from the tenth year to the time of puberty. It first shows itself by limping or unsteadiness in one of the legs, which the patient drags. The hand cannot be steady for a moment. It passes from one position to another by a convulsive movement, however much the patient may strive to the contrary. Before he can raise a cup to his lips, he does make as many gesticulations as a mountebank; since he does not move it in a straight line, but has his hand drawn aside by the spasms, until by some good fortune he brings it at last to his mouth. He then gulps it off at once, so suddenly and so greedily as to look as if he were trying to amuse the lookers-on.[15]

The term chorea has subsequently been used to describe this pattern of involuntary, purposeless, and rapid distal movements of the limbs, whatever its cause. Paracelsus coined the term to describe a movement disorder and also proposed a classification encompassing organic and psychogenic causes of chorea. In contrast, Sydenham studied one specific cause of chorea. Sydenham believed that chorea was due to "some humor falling on the nerves, and such irritation causes the spasms" and did not relate it to rheumatic fever.[4]

Chorea and its relationship with rheumatic disorder

Until the 19th century, physicians failed to recognize the significant relationship between rheumatic (previously termed "rheumatism") and neurological diseases. Little else was written until the work of Bouzet (1754), who stated that earlier descriptions misinterpreted "tarantism", the convulsive movements resulting from the bite of a tarantula, as chorea.[7] The list of distinguished writers on chorea during the 18th and early 19th centuries includes Mead in 1751, Ewart in 1798, Cullen in 1785, Bouteille in 1810, Bright in 1831, See in 1850, and Roger in 1866.[16,17] Richard Bright (1797–1858) noted that chorea was "intimately connected with rheumatism".[17] This view was endorsed by Etienne Michel Bouteille (1732–1816)[18] and German See (1818–1896), followed by Henri Roger (1809–1891).[7,17,20] See wrote, "chorea is the result of a rheumatic diathesis ... for every two rheumatic children there is at least one who is choreic".[7,19] Roger insisted that rheumatism, chorea, and endocarditis shared a common source because cardiac problems occurred in approximately half of his patients with chorea.[20] In contrast, Theodor Meyner (1868), Hughlings Jackson (1864), and others were uncertain that a relation did indeed exist after carrying out a few pathological studies.[7]

Definition of chorea as a syndrome

During the last quarter of the 19th century, both in the United States and in Europe, particularly France and the United Kingdom, the field of neurology emerged as an autonomous specialty of medicine.[21,22] The works of Jean-Martin Charcot (1825–1893), Silas Weir Mitchell (1829–1914), William Osler (1849–1919), and William Richard Gowers (1845–1915) were of paramount importance for knowledge of chorea.[23]

Charcot contributed to the description of chorea and differential diagnosis, but failed to separate SC from Huntington's disease (HD).[2,24,25] In 1884 he gave an assignment to one of his students, Georges Albert Édouard Brutus Gilles de la Tourette (1857–1904), to "sort out the chaos of the choreas",[27] asking him to study patients with tics and culturally related startle syndromes. This suggests that there was a clear imprecision in his definition of the phenomenology of chorea.[26,27] Mitchell's works in Philadelphia described the relation of chorea to season and meteorological conditions, climate, locality, town, and country.[21] Osler took on the task of defining chorea as a syndrome and importantly contributed to the study of choreas, colorfully describing them in the opening of his 1894 book "On chorea and choreiform affections": "in the whole range of medical terminology, there is no such *olle podrida* ["rotten pot," a Spanish stew, i.e., a hodgepodge] as chorea, which for a century has served as a sort of nosological pot into which authors have cast indiscriminately".[28,29] From the very beginning of his book, Osler recognized chorea major as another important group of choreiform disorders, stating that "under this term are now embraced both the dancing mania and the various forms of rhythmical or hysterical disorders of motion". He immediately dismissed this group of disorders from further discussion, declaring that he would "not consider here chorea major which belongs to hysteria".[28,29] Osler reviewed and reported clinical and pathological data on 410 cases of SC treated in Philadelphia since 1876.[28–30] Osler recognized that SC is an infectious disorder frequently associated with endocarditis, particularly affecting the mitral valve.[28–30]

Actually, Charcot's assignment was successfully attempted by Gowers, one of the pioneers in describing chorea as a syndrome and identifying different varieties and etiologies. He had worked at the National Hospital for the Relief and Cure for the Paralyzed and Epileptic at Queen Square, London, since 1870. Gowers is now primarily remembered for his "Manual of the diseases of the nervous system"; the first edition appeared in two volumes and was published in 1886 and 1888.[31–33] In his textbook, there is a lengthy description of chorea, in particular SC, based on his case notes of more than 120 children and young adults admitted to the National Hospital and many more in his outpatient clinic and private rooms. In a recent review of his 42 volumes of case notes from 1878 to 1911,[34] Gowers' description of the phenomenology and natural history of chorea is in keeping with our current notions about the illness (Figure 1). After having treated more than 120 children in hospital with SC, he clearly had an understanding of chorea as a syndrome distinct from other phenomena. Gowers depicted various forms of chorea: senile chorea, probably vascular or late-onset HD; maniacal chorea, with psychosis, most likely related to systemic lupus erythematous or HD; tetanoid chorea, with dystonia, probably Wilson's disease; functional chorea, a psychogenic movement disorder; recurrent SC and paralytic SC. In addition, concerning SC, Gowers noted the female predominance, the pubertal onset, the typical pattern of movements, and factors related to worsening and subsiding.[35,36] Behavioral abnormalities[37–39] and reduced verbal output[40,41] are among the non-motor features described by Gowers in patients with chorea that confirmed SC as a syndromic entity. Indeed, most of his findings have been confirmed by recent studies.[42,43]

Chorea, rheumatic disorder, and diplococcus

As far back as 1894, a diplococcus was isolated from the brain of a fatal case of SC. Since then, many observers such as Triboulet, Croyon (1897), and Wesphal, Wassermann, and Walkoff (1899) have isolated different cocci from the pericardial and cerebrospinal fluids of children who died of rheumatic pericarditis and chorea.[8,44]

In a series of experiments from 1901 to 1903, Ponyton, Paine, and Holmes were able to produce irregular movements, carditis, and arthritis experimentally in rabbits by intravenous injections of the diplococci obtained from their patients who had died.[7,45]

The British physicians John Hughlings Jackson (1835–1911) and William Henry Broadbent (1935–1907) were the first to propose a striatal dysfunction due to embolism to explain childhood chorea in the 1860s.[30,46,47] In the early 20th century, the embolic theory was discarded in favor of a bacterial meningoencephalitis[48] and inflammation in the basal ganglia and cerebral cortex.[49] However, bacteria were not

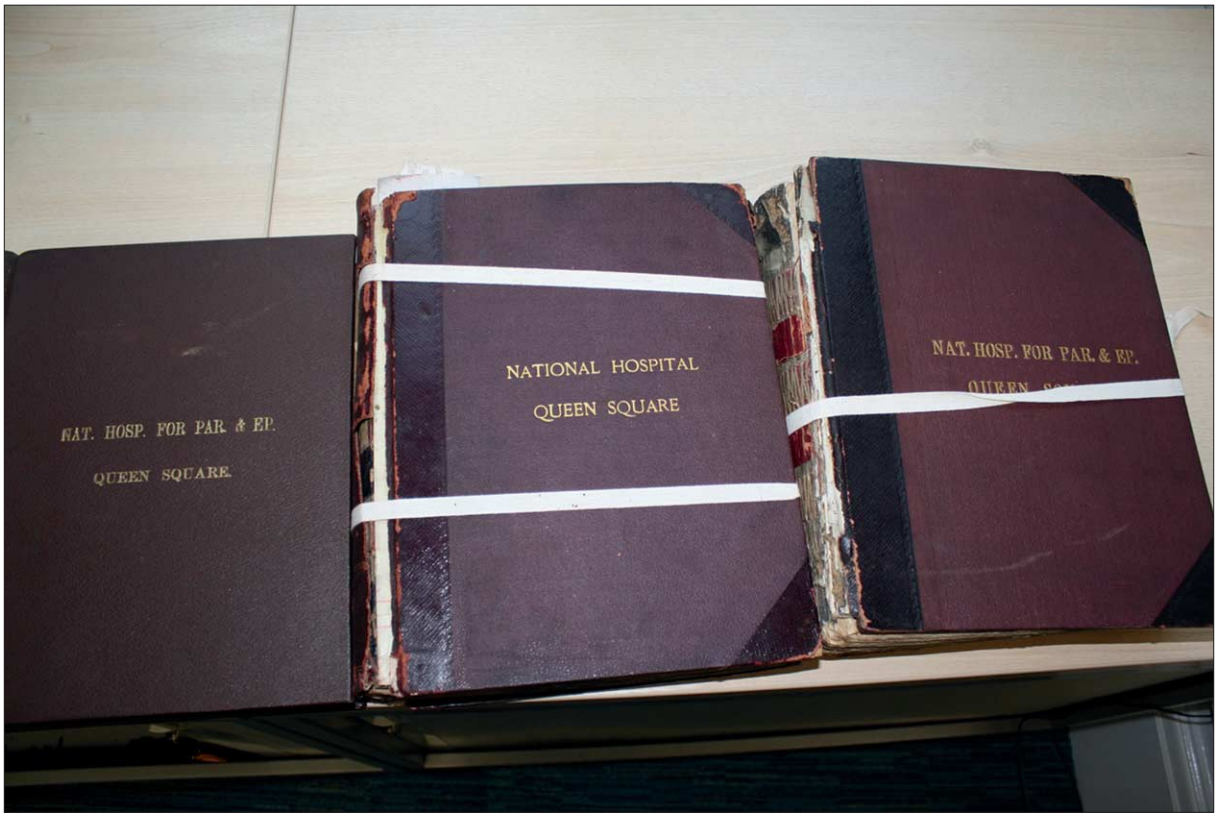

Figure 1. Photograph of volumes Gower's handwritten notes of his patients admitted to the National Hospital for the Relief and Cure for the Paralyzed and Epileptic (now The National Hospital for Neurology and Neurosurgery) at Queen Square, in London. Picture was taken with permission from the Queen Square Library, Archive and Museum. Copyright National Hospital for Neurology & Neurosurgery.

consistently cultured from brain tissue or cerebrospinal fluid of SC patients, weakening this theory.[30,50] Development of the antistreptolysin O titer as a marker of antecedent streptococcal pharyngitis in the early 1930s allowed definite proof that all manifestations of rheumatic fever, including SC, are a sequel to group A streptococcal pharyngitis.[30,51,52] SC is now understood to result from antibody cross-reaction to basal ganglia epitopes following infection with group A β-hemolytic streptococci.[53]

Treatment, which initially consisted of bleeding and purging, combined with resting and reduction of factors that would cause emotional and physical excitement, finally focused on combating the infectious agent responsible for the disease during the 20th century with the advent of penicillin.[7] By the late 1930s, sulfonamides were demonstrated to prevent recurrences of rheumatic fever,[54] and in the 1940s prompt administration of penicillin for group A streptococcal pharyngitis was shown to prevent initial attacks of rheumatic fever.[55] Later, the prevention of rheumatic fever was regularly achieved with antibiotic prophylaxis, which led to a marked drop in the incidence of rheumatic fever and its manifestations, including SC.[30,56]

Huntington's disease: pre-George Huntington's era

In 1832 an English physician named Elliotson noted that when chorea "occurs in adults it is frequently connected with paralysis, idiotism and will perhaps never be cured. It appears to arise for the most part from something in the original constitution of the body, for I have often seen it in hereditary".[57] In 1841, Dr. Charles Oscar Waters from New York wrote a letter describing a disorder known popularly as the "magrums", meaning "fidgets" in Dutch.[58] He gave a concise account of a syndrome likely to have been HD for the first edition of *The Practice of Medicine* in 1842, compiled by Dr. Robley Dunglison.[59,60] Waters noticed the combination of motor and cognitive decline as well as the hereditary nature of the condition:[61,62] "First, it rarely occurs before adult age. Second, it never ceases spontaneously. Third, when fully developed, it wants the paroxysmal character".[16] Dr. Charles Rollins Gorman also contributed with a similar description to the third edition of Dunglison's textbook, but failed to properly recognize the hereditary nature.[12,16,61,62]

In 1846, a thesis entitled "On a form of chorea, vulgarly called 'magrums'" was presented by Charles Foreman to the faculty of Jefferson Medical College (Philadelphia). Unfortunately this has been lost. A Norwegian, Johan Lund, gave a fine description of hereditary chorea in 1860. The impact of his report, however, was limited because of being published in a journal with minimal circulation. This was unrecognized outside his native country until it was translated into English a century later.[12,61,62]

George Huntington's "On chorea"

In 1872, George Huntington (1850–1916),[63] who was born in East Hampton (NY) and graduated from Columbia in 1871, published a report of adult-onset hereditary chorea entitled "On chorea" in the *Medical and Surgical Reporter* after presenting to the Meigs and Mason Academy of Medicine at Middleport, Ohio. Huntington assisted his father and grandfather in their medical practice in his native town and had drafted his manuscript with the help of his father.[62,64] In fact this was one of the three papers he published throughout his career. Hereditary chorea was described in a relatively small section at the end of the paper, which devoted significant attention to SC. In a brief but clear description, he captured the hereditary nature, the onset in adult life, the grave and unrelenting progression of disability, the association of chorea and dementia, inappropriate and uninhibited behavior, frequent suicide, lack of response to treatment and early death.[62] Huntington's reports were considered modest and "not of any great practical importance ... but merely as a medical curiosity" by himself.[62] However, it deservedly drew the attention of the most celebrated neurologists.[64]

Huntington viewed chorea as a spectrum extending from childhood to adulthood although related to distinct causes (SC and HD).[65] Osler, writing his "On chorea and choreiform affectations" (1894), settled this distinction and expanded the clinical and pathological studies of chorea based on his extensive patient population, mostly children, in Philadelphia. In 1896, Anton documented the pathologic changes of caudate atrophy and neuronal degeneration in HD. In the early 1900s, researchers first noted that the brains of HD patients are destroyed as the disease progresses. They identified the caudate nucleus as the central target of brain cell death.[61,62,66]

The San Viteros

In 1955, the Venezuelan physician Americo Negrette published a book describing communities in the village of San Luis in the outskirts of the city of Maracaibo by the homonymous lake in the State of Zulia in Venezuela, with unusual numbers of individuals with chorea. The original progenitor of this family lived in the early 1800s and left more than 18,000 descendants (more than 14,000 of whom are currently living), many of whom are either affected by the illness or at risk.[67,68] Dr. Negrette recorded the history told by the locals, known as "San Viteros", that the first afflicted person in the Maracaibo area was a Spaniard priest named Antonio Justo Doria, who arrived in the area in the 1860s.[69] However, more recently Alice and Nancy Wexler did a field investigation, reviewing all birth and death certificates in the area and failed to identify this Señor Doria.[70] It remains, thus, to be discovered who introduced the gene to the Maracaibo region. Regardless of the failure to define the founder of this family, presumably the largest one with HD in the world, it turned out to play a crucial role in the history of the scientific progress of this disease.

The Venezuela project and its consequences

Dr. Negrette's diagnosis of HD was later confirmed by Andre Barbeau[68] and the family was the subject of a discussion at the historic Centennial Symposium for HD held at Ohio State University in 1972, whose proceedings were published in the first volume of *Advances in Neurology*.[62,69] Interest in this family led the Wexler sisters, along with a group of investigators from the Massachusetts General Hospital, to create the Venezuela Project.[70,71] This resulted in the establishment of a network of social support in the area and the discovery of seminal

findings in HD, including linkage to the chromosome 4 in 1983[72] and subsequent identification of the IT15 gene 10 years later by James Gusella and his colleagues.[73,74]

Conclusions

The works of Paracelsus, Thomas Sydenham, Charcot, Mitchell, Osler, Gowers, Charles Waters, George Huntington, and Americo Negrette were of paramount importance in the definition of choreas. Defined as a syndrome more than a century ago, it is now acknowledged that chorea has various etiologies (genetic, structural, infectious, autoimmune, toxic metabolic, and drug induced) and a wide and complex differential diagnosis. Recent advances on genetics allied with the established role of neuroimaging and laboratory testing now permit the correct classification of chorea in most cases. However, a carefully taken history and a comprehensive neurological examination are still fundamental keys to revealing the motor and non-motor features of this movement disorder. In spite of the recent advances in pathophysiology and investigation, treatment is still daunting for degenerative causes of chorea, particularly HD. However, treatment is successful in many other causes.

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