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Brief History of Multiple Sclerosis Introduction to the History of Multiple Sclerosis

Pedro Covo Torres*

Clinical Neurologist, Postgraduate Coordinator of Clinical Neurology, Universidad Del Sinú - Cartagena, Colombia

***Corresponding Author:** Pedro Covo Torres, Clinical Neurologist, Postgraduate Coordinator of Clinical Neurology, Universidad Del Sinú - Cartagena, Colombia.

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Abstract

MS was initially described in a Scandinavian document and two centuries later in the diary of a Dutch Saint. Long after, at the beginning of the eighteenth century, an isolated case was reported and it was not until the nineteenth century that cases were most frequently reported. During the first half of this century a patient was referenced, for the first time, in the medical literature and two atlas of pathology reported the disease. Thereafter, during the second half of the nineteenth century, the modern conception of MS is developed, based on the stories of Frerichs, in Germany and later Charcot's, head of the Pitié-Salpêtrière. But it is during the past century that MS reaches maturity with the emergence of the diagnostic criteria, the concept of remyelination, neuroimaging and pharmacological treatment. In the XXI century, based on technological advancement and better understanding of the disease, new diagnostic criteria are proposed as well as alternative therapies and oral monoclonal antibodies are used. In this century genetic advances represent a great challenge, as well as biomarkers and more medications of a wider effectiveness.

Keywords: *Multiple Sclerosis; Ollivier d'Angers; Frerichs; Charcot; Poser; MacDonald*

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First Stories

The oldest description of a probable Multiple Sclerosis (MS) is found in "Isla Saga", by San Torlakr (1133-1193), patron saint of Iceland, where blindness and language disturbances of Hala, a Viking woman, are mentioned that she would have recovered after a few days of prayer and sacrifice [1]. There are reasons to believe that MS appears in Scandinavia before the eleventh century and that it was disseminated by the Vikings in Europe [2].

The first known diary of a possible case of MS is the one of Santa Lidwina of Scheidam, Dutch nun of the 14th century (1380-1433), who stamped the symptoms she suffered from the beginning of the disease, at age 16, until her death at 53 years of age. Their disorders involved difficulty in walking, lancinating pains, weakness in the right arm, blindness, sensory disturbances and dysphagia. His suffering is well documented by the church and was fundamental to consecrate his holiness [3].

The two Margarets, Auguste, the poet Heine and Alan Stevenson.

Richard Gough, in "Antiquities and Memoirs of the Parish of Myddles, County of Salop" (1700), related the case of Margaret Davies who presented lameness associated with pregnancy and progressive deficit during a 30 year period. She was examined and treated by doctors, surgeons and apothecaries [4]. Augusto Frederick d'Este (1749-1848), illegitimate grandson of George III, King of Great Britain, narrated his illness in a diary he wrote rigorously for a period of 26 years. He tells how he began in 1822 with loss of vision while attending a friend's funeral. He recovered 10 months and later manifested new symptoms such as paraparesis with episodes of relapse-remission and gradual worsening. Numerous British doctors became aware of his illness, among them the legendary Sir Astley Cooper, Sir Benjamin Brodie and Sir Richard Bright.

Among the recommended therapeutic alternatives we can mention mineral water, baths with sulphate zinc, valerian, various types of herbs and flowers, strychnine, quinine, silver nitrate, hydrotherapy, electrical stimulation, bloodletting, massage and equine therapy. However, he expressed that he only obtained some relief when he traveled through Scotland and was "embraced and invigorated by the air of the high earth" [5]. The German poet of Jewish origin, Heinrich Heine (1797-1856), presented an expensive clinical picture characterized by progressive deficit and visual deterioration, however the presence of ptosis, a rare finding in MS, raises doubts about the real diagnosis [6]. Alan Stevenson (1807-1865), uncle of the British writer Robert Louis Stevenson, was an outstanding architect, builder and supervisor of lighthouses, poet, polyglot and pioneer of optical technology.

He suffered a progressive neurological disorder that began when he was very young and that confined him to the bed; in his letters he reflects great suffering, he refers to rheumatic pains, fatigue, lumbalgia and recurrent paraplegia. His biographer Bella Barthurst considers that he suffered from MS [7]. The Victorian novelist and naturalist Margaret Gatty (1809-1873) began to present a neurological disease when she was 41 years old, her doctor -Thomas King Chamber- published the case in the medical journal "Lancet" (1864) as muscular atrophy and even attributed the cause to that she used the tools of the garden in a masculine way [8]. New symptoms emerged, so in 1868 she consulted Dr. Radcliffe, who maintained that she had an alteration of the spinal cord, a view rejected by Chamber and other physicians who tried to ridicule her for what they believed was a mistake [9].

MS Appears in the Medical Literature

Charles Prosper Ollivier d'Angers (1796-1845) revealed the first scientific case (1824) in the book "Maladies de la Moelle Epiniere" [10]. The pioneer of the pathological descriptions was Sir Robert Carswell who in 1838 mentioned faded areas in the protuberance and spinal cord ("hard, semitransparent and atrophied areas"). He had been born in Scotland (1793) and died in London (1857). He studied and worked as a pathologist in hospitals in Paris and Lyon, was an excellent artist, so good that he drew a pathological atlas on EM ("Pathological Anatomy: Illustrations of the Elementary Form of Disease") published in 12 fascicles [11]. Simultaneously, in the same hospitals, the French pathologist Jean Cruveilhier (1791-1874) produced another atlas of pathology but incorporating clinical aspects, one of which he called "Paraplégie par dégénérescence grise des cordons de la moelle" [12]. He published the "Clinical-pathological correlation of Multiple Sclerosis" in the fascicles of Pathology of the Faculty of Medicine of Paris (1835-1842).

Friedrich Theodor von Frerichs (1819-1885). Was a German pathologist who revealed, in a clear way, the clinical and pathological characteristics of MS. He made known the varied course of the disease with exacerbations, episodes of relapse-remission and subsequent progressive picture. Among the main symptoms stood out the nystagmus, motor predominance and mental disorders, originally recognizing these complications. He also stated that it was more frequent in young people and that the commitment was asymmetrical at the beginning. In 1849, 19 years before Charcot, he suggested calling this pathology "Hernkleroses" [13].

Frerichs is for many the father of the modern conception of MS but he did not have the credibility and support that Charcot would later have, one of the pioneers of modern neurology in Europe. Critics of the time, including the all-powerful "César de la Salpêtrière" (Charcot), argued that there were patients misdiagnosed among those informed by Frerichs, however George Theodor Valentine, his pupil, verified by autopsy the correct diagnosis of his master in a publication of the magazine "Deutsche Klin" in 1856 [14].

German and Austrian School

In the middle of the 19th century, pathologists from Vienna and Germany surpassed the French through the use of the microscope and other laboratory tests. Some teachers of the Pitié-Salpêtrière despised these methods, but not Charcot and Vulpian who assimilated these new techniques and contributed to the development of Gallic medicine. Ludwig Türck (1810-1868), Austrian neurologist and head of a department of neurology in Vienna, contributed to the knowledge of the degeneration of the spinal cord. He detailed the syndrome then recognized as Brown-Sequard, characterized by medullar hemisection [15].

Carl Rokitansky (1804-1878) used advanced techniques in the microscope and created in Vienna an important center of dissection and pathological anatomy. In 1846 he described the fatty corpuscles found in the lesions produced by MS [16]. Eduard von Rindfleisch (1836-1908), a German pathologist, made fundamental observations about the inflammatory changes and the involvement of blood vessels in this process.

He argued that primary inflammation was the cause of demyelination, analyzed post-mortem brain samples from numerous patients with MS, and in 1863 disseminated the theory of inflammatory involvement in its etiology [17]. The German Jewish doctor, Moritz Heinrich Romberg (1795-1873), one of the fathers of modern neurology, propounded, from 1840-46, the systematic neurological text "Lehrbuch der Nervenkrankheiten" [18]. On the other hand the British physiologist Marshall Hall (1790-1857) participated in the study of MS, his main essays were on the reflex function of the bulb and the spinal cord [19].

MS crosses the Ocean

The first patient outside of Europe was presented on December 4th, 1867 at the "College of Physician" of Philadelphia by J.C. Morris and Silas Weir Mitchell (1829-1914), who is considered the father of American neurology. It was a doctor -Dr. Pennock- with progressive paraplegia and bladder disturbances that worsened during the heat. The pathology showed "translucent irregular spots" in the medulla at cervical and dorsal level. Degenerated fibers and fat globules were observed under the microscope [20].

The contribution of the Pitié-Salpêtrière

The building was built by Louis XIII during the sixteenth century to make weapons and store gunpowder, later it would become a charity hospital. Traditionally the modern conception of MS has been attributed to the French neurologist Jean Martin Charcot (1825-1893), who assimilated previous research and concepts that, added to his researches and allowed him to recognize this disease as a unique entity. He detailed the clinical and pathological findings, emphasized the concept of demyelination, determined the form of relapse-remission and expressed that the demyelinated fiber was capable of nerve conduction. He recognized it as a disease in 1868 and named it Sclerosis in Plaques.

He established three clinical symptoms characteristic of MS (Charcot's triad): dysarthria, ataxia and tremor also the presence of atypical symptoms such as amyotrophies [21]. His students Bourneville & Guérard published, in 1869, a work that contained all the knowledge they had at the moment about this disease [22]. Although today Charcot's conception is considered as the starting point of the modern vision of MS, he himself acknowledged the contribution of other researchers on whom he supported, among them Ludwig Turck, Ernst Leyden, Von Frerichs, Albert von Zenker, and Carl Frommann [23]. Latter published an illustrated book with cuts of the marrow (1864) and Ernst Leyden presented in the magazine "Deutsche Klin" (1863) Thirty four cases of MS that designated chronic myelitis.

He established that it was more frequent in women (2: 1) and suggested a genetic predisposition [24]. The importance of French neurology, especially during the second half of the 19th century, was undoubtedly a fundamental factor for Charcot's concepts to spread and be accepted worldwide. Doctors from other European countries and America used to train in Paris, in the Pitié-Salpêtrière, temple of neurology [25]. Edmé Felix Alfred Vulpian (1826-1887) presented 3 cases before the Societé Medicale des Hospitaux and used the term "Sclerosis in disseminated plaques" (1866). Vulpian and Charcot investigated together at the Salpetriere, later Vulpian directed

his interests to other fields while Charcot concentrated on neurology and headed a group of scientists who are part of the history of neurosciences [26].

The School Continues

Pierre Marie (1853-1940) succeeded Charcot at the Pitié-Salpêtrière Hospital in Paris. Research continued to reveal new aspects of MS. During that period the pathology and symptoms of MS were well known, except for its cause, which has not yet been discovered. The findings of Louis Pasteur (1822-1895) gave new light and supported them, Pierre Marie suggested, in 1884, that MS could be produced by an infectious agent. Hypothesis that, still in the 21st century, enjoys some acceptance [27].

Dramatic Testimony

WNP Barbellion (1889-1919) is the pseudonym used by Bruce Fredrick Cummings, famous zoologist affected by EM, who expressed his illness in a newspaper published the year of his death with the title "The Journal of a Disappointed Man". It is a heartbreaking story of the suffering of a person with this disease that documented from its beginning, at age eighteen, until his death, still very young when he was only thirty years old. It is considered one of the most shocking journals of humanity, his brother said that "never was a half-dead more alive" [28].

End of the 19th century and the first half of the 20th century

Eugène Devic (1858-1930), along with his disciple Fernan Gault, related in 1894 a nervous condition that affected the spinal cord and the optic nerve, today known as Devic's Disease or neuromyelitis optica [29,30]. The sign of L´hermitte in MS was described and published by L´hermitte, Bollack & Nicolas and presented at the Neurological Society of Paris on July 3rd, 1924 [31]. The Romanian Israel Wechsler (1886-1962), head of the neurology service of the Mount Sinai Hospital in New York, wrote a neurology text in 1927, which had several editions, where he specified the clinical picture, the differential diagnosis and the treatment of the EM.

He recommended the use of iron, strychnine, arsenic, quinine and salvarsan [32]. Dr. Russell Brain (1895-1966) emerged at the beginning of the 20th century as one of the great figures in the understanding of MS. He published the work "Disseminating Sclerosis" in 1930 and three years later the text "Diseases of the Nervous System", which contains a chapter on this pathology. He provided statistical data on the course of the disease, with which the current treatment approach was born, his books served as a guide in many medical schools, including himself revising the new editions until his death [33].

In the 1930s, experimental allergic encephalomyelitis developed as a model of the disease, starting point of research and better knowledge of MS [34]. Abnormal findings in the CSF of patients with MS were initially reported by Hinton in 1922, Charles Poser would include them in his famous criteria for the diagnosis of MS [35]. In the 1940s, Dr. Elvin Rabat (1914-2000), from Columbia University, used the newly developed electrophoresis technique for the diagnosis of MS and discovered that the CSF had an elevation of gamma globulins that revealed its immunological component [36]. In 1946, based in New York, the National Multiple Sclerosis Society (NMSS) was founded, with more than 500,000 members [37].

Second Half of the 20th Century

During this time, research centers on MS multiplied. Sydney Allinson & Harold Millard were pioneers in establishing "Clinical Criteria for the diagnosis of Multiple Sclerosis" in 1954. They differentiated 3 forms: early disseminated sclerosis, probable disseminated sclerosis, and possible disseminated sclerosis [38]. The concept of "remyelination" and regeneration of oligodendrocytes was revealed in the mid-1960s, having a great impact on MS therapy since it was then thought that oligodendrocytes and neurons were unable to regenerate [39].

George Schumacher., *et al*. of the University of Vermont, established in 1965 such basic criteria that are still valid today. They considered fundamental for the clinical diagnosis of MS six characteristics: objective abnormality in the neurological examination, evidence of two or more separate lesions in the nervous system, involvement of the white matter, commitment of the neuraxis, beginning

between 10-50 years, signs and symptoms that are not better explained by another cause [40]. In 1967 the International Federation of Multiple Sclerosis Societies (IFMSS) was founded, with more than 30 partner countries [41].

The treatment of MS with ACTH began with Miller., *et al*. in 1961 [42] although initial double-blind work was conducted by Rose *et al*. in 1970 with such a good response that its use still persists [43]. The criteria of Douglas McAlpine., *et al*. in 1972, divided the MS into three groups: probable latent multiple sclerosis, probable multiple sclerosis, possible multiple sclerosis [44]. John Prineas (New Jersey-USA) used electron microscopy techniques to examine histological lesions in MS. He confirmed, in 1978, that both microglial cells and macrophages participate in the destruction of myelin.

Their work showed that the process of remyelination is extensive at the beginning of the MS but later decays [45]. We still ask: Why does remyelination stop in MS? What factors intervene in this phenomenon? In 1982, the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) was founded. Charles Poser., *et al*. Published in 1983 the most recognized criteria for the diagnosis of MS, fundamental for researchers around the world. They established a common language and facilitated the publication of articles. They divided the diagnosis of MS into two categories supported by the clinical picture and/or the laboratory result: definitive MS and probable MS.

Thereafter, 85% of the research on MS was based on the Poser criteria [46]. Modern neuroimaging methods revolutionized MS, especially MRI, diagnostic test par excellence since the publication in 1981 of Ian R. Young, "Nuclear magnetic resonance imaging of the brain in Multiple Sclerosis" [47]. In 1986 year the Consortium of Multiple Sclerosis Centers (CMSC) was created, one of the most outstanding organizations in the support to the MS [48]. That same year, Robert I. Grossman discovered that gadolinium-DPTA facilitated the uptake of demyelinating lesions and allowed the identification of new and active lesions [49].

From then on, several authors established diagnostic criteria for MS supported by MRI: 1988 Fazekas, 1988 Paty, 1991 Goodkin, 1997 Barkof, and 2000 Tintoré [50-54]. Preston., *et al*. in 1992, identified a member of aquaporins, structures that allow water to pass through certain membranes and participate in plasma diffusion [56]. Immunosuppressive treatment with cyclophosphamide, cyclosporine and plasmapheresis has been reported since the 1980s; later, in the next decade, there are trials on metrotexate, azathioprine, cladribine, mitoxantrone, intravenous immunoglobulin and sulfasalazine [57].

Preliminary studies on interferons in MS were carried out in 1993 ("IFNB Multiple Sclerosis Study Group"), in the same decade the reports of the "Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in Multiple Sclerosis" were published. In 1996 and the subcutaneous application of interferon beta-1a from the PRISM Study Group by Jacobs., *et al*. 1998. This publication establishes a modifying treatment in the relapsing-remitting form [58]. The demonstration of the existence of oligoclonal bands in the CSF of patients with MS, frequent immunological alteration and data of great diagnostic utility, appeared in the Neurological Act of Scandinavia in 1998 [59].

At the end of the century, other organizations emerged, the American Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS), in 1996; The Latin American Committee for Treatment and Research in Multiple Sclerosis (LACTRIMS), in 1999 and the Brazilian Committee for Treatment and Research in Multiple Sclerosis (BCTRIMS), in 1999 [60].

XXI Century

Professor Ian MacDonald (1933-2006) commanded the group of experts who promulgated the criteria proposed in London in 2001 [61]. These take into account the clinical picture manifested as outbreaks, the spread of the gadolinium MRI lesions in time and space, in addition to the CSF abnormalities. In 2004 Lennon and cols showed that anti-NMO IgG antibodies are observed in optic neuromyelitis and differentiates it from other demyelinating diseases [62]. Polman, Reingold, Banwell., *et al*. Reviewed the McDonald criteria in 2010 [63]. The treatment of MS has evolved greatly since the last decade of the last century, interferons and glatiramer acetate, first generation modifiers for the treatment of relapsing-remitting form of MS have been available since 1990 [64].

Other therapeutic options that have come to occupy an important space in the therapeutic arsenal of MS since the 21st century and that have changed the therapeutic approach to oral medications and monoclonal antibodies. The longed-for oral therapy began with fingolimod, then laquinimod, teriflunomide, and dimethyl fumarate appeared. The monoclonal antibodies in MS started with natalizumab and this opened the possibility of others such as rituximab, alemtuzumab, ocrelizumab and ofatumumab [65,66].

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