

## Myasthenia Gravis – a beginning with no end

Cristina Georgiana Croitoru<sup>1</sup>, Dana Mihaela Turliuc<sup>1,2</sup>,  
Florentina Danciu<sup>1</sup>, A.I. Cucu<sup>1</sup>, S. Turliuc<sup>2</sup>,  
Claudia Florida Costea<sup>1,2</sup>

<sup>1</sup>“Prof. Dr. N. Oblu” Emergency Clinical Hospital Iasi, Romania

<sup>2</sup>“Grigore T. Popa” University of Medicine and Pharmacy Iasi, Romania

**Abstract:** Myasthenia gravis is one of the neurological diseases with a relatively recent history, full of mistakes, in which the British and German neurology schools have attempted to find answers when confronted with the unknown. The paper aims at making a historical account of the disease from its discovery in the 16th century, when the first case of myasthenia gravis was medically diagnosed, to the beginning of the 20th century, when the dawn of modern therapy started to show.

**Key words:** myasthenia gravis, history of medicine, neuromuscular disease

*Disease is very old. Nothing about it has changed. It is only we who change as we learn to perceive what was formerly imperceptible.*

*Jean Martin Charcot (1825-1893)*

### Introduction

Myasthenia gravis (MG) is a neuromuscular disease that may be congenital or not, immune-mediated or not, due to a presynaptic, synaptic or postsynaptic defect. The very etymology of the words myasthenia gravis reflect its definition, as it consists of the Greek words mios (gr.) meaning muscle, asthenia (gr.) meaning weakness and gravis (lat.) meaning severe.

MG history is relatively recent, full of errors and ambiguities, a history in which especially the German and British neurology

schools have attempted, over time, to find answers when confronted with the unknown. Writing is an art and good writings are expression of maturity (14), and various neurologists, psychiatrists, neurosurgeons, anatomists, pathologists and philosophers have tried to write its history throughout the centuries.

Initially called Erb's palsy, a term coined after the name of the German neurologist Wilhelm Erb (1840-1921) who achieved the first classical description of the illness, myasthenia gravis was included in the list of diseases under the name of the Erb-Goldflam

syndrome until 1895, when, at a medical conference in Berlin, the German neurologist and psychiatrist Friedrich Jolly (1844-1904), showed to the audience two patients suffering from this disease, which he called myasthenia gravis pseudoparalytica (1, 12). The first case of MG mentioned in the history of medicine may be considered the case of an Indian tribe chief, the Native-American Opechankanough (1554-1644) who, according to the historical records based on colonial correspondence, suffered from extreme muscle fatigue which made it impossible for him to walk and which was alleviated by rest. Moreover, the historical records also described the fact that Opechankanough suffered from bilateral palpebral ptosis, so that his eyelids were kept open by his servants (19).

***Thomas Willis (1621-1675) – the first description***

Many researchers (1, 2, 12, 20) credit the famous English neurologist Thomas Willis (1621-1675) (figure 1) with the first description of the MG disease. He is especially known in neurology and neurosurgery for Willis polygon, which he named circulus arteriosus cerebri and which he described very well in 1664, thus revolutionizing cerebral circulation physiology (7- 9, 17).

In 1672, Professor Willis notes in several of his patients the occurrence of a chronic condition characterized by muscle fatigue, with fluctuating progress, yet typically aggravated by physical effort and alleviated by rest. It is much later that his descriptions were connected with MG, namely in 1903, by the English pediatricist Leonard George Guthrie (1858-1918), who writes down his

assumptions in the paper entitled Myasthenia Gravis in the Seventeenth Century published by the prestigious Lancet Journal (11).

In one of his books written in Latin, *De anima Brutorum*, and then translated into English in 1688 by the English poet Samuel Pordage (1633-1691), Thomas Willis describes as spurious palsy the case of a woman exhibiting fluctuating muscle fatigue in the limbs and tongue (28).

When he looks for an explanation for these bizarre manifestations, Willis suggests the existence of a substance in the blood that would facilitate muscle contraction, and this type of palsy would be due to fluctuations in the blood concentration of this substance: it may be suspected, that not only de Spirits themselves,...are in fault but...the impotency of local motion doth in some measure also depend upon the fault of the explosive Copula, suffused everywhere from the blood, into the moving fibers (28). This assumption, too daring for the 17th century, cannot be recorded without the slightest shadow of a doubt, since Pordage's work could not be a very faithful translation of Willis' thoughts (13). Therefore, there are scientists who challenged the accuracy of Pordage's description.

***Sir Samuel Wilks (1824-1911) – the grand old man of British medicine***

Two centuries had to elapse until the first modern description of MG was done by another English doctor, Sir Samuel Wilks (1824-1911) (figure 1) rightfully called the grand old man of British medicine (24). Of the four brilliant minds of the Guy's Hospital in London, namely Richard Bright, Thomas

Addison, Thomas Hodgkin and Samuel Wilks, only the last acknowledged the importance of pathological anatomy and promoted it in numerous works published in the Guy's Hospital Reports, which he edited between 1854 and 1865. In all his publications, Wilks supported the performance of autopsy on every occasion in order to set correlations between clinical medicine and pathological anatomy. Samuel Wilks' contributions changed medical thought both as concerns systemic diseases (lymphoma, intestinal inflammatory diseases, bacterial endocarditis, syphilis), and as regards neurological diseases (alcoholic neuropathy, epilepsy, migraine) (22). Moreover, Wilks was also the first scholar who claimed that in epilepsy, the seat of the condition was not in the spinal cord, but in the cerebral cortex (4, 18, 22, 23).

In 1877 Wilks described the case of a woman of uncertain age suffering from bulbar palsy, whose disease progressed in a fluctuant manner from the viewpoint of symptom strength and who eventually died. After an autopsy had been conducted, although he was familiar with the histopathological changes occurring in the brainstem nuclei in case of bulbar palsy and motor neuron disease, Samuel Wilks noted the absence of macroscopic and microscopic changes. At first, he tried to account for the specificity of his case by diagnosing hysteria, but his conclusions were: bulbar paralysis; fatal; no disease found (27).

***Wilhelm Erb (1840-1921) – the first classical description of the disease***

The first classical description of MG may be found in the first book dealing exclusively

with this disease and it was made in 1878, by the German neurologist Wilhelm Erb (1840-1921) (figure 1). Thus, in his work entitled *On a New Symptomatic Complex, Probably Bulbar*, Erb described three cases with similar symptoms and concluded that diplopia, bilateral palpebral ptosis, dysphagia, facial palsy, neck muscle fatigue, all of them with fluctuating progress and numerous recurrences and relapses, were components of a new pathological entity, different from progressive bulbar palsy (6). Erb was also the first scholar who attempted to treat the condition by applying galvanic current and by administering iron, potassium iodide or quinine. The condition of one of the three cases improved after galvanotherapy, the condition of the second patient worsened and that of the third patient improved after quinine had been administered (20).

After 1878 many cases of MG were described in medical literature as particular forms of bulbar palsy, with fatal fluctuating progress. The doctors noted that all these conditions had in common the fact that the forensic examination revealed no pathological findings. Among these cases, the German doctor Eisenlohr published in 1886 the case of an 18-year-old boy who had died due to respiratory muscle paralysis (5), the German neurologist Herman Oppenheim (1858-1919) published the case of a 29-year-old woman in 1887 (21), while the English pathologist Julius Dreschfeld (1845-1907) published, in 1893, the case of a 36-year-old woman, which was very well documented from a pathological anatomy point of view (3).

***Herman Hoppe (1867-1929) – elucidation of the characteristics of the disease***

Starting with 1892 doctors from countries other than Germany and England began to document such cases. The first one to do that was doctor Herman Hoppe (1867-1929), of the United States, who published a complex work dealing with the cases described by Wilks, Eisenlohr and Oppenheim under the name of a single condition, despite their being distinct from a clinical, paraclinical and histopathological point of view. He emphasizes the characteristics of the disease: target muscle groups, no muscle atrophy, circadian fatigability variations (more prominent in the evening) and progress which included remissions and relapses. He also noted that the muscular response to electric stimulation did not have the typical denervation appearance, and the histopathological examination surprisingly revealed no neural mass loss (16).

***Samuel Goldflam (1852-1932) – distinction from progressive bulbar palsy***

A year later, i.e. in 1893, the Polish neurologist Samuel Goldflam (1852-1932) (figure 1) revived Erb's theory and pointed out that muscle fatigue was the cardinal symptom and commented on the disease variants and severity, and suggests the idea of prognostic. In a review of Wilks', Erb's, Eisenlohr's, Oppenheim's and Hoppe's works, he reports three new cases and describes the disease as an apparently curable bulbar paralytic symptom complex (10). This description is considered by many scholars "in many ways the most important ever written in the history of the disease" (25). Just like Erb before him, Goldflam groups the symptoms in a

pathological entity which he clearly distinguishes from progressive bulbar palsy and hysteria, without however giving it a name.

***Friedrich Jolly (1844-1904) – myasthenia gravis pseudoparalytica***

In 1895, the German neurologist and psychiatrist Friedrich Jolly (1844-1904) (figure 1) calls this condition for the first time myasthenia gravis pseudoparalytica when he reports the cases of two 14 and 15-year-old boys. By using faradic current for the electric stimulation of different groups of muscles, Jolly sets the electrophysiological pattern of MG. The test was known by the name of the Jolly test, yet the doctor's residents would call it the not-so-jolly test because of the pain it inflicted.

Jolly thus noted that fatigue also occurred in non-stimulated muscle groups, which virtually reiterated what Thomas Willis had suggested almost 250 years before, namely that MG physiopathology was due to a circulating factor causing muscle fatigue. Moreover, Jolly noticed that fatigability set in on indirect recurrent stimulation, through the nerve, and that muscle contraction stopped at some point. He concluded that MG seemed to be a neuromuscular plate condition (15).

Starting with the 20th century, the number of MG cases increases exponentially, and the following natural step in the medical world was the attempt to clarify disease etiopathogenesis in order to find efficient therapies.

The first connection between thymus and MG was suggested in 1899 by the German doctor Hermann Oppenheim (1858-1919) who discovered incidentally, when performing an autopsy on a MG patient, a tumor the size

of a tangerine (20). A few years later, i.e. in 1901, the German forensic doctor Karl Weigert (1845-1904) detected a tumor in the anterior mediastinum of a MG patient, which originated in the thymus. The 5-5-3 cm tumor was made of lymphocytes, the same cells that also occurred in the striated muscle fibers. Weigert closed the case by concluding that it was a particular form of MG, complicated by a thymus lymphoma, which caused metastases in the deltoid and diaphragm muscles (26).

**Conclusions**

MG has a complicated history, with a golden age in the absence of which scientists would have been unable to elucidate the condition and doctors would have been unable to treat it. Although the beginnings were vague, with a description recorded by

historians, as science and hence the man’s ability to understand things evolved, increasingly relevant proof was collected, which contributed to the current clearly outlined etiopathogenesis of MG and accurate therapeutic guidelines. The complexity of the disease still holds nowadays, as the medical world has been exploring it and placing an emphasis on the genes involved, on new autoantigens and on new therapies to be administered both during seizures and as background therapy. What lasted for almost 350 years may be summarized in a single sentence: the first description originated in England, as did the first modern description of it, then its symptoms and name were set in Germany, whereas its therapy and immunopathological foundations were laid later, starting with 1930, in the United States.

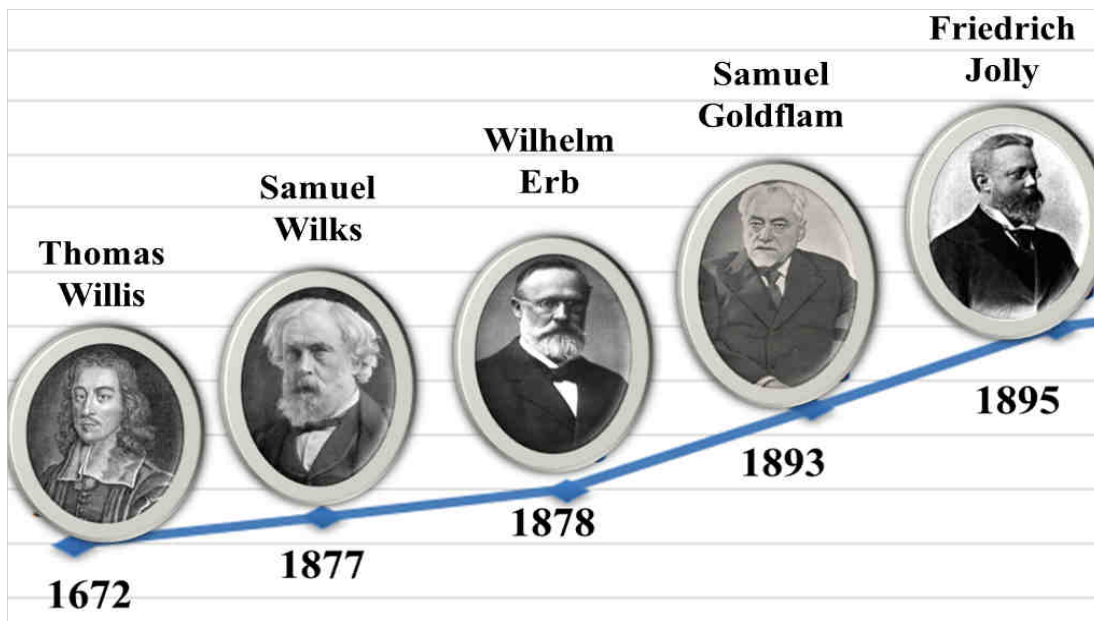


Figure 1 - Contributors to the physiopathology of the myasthenia gravis disease

**Correspondence**

Dana Mihaela Turliuc

“Prof. Dr. N. Oblu” Emergency Clinical Hospital  
Iasi, Romania

E-mail: turliuc\_dana@yahoo.com

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