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The miracle of St. Alfege's Hospital and the history of the treatment of myasthenia gravis

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Abstract: Having a recent history, the neurological condition called myasthenia gravis has raised dilemmas and questions among doctors since it was first discovered in the 16th century and it has not ceased to be a challenge. Nowadays, neuroscience researchers from around the world have been striving to perfect a modern treatment of this condition. Our paper is an incursion into the past, more precisely into the history of the treatment of this disease, from its origin to date, when immunological therapy has progressed.

Key words: myasthenia gravis, treatment of myasthenia gravis, history of medicine

Introduction

The myasthenia gravis (MG) condition has had a relatively recent history, given its discovery as late as the 16th century (Figure 1). Although it is full of misunderstandings and errors, the history of MG has acquired the value of truth later, thanks to neurologists, neuro-psychiatrists and neurosurgeons passionate about science, as they not only tried to understand its pathology, but also to find means of treatment (5). Despite these efforts, until as late as the 1930's, the treatment of MG was empirical and only amount to: bed rest, administration of tonic preparations (iron, quinine, mercury, arsenic and strychnine) and various extracts from animal glands (thymus, ovary, testicle, adrenals), as well as radioactive substance injections and thymus and thyroid irradiations. Thus, we can say that the treatment of MG was in most cases ambiguous, which turned into "a source of discouragement to the patient and a cause of nightmare for the physician" (16).

The first efficient substance: ephedrine

The year 1930 marked an important progress in the history of the treatment of MG, as ephedrine proved to be the first efficient substance in the treatment of MG. This substance is still used as second-line medication in the treatment of this condition. The efficiency of ephedrine in MG was

discovered by the American chemist Harriet Isabel Edgeworth (1865-1916), who suffered from MG herself and who took ephedrine for menstrual cramps and accidently noticed an improvement in her muscle fatigue (9).

In the light of the breakthroughs in the field of muscular contraction, neuroscience researchers focused their attention on creatinine metabolism. Thus, Dr. Walter Boothby published, between 1932 and 1936, various papers on the beneficial effect on the symptoms of the disease of the aminoacid glycine combined with ephedrine (4).

The miracle of St. Alfege's Hospital: physostigmine

The year 1934 marked the beginning of a modern approach to the treatment of MG. While treating a patient suffering from MG, the British doctor Mary Broadfoot Walker (1888-1974) (Figure 2) discovered the beneficial effect of physostigmine on muscle fatigue and palpebral ptosis. The young doctor noticed that the effect lasted between 2 and 5 hours, depending on the concentration of the physostigmine administered subcutaneously. She published her findings that same year in the prestigious journal Lancet: "I think that this effect of physostigmine on myasthenia gravis is important, though it is only temporary, for it improves swallowing and might tide the patient over respiratory crisis. It supports the opinion that fatigability is due to poisoning of the motor end-organs, or myoneural junctions" (31). Thus, physostigmine came to be known as "the miracle of St. Alfege's Hospital", named after one of the hospitals where Mary Walker worked (15).

Table

The main breakthroughs in the history of the treatment of MG, modified after Afifi (1)

Year	Treatment
1930	ephedrine
1932	glycine
1934	physostigmine
1936	first thymectomy
1949	ACTH
1950s	corticotherapy
1966	reintroduced corticotherapy
1967	azathioprine
1973	acetylcholine receptor is autoantigen
1976	plasma exchange
1980	cyclophosphamide
1984	intravenous immunoglobulin
1987	cyclosporine
2000s	immunotherapies

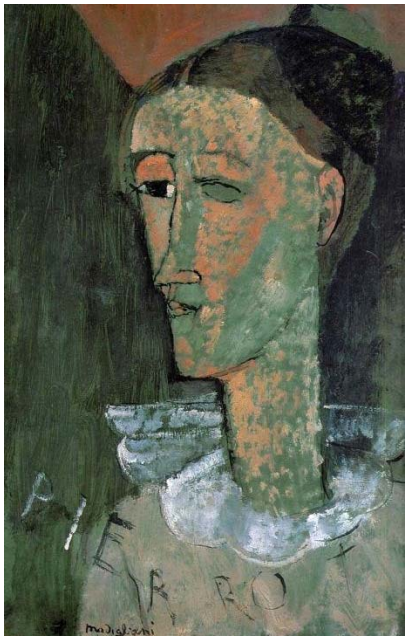

Figure 1 - Possible onset of myasthenia gravis with unilateral left ptosis (Pierrot - Amedeo Modigliani, Paris-1915) (public domain)

Mary Broadfoot Walker

Alfred Blalock

Douglas Fambrough

Figure 2 - Contributors to the treatment of myasthenia gravis

In addition to physostigmine, Dr. Mary Walker also studied the effects of neostigmine and potassium chloride on MG patients with remarkable yet short-lasting results. She noted an improvement in muscle fatigue and the absence of central side effects of physostigmine (18, 30).

Due to her pioneering in the treatment of MG, Mary Walkera still is one of the major contributors to the treatment of MG, with numerous incommensurable achievements: she is the first specialist who suggested the idea of "myasthenic crisis", the first specialist to have noted that MG is located in the neuromuscular junction and also the first specialist to have discovered the clinical effect which was later called "the Mary Walker effect". Of all of Dr. Mary Walker's achievements, the most important is the use of physostigmine as primary therapy. This also stimulated the research of other acetylcholinesterase inhibitors like edrophonium in 1950 by MacFarlane (20) or pyridostigmine in 1954 by Kermit Osserman (23). These are still being used as first-line drugs in the treatment of MG.

The use of neostigmine in the treatment of MG may be also credited to the German Lazar Remen (1907-1974), who published in German literature in 1932, that is 2 years before Mary Walker, a paper that claimed that the symptoms of a patient with MG improved after she had received neostigmine (26).

Total resection of the thymus gland in the treatment of MG

Being aware of Ernst Ferdinand Sauerbruch's (1875-1951) post-thymectomy

results, the American surgeon Alfred Blalock (1899-1964) (Figure 2) performed the resection of a post-radiotherapy cystic tumor. The case was of a 19-year old girl with generalized MG, who underwent surgery during the remission period and who was administered prostigmin before and after the surgery. The case was published 3 years later, in 1939, in a paper in which Blalock claimed that the myasthenic symptoms were remitted. 21 years later the patient was still alive (3, 13). Encouraged by this positive result, in 1941, Blalock started to practice thymectomy in MG patients without thymus tumors. Thus, he published reports on 6 cases of transsternal thymectomy and noticed that three of them did not subsequently require drug therapy (2).

Inspired by Blalock's promising results, the English surgeon Geoffrey Keynes, (1887-1982) also performed 120 thymectomies between 1942 and 1949 in MG patients, and reported a 65% improvement in his cases (17). The treatment of MG through thymectomy had also crossed the ocean, as the American surgeon Oscar Theron Clagett (1908-1990) and the neurologist Lee Eaton (1905-1958), from the Mayo Clinic, had performed 72 thymectomies in MG patients, which they subsequently compared to the 142 MG cases that had not undergone surgery (8). Later, that is between 1950 and 1954, there was a difference of opinion between the two continents as concerns thymectomy efficiency in MG patients. On the one hand, the Americans Clagett and Eaton from the Mayo Clinic, claimed that thymectomy was inefficient, on the other hand, the English Keynes argued against. It was later proven that this difference of opinion was due to the fact that most of the patients that had undergone surgery in the Mayo Clinic had thymus tumors, whereas in England they had thymic hyperplasia (1). This discrepancy was settled in 1955 when Clagett and Eaton set clear thymectomy criteria: absence of thymus tumors and patients' age below 50 (7).

ACTH and cortisol

Wishing to achieve the same effect as thymectomy without the actual surgical procedure, in 1949, the Americans Clara Torda and Harold Wolff from the New York Hospital administered ACTH to 15 patients suffering from MG. Immediately after the administration of 500mg for 5 days, they noted a visible worsening of the symptoms in all the patients, including one dead; yet, they later noted the improvement of the symptoms of 10 out of 15 patients (29). After cortisol had been isolated and discovered in the adrenal glands and its effects had been studied by the chemists Edward Kendall (1886-1972) and Tadeus Reichstein (1897-1996) (14), cortisone started to be administered to MG patients in 1950. Neuroscience researchers noted the same effect as in the case of ACTH, with a significant initial worsening and an improvement after a few days. Nevertheless, due to its life-threatening effects, they do not encourage the use of hydrocortisone in the treatment of MG.

According to the German neuro-psychiatrist Friedrich Jolly (1844-1904) and the British doctor Mary Broadfoot Walker (thirty nine years later) suggested that in MG

the impairment was located in the neuromuscular junction and that acetylcholine was the mediator involved (5), in 1956 the American David Grob et al. shed some more light on the matter by claiming that the seat of MG was at the post-synaptic level (10). A year later, that is in 1957, another neuroscientist, John Desmedt, published in the Nature journal a study in which he considered the post-synaptic component responsible for muscle fatigue in MG (6), and also suggested a possible acetylcholine depletion in the neuromuscular junction (22).

Myasthenia gravis.....an autoimmune disease?

After the neuroscience researchers concluded that in MG the seat of impairment was located in the post-synaptic region, the medical world suggested that MG may be an autoimmune disease, as its association with autoimmune diseases has been noted. Thus, in 1954, in a review of 138 cases of systemic lupus erythematosus patients, Harvey et al. noted that 3 of them also suffered from MG (12). Nevertheless, the first specialist to officially launch in literature the assumption related to the autoimmune nature of MG was Dr. Smithers DW, in 1958 (1). That same year, Kermit Osserman, who had studied the effect of pyridostigmine, made a classification of MG and divided it into four groups depending on symptom severity and location (1). Smithers' assumptions were confirmed in 1960 by the Scottish doctor John Simpson. A review of all 404 cases of MG recorded between 1953 and 1955 enabled Simpson to reach three conclusions: that MG patients had thymus abnormalities, that thymectomy has a positive influence of disease prognosis and that there is a connection between MG and several other diseases like rheumatoid polyarthritis, systemic lupus erythematosus, hyperthyroidism, aplastic anemia, pernicious anemia or sarcoidosis. Thus, Simpson concludes that "myasthenia gravis is a muscular autoimmune response, in which an antibody of the protein in the end-plate can be involved as a reaction to an infection or thymus influenced by the pituitary gland" (27). That same year, i.e. is in 1960, Jacques Miller proved the immunological function of the thymus, in a series of studies that he published a year later in the Lancet (21).

In 1968, in his attempt to discover a serum protein able to inhibit neuromuscular transmission, William Nastuk et al. focused on the study of the complement in MG. He found correlations between the serum complement level and disease activity and argued that "the levels of complement are decreased during the clinical activity of the disease, while during its remission, they increase. This suggests the possibility that MG is an autoimmune mediated disease" (28). Furthermore, in an attempt to identify the generator of these autoimmune reactions – an anti-striated muscle antibody, Arthur Strauss analyzed the serum of 1139 subjects, of whom: 129 were healthy, 386 had MG and 674 suffered from inflammatory, endocrinological and carcinomatous myopathies, muscular dystrophies and thymomas not accompanied by MG (28). Since he discovered that in subjects with MG and thymomas, serum globulins retained the complement, Strauss established a certain connection between thymus abnormalities and impulse transmission alteration in the

neuromuscular junction.

Thus, once the assumption according to which autoimmunity plays an essential role in MG pathogenesis was accepted, the reintroduction of corticotherapy, which had been abandoned for its life-threatening effects, was supported. Initially, cortisol and then prednisone started to be administered for their immunosuppressant functions, in more carefully calculated doses. Subsequent studies showed that symptom worsening was temporary and that an obvious disease symptom improvement was visible after 7 to 10 days (1). "By borrowing" from the lymphoma and leukemia therapy, doctors started to focus their attention on other classes of medicines like: immunosuppressants, chemotherapy drugs or cytotoxic drugs. Thus, azathioprine started with 1967 to be administered to MG patients in Europe and cyclophosphamide since 1980 (14).

Reference year 1973

1973 is considered a reference year in the history of the treatment of MG, since it marks two essential discoveries in understanding the pathology of this condition and its approaching the current level of knowledge. The first occurred in the Johns Hopkins Hospital, when Douglas Fambrough (Figure 2) noted that acetylcholine receptors were located solely in the postsynaptic component after he had used a radioactively labeled from the cobra venom (alpha-bungarotoxin), with high binding affinity to the acetylcholine receptor (11). The second discovery belongs to Jim Patrick and Jon Lindstrom from the Salk Institute, who identified the acetylcholine receptor as the autoantigen responsible for triggering the autoimmune response (24). Lindstrom also isolated acetylcholine receptor antibodies in 1976. He injected rabbits with acetylcholine receptors sampled from electric eels and found that they exhibited flaccid paralysis and breathing difficulties and in addition that the symptoms were partially improved by prostigmin administration (19). The confirmation of the autoimmune pathogenesis and of the existence of acetylcholine receptor antibodies occurred in 1976, when Fueron treated three MG patients by plasmapheresis, with certain clinical improvement (25). This is actually the decisive breakthrough marking the transition towards a modern therapeutic approach and continuation of the immunological and genetic research of MG.

Conclusion

Having a relatively recent history, the treatment of MG has been a challenge for neuroscientists, and especially for doctors, who were faced with an unknown disease the therapy of which was even more unknown. Whereas the first disease description was done in England and the symptoms and name of the disease were later clarified in Germany, we can safely say that the treatment and immunopathological grounds originate in the United States. Although answers have been found to questions that seemed to have no answer, the complexity of MG is still very much visible nowadays, when the medical world has got involved in a process of continuous exploration, which focuses on the genes involved, on new autoantigenes and also on new immunotherapies of an extremely "complex" condition.

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