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History of Myasthenia Gravis Revisited

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ABSTRACT

The first description of myasthenia gravis (MG) was given by Thomas Willis in 1672. MG was the focus of attention after mid-nineteenth century and a great amount of information has been accumulated in a span of 150 years. The aim of this review is to convey this information according to a particular systematic and to briefly relate the experience of Istanbul University. MG history was examined in four periods: 1868-1930, 1930-1960, 1960-1990, and 1990-2020. In *the first period (1868-1930),* all the clinical characteristics of MG were defined. Physiological/pharmacological studies on the transmission at the neuromuscular junction were initiated, and the concept of repetitive nerve stimulation emerged. A toxic agent was believed to be the cause of MG which appeared to resemble curare intoxication. Association of MG with thymus was noticed. No noteworthy progress was made in its treatment. In *the second period (1930-1960),* acetylcholine was discovered to be the transmitter at the neuromuscular junction. Repetitive nerve stimulation was used as a diagnostic test. The autoimmune nature of MG was suspected and experiments to this end started to give results. The hallmark of this period was the use of anticholinesterases and thymectomy in the treatment of MG. *The third period (1960-1990)* can probably be considered a revolutionary era for MG. Important immunological mechanisms (acetylcholine receptor isolation, discovery of anti-acetylcholine receptor antibodies) were clarified and the autoimmune nature of MG was demonstrated. Treatment modalities which completely changed the prognosis of MG, including positive pressure mechanic ventilation and corticosteroids as well as plasma exchange/IVIg and azathioprine, were put to use. In *the fourth period (1990-2020),* more immunological progress, including the discovery of anti-MuSK antibodies, was achieved. Videothoracoscopic thymectomy reduced the morbidity and mortality rate associated with surgery. New drugs emerged and clinical trials were performed. Valuable guidelines were published. In the last part of the review, the experience in MG of Istanbul University, a pioneer in Turkey, is related.

Keywords: Myasthenia gravis, history, treatment, Istanbul University

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INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease causing fatiguable weakness in striated muscles, predominantly in the oculobulbar ones (1, 2). Antibodies against postsynaptic proteins impair conduction in the neuromuscular junction leading to weakness. Presence of thymoma in a small proportion of MG patients and thymic hyperplasia in most young myasthenic patients point to the role of the thymus in the pathogenesis. Anticholinesterases, thymectomy, immunosuppressive and immunomodulatory agents are used in the treatment.

All this information which takes place even in the most basic neurology textbooks has been accumulated as a result of an intense endeavour spanning over 150 years, from the nineteenth to the twenty-first century. We can imagine this as a detective story full of secrets awaiting to be solved with the help of a lot of detectives over one and a half centuries.

We can take the beginning of the story even further back to 350 years ago. Thomas Willis (Oxford, 1621-1675), in his book 'De Anima Brutorum' ('The Animal [brutorum] Soul [anima]'), published in London in 1672, described patients who were well in the morning and fatigued toward noon and were unable to speak for a long time. Let us hear the descriptions from his book, translated from Latin to English a year later, in his own words (3-5):

"... though they are well in their stomach, and have a good and laudable pulse and urine, yet they are as if they were enervated, and cannot stand upright, and dare scarce enter upon local motions, or if they do, cannot perform them long: yea, some without any notable sickness, are for a long time fixed in their Bed, as if they were every day about to dye; whilst they lie undisturbed, talk with their Friends, and are chearful, but they will not, nor dare not move or walk; yea, they shun all motion as a most horrid thing ... in the morning [they] are able to walk firmly, to fling about their Arms hither and thither, or to take up any heavy thing, before noon the stock of Spirits being spent, which had flowed into the Muscles, they are scarce able to move Hand or Foot." Interestingly, Willis believed that the disease was caused by a substance called 'explosive copula' which was in the blood going to the 'moving Fibres'.

He mentioned a woman who had difficulty speaking in addition to limb weakness: "...she for some time can speak freely and readily enough, but after she has spoke long, or hastily, or eagerly, she is not able to speak a word, but becomes mute as a Fish, nor can she recover the use of her voice under an hour or two." Only in 1903 was it realized that his descriptions strongly suggested the diagnosis of MG.

According to the Virginia chronicles, the first patient with MG is considered to be the chief of the native American Powahatan Confederation (at the territories of the present Virginia state in USA), Opechancanough, who died in 1644. This well-known chief who was very strong in his youth and had been victorious in several battles against the whites was so weak in his older days that he was unable to walk and had to be carried; furthermore, "his eyelids were so heavy that he could not see unless they were lifted

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up by his attendants." However, he was able to walk after resting in prison in his last days (6).

In this review, the developments after the ensuing 200 years of silence were organized into four periods. The periods were chosen trying to take into regard a relative uniformity in the period of question. After the first period spanning sixty years, three periods each spanning thirty years include developments in neuromuscular physiology/electrophysiology (designated as 'a'), thymus/immunology (designated as 'b') and treatment (designated as 'c'). Clinical characteristics have only been elaborated upon in the first period. It is possible to find the division into periods quite artificial; if this is the case, the reader can read the review by following the developments under similar headings disregarding the periods.

There are a lot of excellent publications on the history of MG (3-5, 7-12). In this review, this material was extensively used and original articles of importance were evaluated. The aim of the review is to convey this information according to a particular systematic as explained above, and to briefly relate the experience of Istanbul University, a pioneer in the diagnosis and treatment of MG in Turkey.

I. 1868-1930

In this period, all the clinical characteristics of MG were defined. Physiological / pharmacological studies on the transmission at the neuromuscular junction were initiated, and the concept of repetitive nerve stimulation emerged. A toxic agent was believed to be the cause of MG which appeared to resemble curare intoxication. Association of MG with thymus was noticed. No noteworthy progress was made in its treatment.

The first detailed MG patient was reported by Hérard (Paris, 1868) under the diagnosis of 'glosso-labiolaryngeal paralysis' (5): A 30 year-old woman had the onset of speaking and swallowing difficulties, ptosis and hand weakness were added, fluctuations were present, she died during a flu, at a time when she already had breathing difficulties. Interestingly, Hérard had sent her to Duchenne who had applied electrical stimulation and she had been improved for two months after the procedure. Over ten years after this report which remained unnoticed, Samuel Wilks (London, 1877) wrote on a patient without any changes in the brainstem. In many histories of MG, Wilks' patient is considered to be the first reported case of MG (3, 7).

Wilhelm Erb (Heidelberg, 1879) described the most important characteristics of the disease-oculobulbar symptoms/signs and remissions/exacerbations-in the context of three patients. No pathological changes were observed in the cases of Carl Eisenlohr (Hamburg, 1886) and Hermann Oppenheim (Berlin, 1887). It is noteworthy that neuropathology was progressing fast at this time, particularly in Germany, and that neuronal loss in motor nuclei in motor neuron disease was well-known, so that the normal appearance of the brainstem was very surprising. Patients by Lauriston Elgie Shaw (London, 1890), Herman Hoppe (Ohio, 1892) and Julius Dreschfeld (Manchester, 1893) increased the number of cases. Samuel Vulfovitsj Goldflam (Warsaw, 1893), reviewing the literature and reporting three cases of his own, described all the diagnostic/differential diagnostic and prognostic features of the disease. Friedrich Jolly (Berlin, 1895), reporting two cases, thought, as did Oppenheim, that MG resembled curare intoxication (12). A compilation of about sixty cases were done by Oppenheim (8) and Harry Campbell-Edwin Bramwell (13).

For a while, MG was called Erb-Goldflam syndrome, as a tribute to Erb and Goldflam who gave the most precise description of the disease. Jolly proposed the name 'myasthenia gravis pseudoparalytica'; 'myasthenia gravis' was accepted in the meeting of the Berlin Society of Psychiatry and Neurology in 1899. 'Myasthenia' means muscle weakness in Greek, and 'gravis' means severe in Latin.

a. Neuromuscular junction: Physiological and electrophysiological investigations

Physiological investigations

Very little was known about the neuromuscular junction (NMJ) at this time. A discussion on the nature of the transmission at the NMJ ('the war of the soups and the sparks') was continuing among pharmacologists and physiologists, with those saying it is chemical ('soups') against others holding it is electrical ('sparks') (10). Otto Loewi's experiments in the frog heart at the beginning of the 1920's showed the transmission to be chemical. Henry Dale noted that the transmitter Loewi called 'vagus substance' was actually acetylcholine (ACh).

Electrophysiological investigations

Jolly showed that faradic stimulation intermittently applied to striated muscle resulted in progressive diminution of the muscle response volume. This set the basis of repetitive nerve stimulation.

b. Developments prior to immunology: Toxins

In these years, 'horror autotoxicus' put forth by the famous scientist, Paul Ehrlich (1854-1915), was a widely accepted concept: Even if antibodies formed, they would not endanger the body and self-destruction would be prevented by several mechanisms (12, 14). Paroxysmal cold hemoglobinuria, the autoimmune nature of which had already been shown, was accepted as an exception. As per the spirit of the age, MG was thought to be caused by a toxic (12) or a microbic agent (13). Carl Weigert (Frankfurt, 1901) found lymphocytic infiltration in muscles of a myasthenic patient with a thymic tumor. Edward Farquahar Buzzard (London, 1905) called the lymphocytic deposits, present also in the thymus, 'lymphorrages'. While Weigert regarded them to be metastases from the thymic tumor, Buzzard believed that a toxic agent caused them to come via blood vessels to muscles (12).

In this period, publications on the association of the thymus with the disease started to appear. A thymic tumor was discovered in a patient of Oppenheim (1899) (9). In 1901, the pathologist Carl Weigert found a thymic tumor in an MG patient of Leopold Laquer and diagnosed it as lymphoma (detailed above). Ernst Ferdinand Sauerbruch noted improvement of MG symptoms after thymectomy done for hyperthyroidism (Zurich, 1911). Necropsy studies performed in later years strengthened the association between MG and thymic tumor and hyperplasia.

c. Treatment

Several therapies including strychnine, mercury, arsenic, potassium, iron, quinine and electrical stimulation were tried. Oppenheim as well as Campbell and Bramwell (13) thought that none of them had any benefit and that resting was the best remedy (9).

II. 1930-1960

In this period, acetylcholine was discovered to be the transmitter at the neuromuscular junction. Repetitive nerve stimulation was used as a diagnostic test. The autoimmune nature of MG was suspected and experiments to this end started to give results. The hallmark of this period was the use of anticholinesterases and thymectomy in the treatment of MG.

a. Neuromuscular junction: Physiological and electrophysiological investigations

Physiological investigations

Following Loewi's discovery of the chemical nature of the transmission between nerve and cardiac muscle, the studies of Dale, Feldberg and Vogt showed ACh to be the transmitter also in the NMJ (15). Loewi (Austria)

and Dale (United Kingdom) received the 1936 Nobel prize due to these discoveries. However, the chemical/electrical discussion continued until chemical was finally widely accepted at the end of this period (16). Another important development was the demonstration by Fatt and Katz (17) in 1952 of resting subthreshold electrical discharges (miniature endplate potentials, MEPP) at the motor nerve endings which originated from special areas, probably related to ACh release.

Around this time, another discovery, which later had an important role in the elucidation of MG pathogenesis, took place. At the end of the nineteenth century, electrical organ of the electrical eel (*Electrophorus* and *Torpedo*), which had drawn attention since the seventeenth century, had been discovered to be striated muscle which had lost its contractile elements and had developed into a modified endplate. Right before the second World War (1939), David Nachmansohn and Alfred Fessard, working in France, insisted Wilhelm Feldberg from London who had just discovered ACh to be the transmitter at the NMJ, to cooperate with them and with his help, they were able to demonstrate that what stimulated the electrical organ was also ACh (18). A motor endplate with abundant cholinergic supply and possibly a rich source of acetylcholine receptor (AChR) was thus obtained to be conveniently used in future experiments.

Electrophysiological investigations

Donald Lindsley (1935) was the first to use repetitive nerve stimulation (RNS) in the diagnosis of MG. RNS was improved by Harvey and Masland (1941), in fact the test was called 'Harvey-Masland test' for a while. In the 1950's, the pathology in MG was believed to be postsynaptic, particularly among the American school of electrophysiologists (19, 20).

b. Seeds of autoimmunity

'Something in the blood'

Jolly had observed that the fatigue of one part of the body caused weakness in another part. This was later called 'Mary Walker phenomenon' and some regarded it as an injustice done to Jolly (21). However, the experiment done by Walker in one of her patients was different (22). It might be of benefit to relate this experiment in detail: The circulation was stopped by inflating the sphigmomanometer to 200 mm Hg in both arms for four minutes, the arms were exercised for one minute at the beginning of this time period. The increase in the left ptosis occurred one and a half minutes after the pressure in the cuff was released, not one and a half minutes after the exercise. If the experiment was done without a sphigmomanometer, the increase occurred one and a half minutes after the exercise. Prevention of the circulation delayed the appearance of the increase of the ptosis, pointing to a chemical agent going to an endplate at another location via blood. In the following years, a curare-like substance was intensively searched in the blood. Neonatal MG where an agent was thought to pass from mother to child supported this hypothesis (12). In the 1950's, the search for a curare-like substance accelerated; William Nastuk and Arthur Strauss showed in 1959 that MG blood resulted in a cytolytic activity in the muscle cells of frogs (23).

Autoimmunity in other diseases

After the mid-1950's, the concept of autoimmunity began to change radically in rheumatological and endocrinological diseases. Systemic lupus erythematosis (SLE) was proposed to be an autoimmune disease in 1953 (24). Thyroid antibodies were observed in experimental thyroiditis in 1956, followed by the discovery of autoantibodies in the serum of patients with Hashimoto (14, 25). Smithers drew attention to the resemblance of thymic changes in MG to the thyroid pathology in Hashimoto, and proposed in 1959 that MG, similar to Hashimoto, is an autoimmune disease (26).

c. Treatment

Although not specific to MG, the use of antibiotics in the 1940's to treat complications such as pneumonia, which caused exacerbation of MG, was a very important step. The most striking progress of this period, however, was the emergence of treatment specific to MG: Anticholinesterases and thymectomy.

Symptomatic treatment (ephedrine and anticholinesterases)

The prognosis of myasthenia started to change owing to the curiosity and courage of two women. Dr. Harriet Edgeworth (Arizona, 1930), who was herself a myasthenic, reported that ephedrine which she took for menstrual cramps improved her myasthenic symptoms (27). Ephedrine soon started to be used.

Prostigmine was used in MG thanks to Mary Walker (London, 1934) (3, 4, 21). Walker's chief Derek Denny-Brown had likened myasthenia to curare intoxication. With this information, Walker initially used physostigmine injection in a myasthenic patient and obtained a dramatic response (28). Later, she tried prostigmine, upon the suggestion of a pharmacologist, Philip Hamill, with success (29). This was called *St. Alfege miracle* as a tribute to Walker who worked in this hospital. Walker thought that these observations showed the pathology to be at the NMJ rather than at the muscle.

In actuality, the first to report the beneficial effect of prostigmine in MG was Lazar Remen (Munster, 1932) (4). However, the subject of the article he wrote was glycine in MG; as he did not emphasize it in his article, no attention was payed to prostigmine. Jolly had also suggested that physostigmine might be beneficial, but had not dwelled upon it because of its toxicity. Keesey quotes Francis Darwin: "In science the credit goes to the man who convinces the world, not to the man to whom the idea first occurs" (21).

Within a few weeks, prostigmine was widely used. The first myasthenia outpatient clinic was established at this time by Henry Viets in Massachusetts General Hospital in Boston. Edrophonium chloride was used in 1950, pyridostigmine bromide in 1954 and ambenonium chloride in 1955 (9).

Thymectomy

A very important development of this period was thymectomy. Sauerbruch's two further patients with thymoma after the one mentioned above had died after surgery. Alfred Blalock, a cardiac surgeon, performed the first thymomectomy successfully in a young patient with severe generalized MG and a thymoma (Baltimore, 1936). He chose a time when the patient was relatively well and prepared very carefully for the surgery. The patient went into remission after surgery and continued to be well during 21 years of follow-up, even though she had a thymoma (in view of the fact that thymomatous MG does not have considerable benefit from surgery). Blalock operated on around 20 patients without thymoma between 1941-1944 and reported good results in over half of them (4, 9).

A later dispute over thymectomy is worth relating. Geoffrey Keynes (London), who was a surgeon with expertise in thyroid surgery, thymectomized approximately 300 patients between 1942 and 1956. He reported a complete or almost complete remission in 65% of his patients after thymectomy. The best results were obtained in younger patients (<50 years of age) (30). These favorable results, however, were not in accordance with the unfavorable ones reported in 1950 by Lee Eaton (neurologist) and Theron Clagett (surgeon) from Mayo Clinic. The superiority of the study from Mayo Clinic was the comparison done with non-thymectomized patients (31). Keynes, a fervent advocate of thymectomy, was very annoyed with this report and said "We therefore

ignored their report and proceeded on the course we had already set, closing our ears to the murmurs uttered on all sides that of course the Mayo Clinic had proved the operation to be useless and why did we go on doing it" (3). Sensing that there was a basic problem, Keynes scrutinized the Eaton-Clagett study and realized that they had a disproportionate number of thymomas which caused the results to be negative. Keynes had noticed that myasthenic symptoms were not much affected by thymomectomy and had excluded thymomas. Finally, Eaton and Clagett accepted in 1955 that thymectomy was beneficial in women (32). They were still on opposite corners with respect to men; Keynes attributed this discrepancy to the fewer number of men making statistical analysis less reliable. He remarked that this was "an object lesson and a warning of the harm that can be done by a misuse of statistics and by the exaggerated importance sometimes given to an opinion because it happens to emanate from a well-known medical centre (3)". Keynes played a very important role in the continued performance of thymectomies.

Immunosuppressive treatment

Several drugs were tried, in addition to thymectomy. Although anterior hypophysis extract gave good results in a few patients, it was useless in a higher number. Clara Torda and Harold Wolff reported good results with ACTH in two thirds of 15 patients (33) while others reported no benefit. Toward the end of this period, David Grob, who was an eminent figure in MG, held that cortisone and ACTH either did not have an effect on MG or even worsened it (34).

III. 1960-1990

This period can probably be considered a revolutionary era for MG. Important immunological mechanisms (acetylcholine receptor isolation, discovery of anti-acetylcholine receptor antibodies) were clarified and the autoimmune nature of MG was demonstrated. Treatment modalities which completely changed the prognosis of MG, including positive pressure mechanic ventilation and corticosteroids as well as plasma exchange/IVIg and azathioprine, were put to use.

a. Neuromuscular junction: Physiological and electrophysiological investigations

Physiological investigations

That ACh released from motor nerve endings was the transmitter in the NMJ had been confirmed, but a putative receptor at the postsynaptic membrane had not yet been found. Electrical organ of the electrical eel was very suitable for the isolation of AChR because of its rich cholinergic supply (18). However, experiments involving the nicotinic synapses of this fish did not yield any results. Like a lot of scientists, Changeux was also working on this subject. Meanwhile, in 1963, Chang and Lee had isolated alpha-bungarotoxin which disturbed the transmission at the NMJ, from the toxin of a snake called Bungarus multicinctus found in Taiwan. An unexpected visit of Lee to the laboratory of Changeux at Pasteur Institute solved the problem. Changeux was soon able to isolate AChR in 1970 with the help of the toxin supplied by Lee (35). This discovery of key importance in the elucidation of MG pathogenesis was possible thanks to the abundant amount of AChR in the electrical eel and alpha-bungarotoxin which bound to it irreversibly (18). In the 1980's, the immunologically important alpha subunit of the AChR was cloned (36).

Three years after the isolation of AChR, Fambrough, Drachman and Satyamurti were able to show decreased number of AChR postsynaptically in MG, using alpha-bungarotoxin which has strong affinity to AChR (37). Prior to this discovery, Andrew Engel and Santa had analyzed the postsynaptic region with electron microscope and had found the postsynaptic region to be simplified and had thus shown the pathology of MG to be postsynaptic (38).

Electrophysiological investigations

While the American school maintained that the pathology in MG was postsynaptic toward the end of the 1950's (19, 20), the dispute between presynaptic/postsynaptic resurfaced in the mid 1960's. Dan Elmqvist and colleagues based on experiments with intracellular electrodes (39), and John Desmedt, based on studies with RNS (40) were on the presynaptic side of the dispute. The developments in basic sciences in the 1970's determined the pathology to be postsynaptic. RNS studies by Coşkun Özdemir and Robert Young (41) supported postsynaptic involvement and demonstrated all the characteristic patterns of RNS in MG. Eric Stålberg and colleagues developed single fiber EMG (SFEMG) and it was established as an important diagnostic test in MG in early 1970's (42).

b. Immunological and genetic investigations

Initial laboratory and clinical clues

Nastuk and Strauss continued with their experiments which they had started in the 1950's into the 1960's. They had shown that MG blood caused cytolysis of the frog muscle cells (23). Nastuk and colleagues observed that serum complement activity fluctuated in attacks and remissions in MG (43).

John Simpson (London, 1960), in a meeting in Edinburgh, proposed that MG is an autoimmune disease caused by antibodies against the endplate receptors, based on his interview of 440 myasthenic patients and the analysis of their medical records (44). At the beginning of his talk, he asked his audience to forget everything they were taught and to view myasthenia from another perspective.

Being aware of the experiments of Nastuk, he had proceeded to find a unifying hypothesis which took into consideration all the clinical phenomena and all known evidence including pathophysiological and pharmacological ones without exception. As noted above, there were publications reporting that SLE and particularly Hashimoto were autoimmune diseases. High frequency of thyroid disease in MG patients and their families, resemblance to SLE with respect to gender and age, similarities of the lymphocytic infiltrations in the muscles to those in rheumatological diseases, all led Simpson to conclude that MG is an autoimmune disease. He did not think that the structural changes in the nerves and muscles could be the result of a simple chemical event and held that the thymus possibly played a reticuloendothelial role. In line with those who advocated that the pathology is in the endplate, he proposed that a competitive-blocking agent must be present in the endplate. Let us hear his conclusions to which he reached by reasoning in his own words (44):

"In summary then, my suggestion is that myasthenia is an 'auto-immune' response of muscle in which an antibody to end-plate protein may be formed. This [antibody] would have the properties of an acetylcholine-competitive-blocking substance, specific to the individual, and occasionally to the foetus of a myasthenic mother. ... [Myasthenia] may be the result of an auto-immune response to an infection, usually of the upper respiratory tract, or the reticuloendothelial system, specifically the thymus, may react to muscle end-plate protein as if it were 'foreign' in disorders of the thymus."

He finished his talk by a citation from Hughlings Jackson: "A hypothesis or supposition is not a conclusion; it is only a starting point for methodical observation and experiment, the endeavour being not only to prove it, but to disprove it" (44). This hypothesis, the novelty of which he had emphasized at the beginning, was later confirmed by observations and experiments. Meanwhile, autoimmunity in MG was still disputed in the years 1960-1970 (12)

Discovery of anti-acetylcholine receptors

The 1970's witnessed revolutionary immunologic discoveries in MG. James Patrick and Jon Lindstrom administered AChR, found abundantly in electrical eels, to rabbits in 1973, aiming to produce antibodies. With repeated injections, flask paralysis and difficulty breathing occurred in rabbits (Experimental Autoimmune Myasthenia Gravis, EAMG). This was likened to MG and was ameliorated with prostigmine (45). In fact, the aim was not to produce an MG model, but to investigate the AChR. Finally, in 1976, Lindstrom and colleagues found anti-AChR antibodies in 87% of their MG patients (46). Development of weakness and decrease in the number of AChR after injection of IgG from MG patients to mice by Klaus Toyka and colleagues (47), improvement of MG symptoms after plasma exchange (48), detection of IgG and complement at the NMJ of MG patients by Andrew Engel and colleagues (49) all pointed to the pathogenicity of these antibodies. In the 1980's, more information accumulated on AChR and anti-AChR antibodies. The importance of T cells began to be understood (1, 8, 11).

Genetic investigations

In the 1970's, the frequency of HLA-B8 in young women and of HLA-A3 in older patients were reported. Based on their study of HLA in their own patients, taking into account onset age of MG and presence of thymoma, Compston and colleagues identified three groups: 1.) Below 40, predominantly women, associated with HLA-A1, B8, DRw3, 2.) Above 40, predominantly men, associated with HLA-A3, B7, DRw2, 3.) No thymoma, no HLA association (50). Owing to this study, the importance of studying MG within subgroups was realized and this has since been used, with changes and additions (2).

c. Treatment

Mechanic ventilation

Positive pressure mechanic ventilation had first been used in MG at the New End Hospital in London in 1957 and became widespread after 1958 (51).

One of the main factors decreasing the mortality rate which was 40% at the beginning of the 1960's to 5% in the 1970's is thought to be positive pressure mechanic ventilation and Intensive Care Units (ICUs) (52).

Thymectomy

Confusion about thymectomy once again re-surfaced. The main factors leading to the confusion included the different characteristics of the patient population (with and without thymoma) and the timing of thymectomy (early and late thymectomy). In this period, two important studies from Mayo Clinic, one on 156 patients 17-50 years of age, half consisting of computer-matched non-thymectomized controls with a mean follow-up of 20 years (53) and the other on 149 children below 17 years of age, half consisting of non-thymectomized controls with a mean follow-up of 17 years (54), though not prospective, were quite revealing. Remission rate was found to be higher in the thymectomized group in both studies. Thymectomy was reported to be more successful in early thymectomized patients with bulbar symptoms in the juvenile study (54). Looking back, the fact that these studies as well as those of Keynes were done at a time when corticosteroids were not in use can be considered to increase their value.

Immunosuppressive treatment

Corticosteroids and azathioprine were initially viewed with a lot of scepticism, and their widespread use took some time (9, 55). High dose ACTH, which was reported to be beneficial toward the end of the 1960's (56) was started to be accepted after several years (57). Although King Engel and colleagues reported good results with high dose corticosteroids (58), widespread acceptance again took several years (9, 59). Azathioprine was used in Europe earlier than USA. The beneficial effect was observed toward the end of the 1960's (60), its widespread use was after mid-1970's (61).

The contribution of plasma exchange (62) and IVIg (63, 64) to the management of myasthenic crisis was accepted after 1976 and 1984 respectively. Cyclophosphamide was included in the list of drugs in MG after 1981, with caution to its potential toxicity.

By 1990, the basic outline of the conventional MG treatment as practised today had been established.

IV. 1990-2020

In this period, more immunological progress, including the discovery of anti-MuSK antibodies, was achieved. Videothoracoscopic thymectomy reduced the morbidity and mortality rate associated with surgery. New drugs emerged and clinical trials were performed. Valuable guidelines were published.

a. Neuromuscular junction: Physiological and electrophysiological investigations

Physiological investigations

Epsilon and gamma subunits of the AChR molecule were cloned in the 1990's (65). A protein called muscle specific kinase (MuSK) localized to the postsynaptic region was identified and later the proteins in the MuSK pathway were discovered (2).

Electrophysiological investigations

In this period, RNS and SFEMG were technically refined and new information was obtained. That the most prominent decrement was obtained from the orbicularis oculi (OO) muscle in MuSK MG was observed whereas OO was known to be a muscle least likely to manifest decrement in generalized anti-AChR positive MG (66). The decrement pattern at low frequency RNS in Lambert Eaton myasthenic syndrome was reported to be usually different from that in MG (67, 68). The use of concentric needle in SFEMG was established (69). A very useful progress was the formation of guidelines (70, 71).

b. Immunological and genetic investigations

One of the most important developments in this period was the discovery of anti-MuSK antibodies (72). The unique clinical-immunological features of MuSK MG including severe progression, poor response to anticholinesterases, possible resistance to treatment with conventional immunosuppressives and unresponsiveness to thymectomy were noted (2, 73, 74). Different from anti-AChR positive MG, antibodies in MuSK MG were predominantly in the IgG4 subclass. Although their clinical relevance was not as clear as that of MuSK antibodies, new antibodies including anti-titin, anti-ryanodin (75) and anti-LRP4 (76) were detected.

Genetic investigations revealed new associations between MG subgroups and HLA (77, 78). A distinct association was reported between MuSK MG and HLA (79, 80).

Immunological investigations on T and B cells as well as the thymus is continuing in selected laboratories in several countries. The details of these investigations are beyond the scope of this review.

c. Treatment

Videothoracoscopic thymectomy

A very important progress was videothoracoscopic thymectomy which markedly reduced the morbidity and almost eliminated mortality associated with the surgery. Thoracoscopic surgery for anterior

mediastinal masses had first been performed in 1993 (81). It began to be widely used in MG after the beginning of the 2000's (82).

Clinical trials and new treatment options

In the 1990's, relatively more scientific single center prospective studies replaced the retrospective studies of previous years. Cyclosporine was evaluated with a randomized, placebo-controlled, double blind study (83) and was started to be used in some centers due to the partly positive results. A small trial showed that azathioprine added to corticosteroids was more effective than corticosteroids alone (84). Trials with IVIg and plasma exchange were performed (85).

New scales to be used in MG played important roles for later clinical trials (86). Kermit Osserman's 'Osserman classification' was abandoned and MG Foundation of America (MGFA) scoring, MGFA Postintervention Status (MGFA PIS) (87) and MG Activities of Daily Living (MG ADL) (88) were developed. Quantitative MG (QMG) scale (89) was tested for reliability (90). An easier to use MG-Composite scale (91) was derived from QMG and MG ADL.

According to Kaminski (92), the turning point for clinical trials was the two studies on mycophenolate mofetil. These were multicenter, randomized, double blind phase 3 studies (93, 94). The negative results of these trials disclosed the difficulties of evaluating MG with clinical trials. Corticosteroids which had to be used ethically in both groups were effective even at low doses and had probably masked the effect of the new drug. Included among possible reasons for the negative results were the short study period and the inefficiency of clinical outcome measures (95). This situation necessitated resorting to 'expert opinion' to show that mycophenolate mofetil can be beneficial (96). A clinical trial of methotrexate with negative results was considered to have a similar fate (97). Differing results were obtained from clinical trials on tacrolimus (98).

Although several studies had shown the beneficial effect of thymectomy, John Newsom-Davis (Oxford) realized that its widespread acceptance would not be possible without a clinical trial and pioneered a Phase 3 clinical trial on thymectomy (99). Positive results of the study were relieving for many pro-thymectomy myasthenia experts who were scared that the trial would have the same fate as that of mycophenolate mofetil.

An important drug which was started to be used in MG was rituximab (100). It was reported to be very effective, particularly in MuSK MG. Since a phase 3 trial could not be done in MuSK MG because of its rarity, it was evaluated with a novel method where an international group of specialists compared blindly the clinical data of patients who had received rituximab with those who had not, using well-defined criteria (101). Rituximab was found to be beneficial in MuSK MG (Class IV evidence). Since it was not possible to use a quantitative scale in this study, MGST 1 (Myasthenia Gravis Status and Treatment Intensity) scale, a modified MGFA PIS which also took into account the immunosuppressive dose, was used. A phase 3 trial with negative results was with a complement inhibitor, eculizumab, to evaluate its effect on anti-AChR positive MG (102).

The difficulties of clinical trials in MG became evident because of problems in finding suitable patients, the strong effect of corticosteroids and the insufficiencies of the scales in use. It is to be expected that in the future, utmost care will be given when starting clinical trials, and of necessity, studies with novel methods such as that in rituximab will be planned. At present, importance is laid on developing guidelines for management and treatment (103, 104). It can be predicted that future guidelines will be prepared more carefully with stricter criteria (105).

Looking at the history of MG, we realize that knowledge was accumulated very slowly, that new discoveries were only possible in the light of previous ones, and that progress was achieved by the interaction of different disciplines. The most important factors, no doubt, were industrious and inquisitive people, the names of all of whom could not be listed in this review: Neurologists who did sharp clinical observations, pathologists-pharmacologists-physiologists who did meticulous studies to support these observations, and surgeons who took keen interest in the disease. The importance given to basic sciences and the means provided to do research made a lot of discoveries possible. In addition, characteristics including courage to think critically, to be able to put forth new hypotheses, perseverance and motivation to struggle for one's beliefs all contributed to the progress. The concentration of a lot of patients in single centers gave the opportunity to investigate the disease in detail. Ample publication of the experiences in journals, and presentations-discussions in meetings helped to disseminate the knowledge accumulated.

We cannot overlook 'presents of nature' such as the snake venom and the electrical eel (106) as well as serendipity and chance. EAMG was serendipitously discovered in an experiment done for a different purpose. If the toxic physostigmine administered by Walker had caused the loss of the patient by bad chance, or the initial thymectomies had been unsuccessful, there would be no motivation to continue with these treatments and many years might have gone by before new attempts were made.

Has the story ended? Has the culprit in the detective story been caught? Not yet! The association between thymus and MG has not been elucidated. There is a long way to go in order to enlighten the immunological mechanisms. The biggest mystery has yet to be solved: What causes MG?

MG EXPERIENCE OF ISTANBUL UNIVERSITY

Istanbul University (IU) and Coşkun Özdemir, a professor from the Department of Neurology of IU Istanbul Faculty of Medicine (IFM), have pioneered in the establishment of the diagnosis and treatment of MG in Turkey. Özdemir's interest in MG, supported by his chief, Şükrü Hazım Tiner, goes back to the beginning of the 1950's when he was working at the Neurology Clinic of Haseki Hospital. This interest continued since then and he played a very important and inspiring role in the progress of MG in Turkey, in both clinical and immunological fields. After prostigmine was started to be used in MG, his first patient with a thymoma who was operated in 1954 expired. Following this unfortunate event, Özdemir sent a young woman to Şevket Tuncel from IU for thymectomy, the operation was very successful, the patient continues to live and is still in good condition. However, due to the poor results of two of the three ensuing patients, he decided that thymectomy should not be done without effective ICU's. When Istanbul Cardiac and Thoracic Surgery Hospital (today's Dr. Siyami Ersek Cardiothoracic and Vascular Surgery Training and Research Hospital) was established in 1962, Özdemir began to send his patients to this hospital with an ICU and patients were no longer lost during surgery.

Here, we need to mention a noteworthy endeavour. In 1959-1960, to follow-up with investigations to find a curare-like substance in MG, Özdemir together with Alaeddin Akçasu from the Pharmacology Department in IU, did an experiment which was important at that time: MG serum was added to the Tyrode's solution of an isolated phrenic nerve-diaphragm preparation from mice and the presence of decrement in the diaphragm was searched for after stimulating the nerve electrically. This procedure was repeated in eight patients and decrement was observed in six of them. Thus, an agent inhibiting the neuromuscular transmission in MG serum was confirmed.

After 1970, ICU was established in IU IFM by Cemalettin Öner. Özdemir who was now in the staff of IU had his patients operated in IFM by the group of Cemil Barlas from the Department of Chest Heart and Vascular Surgery. At this time, IU IFM had become the most important center for MG. Videothoracoscopic thymectomy was started in 2002 by Alper Toker, supported by Göksel Kalaycı, both professors from the Department of Thoracic Surgery at IU IFM.

As for medical therapy, pyridostigmine was introduced to Turkey to be widely available through Coşkun Özdemir's efforts in 1958; prostigmine was already in use since 1954. Corticosteroids were started to be used in 1974 and azathioprine in 1987. The ICU in IFM has much improved over the years and has become one of the best centers for MG patients. MG continues to be an area of main interest for the Neuromuscular Unit of IFM Neurology Department.

Electromyography at IU was started by Aynur Baslo, a professor from IFM Neurology Department. Anti-AChR antibodies were started to be tested in 1995 and anti-MuSK antibodies in 2003 in the laboratory of Güher Saruhan-Direskeneli, an immunologist in the Physiology Department of IU IFM. Research and investigations on MG are continuing by the group of Saruhan-Direskeneli in collaboration with the Neuromuscular Unit of IFM Neurology Department. Erdem Tüzün from Aziz Sancar Institute of Experimental Medicine, IU, also does research on MG, particularly experimenting on animals.

There is no doubt that a lot of people including residents, specialists and staff from the departments of Neurology, Thoracic Surgery, Anesthesiology and Reanimation, Pulmonary Diseases and Physiology spent a lot of effort over the years for MG. Enumerating their names requires making a very long list. I only gave the names of people who were pioneers in a certain area, either in Turkey or in IU. Although the focus of this section is IU, it has to be strongly emphasized that MG is now managed successfully and is an area of interest in many universities and hospitals throughout Turkey.

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