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REVIEW

Myasthenia gravis and the thymus gland. A historical review

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Abstract The first report of an association between myasthenia gravis (MG) and the thymus gland was in 1901. Although the underlying mechanisms are uncertain, thymic abnormalities are clearly associated with MG. This review article summarises, from a historical point of view, our knowledge of these associations, and the surgical and medical treatment of MG, including symptom management, immunosuppression, intravenous immunoglobulin and plasmapheresis.

Keywords History of medicine · Myasthenia gravis · Thymus gland

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The link between myasthenia gravis and thymus gland

The first indication of an association between myasthenia gravis (MG) and the thymus gland was in 1901, when the German neurologist Hermann Oppenheim reported a tumour found in the thymic remnant at necropsy in a myasthenic patient. Although the underlying mechanisms are uncertain, thymic abnormalities are clearly associated with MG: 10–20% of patients with MG also have thymic tumours, and about 70% have follicular hyperplasia, sometimes even in the involuted thymic tissue in older subjects. This indicates an active immune response, which is thought to be induced by antibodies against myoid cells. The myoid cells are significantly more numerous in the thymus of patients with MG than in normal conditions. Their thymic tissue contains all the elements that are necessary for the development of MG: besides myoid cells that express the target acetylcholine receptor (AChR), there are antigen-presenting cells, T and B cells. The pathogenesis of MG was demonstrated in an elegant experiment; when implanted into immunodeficient mice, MG thymic tissue induced the formation of antibodies against AChR in the recipients [1].

MG and thymoma

The association between MG and thymoma is well known; usually, patients with thymoma have more severe clinical symptoms, higher levels of AChR antibodies and more severe electromyographic abnormalities than those without.

Carl Weigert (1845–1904), a German pathologist and histologist, in a paper published in 1901, noticed the association between MG and a thymic mass in a patient who

died one year after the diagnosis of MG [2]. The thymic tumour was of lympho-epithelial type, adherent to the pericardium, and he hypothesised that thymoma might be related to the MG. It was the first report of an association between a thymic tumour and a muscle disorder. An association between MG and mediastinal tumours was also reported by other authors: Oppenheim and Goldflam mentioned cases with malignant lymphoma of the mediastinum; in 1904 Link reported infiltrates with round cells into the thymus, and Buzzard (1905) noticed a metastasis [3]. These tumours were thought to be coincidental, with no proofs of any links with MG, except for the thymoma.

In a case report from 1939, Blalock et al. showed beneficial effects of thymectomy in a patient with a tumour of the thymus associated with MG but later these proved not to be typical [4].

Surgical treatment of MG with thymus involvement: from Sauerbruch to Blalock

Though still controversial, thymectomy is one important arm of the treatment of patients with MG, especially for those with onset before age 40 years and those with associated thymomas. Usually, it is performed in one of two ways: by trans-sternal or trans-cervical approaches. Remissions after thymectomy are unusual in thymoma patients: however, in some MG patients, temporary or permanent remissions may be observed, leading to the complete elimination of symptoms without medication. Such remissions are not expected immediately after surgery, but the improvement of muscle function may last for months or years. In most cases, symptoms of MG and quality of life can be controlled with a combination of procedures, including thymectomy.

Thymectomy is not a new treatment for MG; it was first performed almost 100 years ago, by the German surgeon Sauerbruch. Ernst Ferdinand Sauerbruch was born in Bremen (Germany), in 1875. He studied medicine in Marburg, Greifswald, Jena and also Leipzig, where he graduated in 1902. In 1903, in Breslau, he developed a low-pressure chamber for operating on the open thorax, which enabled him to introduce many advances in the surgery of the lung (e.g., the two-stage thoracoplasty, lung resections). However, he used the trans-cervical approach for his first documented thymectomy in 1911, in Zurich. He was extremely inventive; in response to soldiers' wounds in World War I, he designed "the Sauerbruch hand", an artificial limb controlled by the muscles of the amputated stump. During World War II he was appointed Surgeon-General of the Armed Forces. In the last years of his life he became insane and aggressive towards patients, and died on 2 July 1951, in Berlin, one day before his 76th birthday. In the first half of the 20th century, there were probably very few individuals who so decisively influenced the progress of surgery. His masterwork, Surgery of the Organs of the Chest (1920–1925), was the first to treat this subject systematically and it laid the foundations for future development in the field.

Although the first thymectomy was performed by Sauerbruch, only 20 years later the anatomical basis for the surgical technique was described by Alfred Blalock. In 1936, Blalock performed a trans-sternal total thymectomy for a thymoma associated with severe MG. The patient's MG improved markedly for several years [3]. Blalock and associates then reported a series of patients with MG who were successfully treated by thymectomy [4, 5]. In a few years, he had accumulated 20 patients, and firmly established the role and place of thymectomy in the treatment of these patients [6]. In 1939, Blalock reported a positive clinical response in patients with MG with or without thymoma, after thymectomy.

By 1954, Keynes had done over 200 thymectomies for MG. Brother of the famous economist, he was the first to point out that, although thymomas need to be removed to prevent spread, the MG responds poorly to surgery in this subgroup (if at all), which initially created some confusion and much controversy. The MG apparently responds much better in the young patients without thymoma, and has routinely been treated by thymectomy since the 1940s. Many patients show some improvement 6–12 months afterwards; most European specialists believe that their MG remits in 25%, improves in another 50% and is unchanged in 25%, though that is still debated. The exact mechanism by which thymectomy might improve the symptoms of MG is not completely understood, but it may interrupt pathogenetic events in the hyperplastic thymus.

An alternative to the trans-sternal approach used by Blalock is the trans-cervical approach, introduced by Kark and Papatestas [7].

Medical treatment of MG with thymus involvement

Nowadays, the treatment of MG includes symptom management, immunosuppression, intravenous immunoglobulin and plasmapheresis. For controlling symptoms, the efficacy of pyridostigmine is well known because it is a cholinesterase inhibitor that acts at the neuro-muscular junction. The history of this type of drug goes back to the 1930s, in London, when it superseded another recently introduced drug, ephedrine.

Ephedrine came into use for the medical treatment of MG entirely by chance. Harriet Isabel Edgeworth, an American biochemist, suffered from MG. In 1925 she was hospitalised for the first time, and the diagnosis of MG was confirmed. Her MG deteriorated, but in the summer of 1929 she took tablets containing ephedrine for a different purpose. In the following years, she tested ephedrine in

clinical trials and showed that it was effective in the treatment of MG [8]. Her report was followed up by the American surgeon Walter Meredith Boothby (1880–1953), from the Mayo Clinic, who introduced aminoacetic acid in the treatment of MG, together with ephedrine, in 1932 [9].

Mary Broadfoot Walker (1888–1974), a medical assistant at St. Alfege's Hospital in London, first introduced physostigmine (a forerunner to pyridostigmine (Mestinon) and neostigmine) in the treatment of MG in 1934, in a 56-year-old woman. In the article published in *Lancet* of 2 June, she wrote: "treatment with hypodermic injections of physostigmine salicylate, gr. 1/69, once a day was begun. In from half an hour after the injection the left eyelid goes up, arm movements are much stronger, the jaw drops rather less, swallowing is improved, and the patient feels less heavy… I think that this effect of physostigmine on myasthenia gravis is important, though it is only temporary…It supports the opinion that fatiguability is due to poisoning of the motor end-organs, or myoneural junctions…" [10].

Mary Walker's report on physostigmine for MG was ignored at that time, and one year later her demonstration of the beneficial effect of neostigmine was viewed with scepticism, because of the rapidity with the patient's symptoms of myasthenia improved. She finally demonstrated the efficacy of this drug in 1938, and others soon confirmed her results. The remarkable improvement of symptoms using these drugs was hailed as the "miracle of St. Alfege's Hospital". She also described a clinical sign, known as the "Mary Walker effect": the patient exercises the forearm with a tourniquet applied at the elbow, inflated at 200 mmHg; it is released when the patient tires and partial ptosis develops a few minutes later.

Besides the above reports, it must be noted that neostigmine was already introduced into treatment by Lazar Reman in 1932, and published in the *Deutsche Zeitschrift fur Nervenheilkunde* [11]. The ground-breaking contribution of Mary Walker consisted in offering not only a symptomatic treatment for MG, but also in providing convincing evidence that the neuromuscular junction was the focus of the disease [12]. "Mary Walker had made one of those few therapeutic discoveries for a specific disorder, like finding the key for a locked gate" [13]. Soon afterwards (1936), the work of Henry Dale (1875–1968) complemented her findings. He identified acetylcholine as the key neuromuscular transmitter and showed that it is then destroyed by cholinesterase. The practical application came in the recognition of physostigmine, and related drugs, that block the destruction of acetylcholine so that it accumulates and has a better chance of triggering AchR-deficient muscles, as in MG.

In 1960, another Scot, John Simpson, noticed the frequent association between MG and other presumed autoimmune diseases in both the patients and their families. He postulated at that time that MG is the effect of some autoimmune attack on the motor endplate [14]. As the neuromuscular junction was known to be the key target in MG, many researchers next focussed on the pre- or post-synaptic defects. Simultaneously, work from Johns Hopkins University and the Salk Institute [1] demonstrated the autoimmune nature of MG, conclusively confirming Simpson's prediction [15]. That paved the way for new medical treatment of MG, such as immunosuppression and depletion of the antibodies by plasma exchange or dilution by intravenous immunoglobulins. Simon first tried hormone therapy of MG with anterior pituitary extract in 1935, but without notable results. It was not until the 1960s that results of successful therapy with prednisone were reported by Kjaer. In the late 1970s, Johns and colleagues, from the University of Virginia, opened the doors to immunosuppressive therapy [16].

Concluding remarks

One symptomatic treatment of MG has been in use for more than 70 years: a surgical one became routine when thymectomy was introduced by Blalock in the 1940s, and has apparently helped many patients since then. An alternative to this trans-sternal approach by Blalock is the trans-cervical approach, introduced by Karl and Papatestas [7]. Video-assisted thoracoscopic thymectomy (VATS) was developed and first reported 10 years ago by Mack et al. [17] for patients with MG, but is not yet widely applied. The growing interest in minimally invasive surgical techniques in the last decade has led to the recently introduced robotic thymectomy, which was first reported by Ashton et al. [18] and Rea et al. [19].

Several promising strategies for future treatments of MG have already been invented: they target the antigen-specific B cells and $CD4^+$ T cells, treatments that interfere with co-stimulation by antigen presenting cells, or interfere with cytokine functions and depress autoimmune response. New alternatives are sure to emerge from forthcoming advances in autoimmune diseases and animal models.

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