Editorial

Thymectomy for myasthenia gravis: what we know and what we don't

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In August 2016, the NEJM published the results of the MGTX prospective multicenter randomized trial comparing extended trans-sternal thymectomy and prednisone versus prednisone without surgery as primary treatment for myasthenia gravis (1). A total of 126 patients ranging in age from 18 to 65 years were randomized over 6 years at 36 sites. The thymectomy arm was statistically superior for both improved symptoms (as evidenced by a time-weighted average Quantitative Myasthenia score and less hospitalizations for exacerbations) and lower dose of both prednisone and azathioprine. This trial is of historic interest due to the accomplishment of completing such a trial in MG. It is also of interest due to the additional insight that it provides in regards to the contribution of surgery to treat a systemic disease.

The historical development of thymectomy as an accepted treatment for MG was nicely summarized by Sambrook *et al.* in 1976 (2). The relationship of Myasthenia Gravis to a thymic tumor was first made by Weigert in 1901 (3). Schumacher and Roth reported a myasthenic patient had symptomatic improvement following thymectomy for an enlarged but non-neoplastic gland by the illustrious Sauerbrach in 1911 (4). Two other patients treated with thymectomy by Sauerbrach died of infections (5). In 1939, Blalock reported from Vanderbilt on the removal of a large cystic thymus for a 19 year old MG patient with near complete resolution of her symptoms (5). This was believed to be only the 5th operation in the world to remove a thymus specifically to influence MG. Dr. Ropper reminds us of Dr Ravitch's memory of Blalock's colleagues meeting in his office and deciding to offer thymectomy for MG whether or not gland enlargement was seen on lateral chest X-rays (6,7). In view of the subsequent link of Blalock's name to thymectomy for MG, it is interesting to note that his operation was performed through a partial sternotomy to the 3rd interspace (5).

Thymectomy for MG has not been universally accepted for several reasons: (I) the most obvious is the lack of understanding how removal of the thymus gland could produce a remission when lymphocytes remained in the bone marrow and nodes; (II) there were no prospective blinded randomized trials prior to the NEJM publication, and previous comparison studies were confounded by inconsistencies in the thymectomy versus medical management groups. For instance, surgical patients were frequently younger, more often women, and more likely to have severe symptoms (8); (III) spontaneous remissions of the disease were known to occur in Blalock's time (5), and may occur in 10–20% of patients treated without surgery (9). Probability of remission after transcervical thymectomy increased as a function of time, up to 5 years or more (10). Few operations require 5 years to achieve maximal benefit. Was this surgical effect or natural burn-out of the disease?

Partly fueled by these scientific confounders, the surgical community broke into distinct camps based on surgical approach. Dr. Alfred Jaretzki became a vocal champion of trans-sternal extended thymectomy, removing all mediastinal fat from diaphragm to neck and from phrenic nerve to phrenic nerve through a full-length median sternotomy (11). The advantage was removal of the maximum amount of thymic tissue, including microscopic thymic rests in the peri-thymic fat left over from the migration of the gland into the mediastinum in utero. The clear disadvantage was the sternotomy. Other techniques included (I) partial sternotomy through the manubrium and

upper body of the sternum to the 3rd interspace; (II) trans-cervical thymectomy with a collar incision and no division of bone; (III) VATS thymectomy from left, right or both pleural spaces with no bone division; and (IV) most recently robotic thymectomy.

The design of the MGTX trial grew out of this background. The strengths of the trial include building consensus for a standard approach and the extensive quality assurance built into the design. Trans-sternal extended thymectomy was chosen to be the only acceptable surgical approach, because it provided the maximal removal of thymic tissue and thymic rests. Participating surgeons had to view a video of the procedure and pass a certification quiz. All investigators had to attend training and achieve certification. Patients were provided neck high clothing to hide whether or not they had a sternotomy during long-term assessments.

The challenges of the trial included difficulty recruiting and the semi-quantitative nature of the data. It is hard to recruit to a surgical trail with such a difference in the two treatments and 105 of the 231 eligible patients declined to participate (1). Explaining to a patient that they will be randomized between a full sternotomy or medication because you don't know which treatment is better is a challenging conversation. Since both treatment arms are readily available, the patient may feel free to choose medication outside the trial. If the patient sitting next to you in the neurologist's waiting area is telling you how wonderful their minimally-invasive thymectomy was, you may choose a surgical option outside the trial. The trial accrued slowly and eligibility criteria were revised to stimulate accrual, but it did accrue. The Quantitative Myasthenia Gravis score was a scale from 0 to 39, based on a measure of 13 individual measures of strength. The ability to detect a change was thus based on the uniformity of scoring across multiple centers and the time weighted average.

So, what can we tell our patients about the specific value of thymectomy for MG? This trial has clearly shown that patients can expect a reasonable probability that doses of medication will reduce with a third less prednisone, and that symptoms on average will be less severe. They can expect fewer hospitalizations for exacerbations of their disease. Most importantly, they have a 67% chance of achieving minimal manifestation status within a year after thymectomy, as compared to a 37% chance after a year or a 47% chance after 3 years of medical therapy.

Are these important enough endpoints? If we had MG, would we choose to have a thymectomy? Yes. We are willing to accept recovery from a sternotomy for the probable reduction to a third less prednisone, milder symptoms, fewer hospitalizations for exacerbations, and a two thirds chance of having minimal symptoms within 1 year, and having that sustained over the next 3 years. Furthermore, we believe the greatest contribution of this randomized multicenter prospective trial is "proof of principle." The MGTX trial provides us conclusive evidence that an extended thymectomy does, indeed, provide important improvements in the quality of life of MG patients.

The most important remaining question is whether or not other surgical techniques do, as well? We have witnessed a remarkable revolution in the surgical approach to the thymus, and we believe extended resections can be achieved by minimally invasive techniques. We do not think we have to be enslaved to only offering trans-sternal extended thymectomy to MG patients because that was the technique chosen in this trial. We believe it is unlikely that a repeat randomized prospective clinical trial will soon be concluded providing head-to-head comparisons of surgical techniques. The investigative techniques of the MGTX trial, however, provide us the ability to compare data from centers of excellence that champion these different surgical techniques. Finally, the MGTX trial also provides us benchmarks for comparison of other treatments, both surgical and medical.

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Footnote

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