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Effective Thymectomy in Autoimmune Myasthenia: When, Why and How?

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Myasthenia Gravis (MG) is an autoimmune disease mediated by antibodies against molecules of the neuromuscular junction, the main antigen being the acetylcholine receptor (AChR). The thymus in MG presents histological abnormalities such as follicular hyperplasia or thymoma. While thymectomy for thymoma patients is not disputable, whether thymectomy in patients without thymoma is of any clinical benefit has been questioned for many years. Many retrospective studies showed that thymectomy might be favorable, and several meta-analyses confirmed these assumptions [1] [2], but a randomized trial was really missing. The courage and the determination of late Professor Newsom-Davis have embarked many clinicians on such a challenging adventure with the organization of an international randomized clinical trial (MGTX) comparing thymectomy plus prednisone with prednisone alone. The study was performed across 36 academic medical centers in 15 countries. Happily, the controversy on this subject has finally found a definitive answer.

The first results were presented in Oxford in 2016 with immense suspense. Indeed, the opinions were very divided among the experts in MG disease, and many considered that the results would be blurred. However, the study clearly revealed after a three-year follow-up of patients that thymectomy improved clinical outcomes in patients with non-thymomatous MG [3]. Whether the beneficial effects of thymectomy continued over time has been addressed in the current issue of "The Lancet Neurology" [4]. At five years, the authors conclude that benefits conferred by thymectomy increase over the next two years. These findings are based on 1) the clinical status, 2) the prednisone requirement, 3) the percentage of patients reaching the Minimal Manifestation Status (MMS) and 4) the hospitalizations for disease exacerbations. These results show that thymectomy has long-term beneficial clinical effects.

The MGTX study has not yet published the potential associations between the thymus pathology, the level of anti-AChR antibodies and the improvement after thymectomy. However, it is known that the MG thymus commonly presents an increased production of inflammatory cytokines and chemokines leading to B cell recruitment and the development of ectopic germinal centers [5]. The production of anti-AChR antibodies by thymic B cells has been definitively demonstrated in a model of immunodeficient mice grafted with MG thymus and presenting MG symptoms, in which significant levels of human anti-AChR antibodies are detected in the sera of the mice [6]. Locally, the inflammatory cytokines affect the function of regulatory T cells [7]. Interestingly, type I and II interferon increase thymic expression of the AChR that could explain the link between thymic inflammation and the specific response to the AChR [8].

Corticosteroids result in a reduction in the number and size of germinal centers [9], and yet thymectomy plus prednisone is more effective than prednisone alone. These data suggest that thymic ablation allows the elimination of molecules and cells other than only germinal centers. It can

be hypothesized that the inflammatory molecules, such as cytokines or miRNAs, produced by the MG thymus, as well as the activated T cells contribute to the peripheral pathogenic mechanisms. In favor of this hypothesis, it was shown that thymectomy lowers the level of miR-150-5p [10]. It is also possible that inflammatory molecules influence the biological status of the muscle, hindering the compensatory mechanisms or increasing the pathogenicity of the antibodies. Whether thymectomy is more efficient than prednisone for the decline in the level of antibodies needs to be investigated.

The question of the age-limit for recommending thymectomy is an essential clinical issue for patients with MG. In their previous article, the authors showed that after 50 years, the beneficial effects of thymectomy are less striking than for younger patients [3]. In the manuscript published in this volume, the number of patients was too small to make the same analysis [4]. Since thymic hyperplasia is mainly found in young patients (under 50), it seems quite reasonable to propose the surgery to patients at high risk of thymic hyperplasia [9]. However, it will be important in the future to define more precisely the group of patients likely to respond to thymectomy to avoid surgery to patients unlikely to respond to this therapy. The investigation of the commonalities between the non-responders patients would be useful to address this point.

In conclusion, the work by Wolfe et al. clearly and definitively shows the favorable effect of thymectomy [4]. The surgery was performed by an extended transsternal approach to ensure total ablation of the gland. However, many surgical procedures are now available including thoracoscopic thymectomy that reduces hospitalization and scars, making these new interventions more popular nowadays.

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