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COMMENTARY

Thymectomy in myasthenia gravis: "The real world" experience beyond studies

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Myasthenia gravis (MG) is an autoimmune disorder caused by specific, most commonly acetylcholine receptor (AChR), antibodies, expressed at the neuromuscular junction. The thymus is affected in most patients with AChR+ MG; approximately 70% of patients have thymic follicular hyperplasia, 10% have thymoma and the remainder have either a normal or atrophic thymus [1].

The thymus gland is not only essential for T cell maturation and removal of self-reactive T cells (central tolerance) but is also believed to be the initial site for triggering humoral immunity in MG. Under physiological circumstances, B cells are almost non-existent in the thymus. However, in non-thymomatous MG, an initial inflammatory reaction characterized by the release of cytokines, particularly type I interferon and chemokines, leads to several associated immune processes including upregulation of thymic expression of AChR by both thymic epithelial cells and myoid cells; neogenesis; recruitment of immune cells to the thymus; and downregulation of regulatory T cells. This is followed by sensitization of AChRs and organization of B and T cells into germinal centers leading to the production of anti-AChR antibodies, thus turning the thymus into a tertiary lymphoid organ [2].

Whilst thymectomy is a standard indication for thymomatous MG, its role in non-thymomatous generalized MG was established in the MGTX trial and its 2-year extension which showed the superiority of thymectomy plus prednisone compared to prednisone alone [3, 4]. Although corticosteroid treatment reduces the number and size of germinal centers [5], the superiority of thymectomy + prednisone over prednisone alone in this trial implies that, in addition to germinal centers, thymectomy eliminates molecules and cells that may play a role in disease causation. The results from the MGTX trial provided the basis for the creation of the international consensus guidance statements for early thymectomy in non-thymomatous generalized MG, in subjects aged 18–50 years. The adoption of these guidance statements will probably improve clinical outcomes and not only minimize the requirement for immunotherapy but also the need for hospitalization for exacerbation of the disease [6].

Despite the positive results in the MGTX trial, several questions regarding the significance of additional factors remained, which preclude study [3, 4] of well-defined inclusion criteria needed in randomized clinical trials. In the retrospective single-center study published in this journal, Rath et al. [7] have attempted to address these concerns whilst transferring the issues to utility in a daily clinical setting. They investigated the rate of short-term and sustained clinical remission after thymectomy in 94 AChR+ MG patients (68% non-thymomatous). In addition, they examined the value of predictors of clinical remission together with changes in serum AChR antibody levels before and after thymectomy. They found that 28% of patients never went into clinical remission; 72% achieved initial remission lasting for at least 12 months, compared to 38%–72% success reported in previous reports. In contrast to a significantly reduced sustained remission rate seen in the MGTX extension trial, half of the patients with initial remission (32% of the whole cohort) eventually relapsed in the long-term follow-up of a median of 7 years and up to 28 years. No predictors of both short-term and sustained clinical remission were detected. In 24 patients who had not received immunosuppressive therapy before thymectomy, a high reduction rate of the AChR antibody titer in percent per day after surgery was associated with a higher chance of achieving initial remission.

Even though the report by Rath et al. [7] is from a small, single-center and retrospective study, it provides some useful practical information required for counseling and the informed consent process for thymectomy in MG. The following takeaway points could be gathered from this study.

1. Thymectomy in generalized MG is not a cure. The benefit is not immediate and may not be sustained, potentially requiring the use of long-term immunosuppressive medications even after thymectomy, perhaps in a smaller dose. The latter point could be explained by the peripheral spread of the autoimmune process from the thymus to the peripheral secondary lymphoid organs, which then contribute to continuous disease activity even after thymectomy [2].
2. Compared to the extended trans-sternal approach to ensure total thymus ablation employed in the MGTX trial, the study by Rath et al. [7] confirms the efficacy of minimally invasive, particularly robotic, thymectomy as reported in some other studies [8].
3. The finding of a relative reduction of AChR antibodies after thymectomy, once confirmed in future prospective studies, might serve as a biomarker for tailored treatment of MG patients.
4. Due to the heterogeneous nature of the disease, and the different pathophysiological mechanisms in MG, clinical and demographic factors might not be helpful to predict outcomes after thymectomy. MicroRNAs (miRNAs) are short, endogenous, non-coding RNA molecules that mediate post-transcriptional gene silencing and are dysregulated in several autoimmune disorders. Specific miRNA profiles have been identified after thymectomy in MG subtypes, such as the reduction of miR-150-5p, supporting their potential role as objective markers for mechanism-based personalized medicine [9].

AUTHOR CONTRIBUTIONS

Waqar Waheed: Conceptualization (lead); writing – original draft (lead). **Rup Tandan:** Writing – review and editing (lead).

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

No data availability statement applies.

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