

Additional work is needed to better understand the trajectories of cognitive function after transient ischaemic attack and stroke, including how the determinants of delayed-onset dementia (ie, dementia that manifests months or years from stroke) differ from those of immediate-onset dementia;² the mechanisms underlying the association between diabetes and dementia risk, and whether this risk can be modified by more intensive glycaemic control;⁹ and whether the risk of dementia in patients with atrial fibrillation can be lowered by oral anticoagulation (which would be expected as a result of the effects on stroke prevention). Finally, whether the risk of post-event dementia can be reduced by acute stroke therapy needs to be investigated. Secondary analyses from the REVASCAT trial suggest that endovascular treatment in patients with anterior circulation proximal arterial occlusion improves cognitive outcomes, particularly in patients with good functional outcomes.¹⁰

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Thymectomy in myasthenia gravis: when, why, and how?

Myasthenia gravis is an autoimmune disease mediated by antibodies against proteins expressed in the neuromuscular junction; the main antigen is the acetylcholine receptor. In patients with myasthenia gravis, the thymus can have histological abnormalities, such as follicular hyperplasia or thymoma. Although thymectomy is standard treatment for patients with myasthenia gravis who have thymoma, whether the procedure is of any clinical benefit in patients without thymoma has been questioned for more than 40 years. Many retrospective studies showed that thymectomy might be clinically beneficial, and several meta-analyses supported these findings,^{1,2} but a randomised clinical trial was needed. Prof Newsom-Davis (1932–2007), with courage and determination, was able to promote the organisation of an international randomised clinical trial to compare thymectomy plus prednisone with prednisone alone in patients with non-thymomatous myasthenia

gravis. The results of the Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone (MGTX) were eagerly anticipated, and were first discussed at the MGTX Conference in Oxford, UK, in 2016. The study clearly showed that, after follow-up of 3 years, thymectomy plus prednisone significantly improved clinical outcomes compared with prednisone alone in patients with non-thymomatous myasthenia gravis.³ In *The Lancet Neurology*, Gil I Wolfe and colleagues⁴ now report the results of the two-year extension phase of MGTX, bringing the total follow-up to 5 years. The authors concluded that the benefits conferred by thymectomy plus prednisone, compared with prednisone alone, were still apparent after the 2 years of the extension study. This conclusion was reached on the basis of reductions in mean Quantitative Myasthenia Gravis scores (5.47 [SD 3.87] vs 9.34 [5.08]; $p=0.0007$) and alternate-day prednisone doses (24 mg [SD 21



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vs 48 mg [29]; $p=0.0002$), and an increased proportion of patients reaching the minimal manifestation status (23 [88%] of 26 vs 14 [58%] of 24). These results show that thymectomy has long-term beneficial clinical effects.

However, the potential associations between thymus pathology, concentrations of anti-acetylcholine receptor antibodies, and clinical improvement after thymectomy need further investigation. In patients with myasthenia gravis, thymus pathology commonly causes increased production of inflammatory cytokines and chemokines, leading to B-cell recruitment and the development of ectopic germinal centres.⁵ The production of anti-acetylcholine receptor antibodies by thymic B cells has been shown in a mouse model of immunodeficiency grafted with human myasthenia gravis thymuses. Half of these animals developed myasthenia gravis symptoms, whereby significant concentrations of human anti-acetylcholine receptor antibodies were detected in their sera.⁶ Locally, the inflammatory cytokines affect the function of regulatory T cells.⁷ Type I and II interferon increase thymic expression of acetylcholine receptors in human thymic epithelial cells, which could explain the link between thymic inflammation and the specific autoimmune response to acetylcholine receptors.⁸

Corticosteroid treatment results in a reduction in the number and size of germinal centres,⁹ yet thymectomy plus prednisone was more effective than prednisone alone in MGTX³ and its extension study.⁴ These data suggest that thymic ablation also eliminates molecules and cells with potential roles in disease production other than those in germinal centres. It can be hypothesised that, in addition to activated T cells, inflammatory molecules such as cytokines or miRNAs produced by the thymus contribute to peripheral pathogenic mechanisms in myasthenia gravis. The fact that thymectomy lowers concentrations of miR-150-5p lends support to this hypothesis.¹⁰ Inflammatory molecules could also affect the biological status of muscle by hindering the compensatory mechanisms or increasing the pathogenicity of anti-acetylcholine receptor antibodies. Whether thymectomy is more efficacious than prednisone for the reduction of anti-acetylcholine receptor antibody concentrations should be investigated.

The age limit for thymectomy is an essential clinical issue in the treatment of patients with myasthenia gravis. In MGTX,³ Wolfe and colleagues reported that

the beneficial effects of thymectomy were less striking in patients older than 50 years than in younger patients. In the extension study,⁴ however, the number of patients was too small to allow for such analysis. Because thymic hyperplasia mainly occurs in patients younger than 50 years, it seems reasonable to propose thymectomy for patients at high risk of thymic hyperplasia.⁹ However, more precise definition of the group of patients most likely to respond to thymectomy will be important to avoid use of this procedure in those who are unlikely to benefit. Investigation of commonalities in non-responders would be useful to address this point.

Overall, Wolfe and colleagues' work clearly and definitively shows the beneficial effects of thymectomy plus prednisone versus prednisone alone.⁴ Thymectomy was done by an extended transsternal approach to ensure total ablation of the gland. However, many other surgical procedures are now available, including thoracoscopic thymectomy, which reduces hospitalisation and scars, making these new interventions more popular nowadays.

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