Review Article

Physiological and pathological roles of the thymus and value of thymectomy in myasthenia gravis: a narrative review

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Contributions: (I) Conception and design: W Waheed, R Tandan; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Myasthenia gravis (MG) is a well-elucidated autoimmune disorder affecting the neuromuscular junction. Given the relationship between MG and thymic pathologies, with T cell and antibody-mediated pathogenesis, surgical (i.e., thymectomy) and non-surgical approaches remain a mainstay of management of the disease. This review seeks to outline the involvement of the thymus in the development of lymphocytes leading to MG.

Methods: Different databases were searched exploring the role of thymectomy in treatment and outcomes in various MG patient subpopulations, including in ocular versus generalized disease, different age groups, and antibody status.

Key Content and Findings: Overall, the findings of multiple studies and reviews provide evidence to support the efficacy and long-term success of thymectomy in the management of MG; outcomes have included remission status, symptom severity, and need for adjunctive therapy. However, the heterogeneity in the MG population suggests that there are multiple factors that may confound the results of thymectomy and still need further examination. Separately, other autoimmune diseases develop following thymectomy, and further research is required to elucidate this susceptibility. Finally, our review will discuss the different surgical approaches for thymectomy, including their advantages, limitations, and perioperative complications.

Conclusions: Overall, in light of the known pathogenesis and association of the thymus with MG, thymectomy remains an extremely effective approach for long-term management and improved clinical outcomes.

Keywords: Myasthenia gravis (MG); T cell development; thymic pathologies; thymectomy

Received: 26 September 2023; Accepted: 15 January 2024; Published online: 21 May 2024.
doi: 10.21037/med-23-43
View this article at: https://dx.doi.org/10.21037/med-23-43

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Introduction

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction (NMJ), with prevalence rates for acetylcholine receptor (AChR) MG and muscle-specific kinase (MuSK) MG ranging from 70 to 163 per million, and 1.9 to 2.9 per million, respectively. Although MG can occur at any age, there is a bimodal distribution in terms of age and gender predominance, with an early peak in the second and third decades (female predominance) and a late peak in the sixth to eighth decades (male predominance) (1). The defining feature of MG is fatigable skeletal muscle weakness that primarily affects the ocular muscles, with a 2-year risk of progression to generalized weakness. Up to 20% of AChR+ MG patients develop myasthenic crises due to the involvement of the respiratory and bulbar muscles. The diagnosis is confirmed by the presence of known serum autoantibodies, characteristic findings on electrophysiological testing (single-fiber electromyography and repetitive nerve stimulation), and improvement of symptoms following the administration of acetylcholinesterase inhibitors or following the cold pack test (2).

Although MG is linked to a variety of thymic pathologies, there is scarcity of literature addressing its pathogenesis in relation to the various thymus abnormalities. Since the initial pivotal trial showed that thymectomy improves outcomes in non-thymomatous AChR+ MG patients (3), there have been numerous published studies to support this, which will be subsequently discussed in the "*Evidence supporting role of thymectomy in MG*" section. In this review, we examine the role of the thymus in T lymphocyte development and its significance in the pathophysiology of MG; review data supporting the relevance of thymectomy in MG; and address the practical management in relation to thymectomy. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-23-43/rc).

Methods

For this narrative review, we used the following keywords to search the Cochrane Central Register of Controlled Trials, EMBASE, LILACS, and PubMed from January 1900 to July 2023: "thymectomy", "myasthenia gravis", "non-thymomatous and thymomatous myasthenia gravis", "pathogenesis", "myasthenic crisis", "perioperative management", and "remission". See *Table 1* for search strategy summary.

T cell development during life

The body's immune system is akin to the defense system of a country. Comparable to well-trained soldiers, T cells in the immune system go through several stages during their development, maturation, and differentiation.

Origin of lymphoid cells and their early development and migration to the thymus (Figure 1)

The formation of the blastocyst from the zygote, created during the process of sperm and egg fertilization, marks the beginning of the origin of lymphoid cells. The inner cellular mass of the blastocyst is the source of totipotential stem cells, which are capable of self-renewal and differentiation into cells of all tissue lineages, i.e., developing into an entire organism. These include hematopoietic pluripotent stem cells that originate in the yolk sac, fetal liver, and bone marrow that differentiate into multipotent lymphoid progenitor cells (LPCs) and myeloid progenitor cells (MPCs) responsible for adaptive immunity, and innate immunity, respectively. B cell precursor-producing LPC remain in the bone marrow for continued development, whereas T cell precursors proceed to the thymus for maturation. T cells derive their name from the thymus. By 9 weeks of gestation, T cell progenitors are visible in the thymus in humans, and by 24 weeks, mature T cells are seen in the peripheral lymphoid organs.

Settlement in secondary lymphoid organs (Figure 1)

The thymus and bone marrow constitute the primary lymphoid structures responsible for the initial generation of T and B cells, respectively. Following their maturation, T cells leave the thymus and circulate through the blood to subsequently settle and segregate into distinct domains in secondary lymphoid tissues. These include lymph nodes, spleen, tonsils, and the aggregations of lymphoid tissue located in the gastrointestinal and respiratory tracts. On the other hand, tertiary lymphoid organs form in response to inflammatory, infectious, autoimmune, and neoplastic events (discussed in section "*Pathophysiology of MG*").

T cell activation and differentiation

Upon stimulation by an antigen that is presented by antigen-presenting cells (APCs) in secondary lymphoid organs, T cells enlarge and undergo rapid proliferation. Activated lymphocytes exit into the lymph to return to the

Table 1 Search strategy summary

Items	Specification
Date of search	July 1st–November 21st, 2023
Databases and other sources searched	Cochrane Central Register of Controlled Trials, EMBASE, LILACS, and PubMed
Search terms used	"thymectomy", "myasthenia gravis", "non-thymomatous and thymomatous myasthenia gravis", "pathogenesis", "myasthenic crisis", "perioperative management", and "remission"
Timeframe	Between January 1900 and July 2023
Inclusion and exclusion criteria	Inclusion: (I) English speaking articles; (II) article types: retrospective, prospective, randomized control trial, case-series, original research, meta-analyses, systematic review
	Exclusion: (I) non-English speaking articles; (II) articles with incomplete or irrelevant data
Selection process	W.W. conducted the literature search. All authors subsequently discussed and agreed on the literature selection

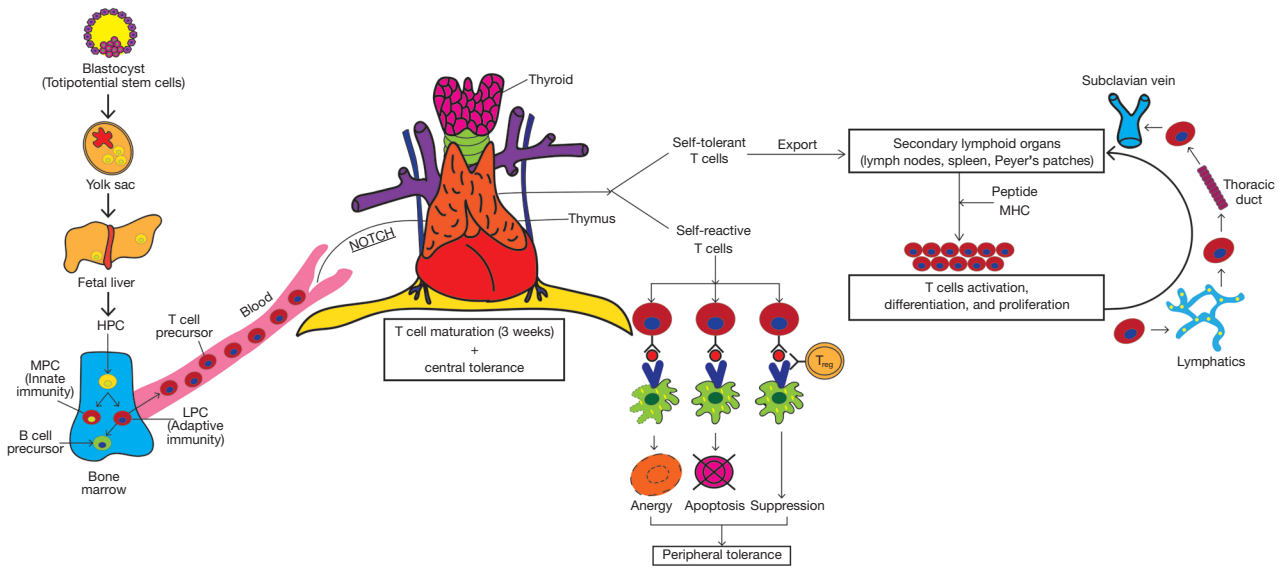

Figure 1 Journey of T cells. Hematopoietic pluripotent stem cells originating in the yolk sac, fetal liver, or bone marrow differentiate into T cell precursor-producing LPCs, which move to thymus for antigen independent T cells maturation. Naive T cells then migrate to secondary lymphoid organs for antigen dependent differentiation and activation. They then leave into the lymph and return to the blood via the thoracic duct. HPC, hemopoietic precursor cell; MPC, myeloid progenitor cell; LPC, lymphoid progenitor cell; MHC, major histocompatibility complex; Treg, regulatory T cell.

blood via the subclavian vein through the thoracic duct (4-6).

Thymus

Location

The thymus is a training school for T cells; it possesses a particular role within the lymphoid system and differs from other lymphoid structures both in structure and functionality. It is located within the superior mediastinum behind the sternum, above the heart, and extends up into the neck for a short distance.

Evolution of thymic weight

The thymus is relatively large at birth (weighs around 15 grams), and reaches its maximal size and weight of

35 to 40 grams at puberty. Thereafter, it regresses and is practically reduced to a vestige and largely replaced by fat (weighs 5 grams at age 70 years). This is reflected functionally by a reduction in thymopoiesis, which begins to decline after puberty and is minimal in most individuals >40 years of age (7).

Main cell types within the thymus

The main cell types found in the thymus are cortical and medullary thymic epithelial cells (TECs) which provide the milieu for T cell development; developing T cells called thymocytes; professional APCs that include macrophages and dendritic cells; and myoid cells. In contrast to TEC that display unfolded AChR, myoid cells are the only known cells, aside from skeletal muscle, to express AChR in its native folded form. Myoid cells also express additional important target autoantigens, such as ryanodine receptors (RYRs) and titin. Myoid cells also help in the development of tolerance by transferring muscle self-antigens to dendritic cells for cross-presentation to T cells because they are major histocompatibility complex (MHC)-II-negative. Under physiological circumstances, B cells are almost non-existent in the thymus (8).

Histology

The thymus is an encapsulated bilobed primary lymphoid organ in which each lobe is divided into multiple small lobules by trabecular connective tissue. The different regions within each lobule include subcapsular cortical, cortical, corticomedullary junction, and medulla. While epithelial cells are more noticeable in the less cellular medulla, the cortex is hypercellular and filled with developing T lymphocytes.

T cell maturation in the thymus (*Figure 2*)

T cell maturation occurs in the thymus and involves collaboration between thymocytes, TECs, and other stromal cells such as dendritic cells and myoid cells (9,10).

Thymic progenitor cells

T cell precursor-producing LPC enter the thymus through the circulation, passing through high endothelial venules (HEVs) located close to the corticomedullary junction, before moving to the outer cortex. These precursors sense cues in the thymus microenvironment that are capable of activating notch one receptor. Notch signaling induces a gene expression program that differentiates T cell precursor LPC into thymic progenitor cells. This represents the first stage in the development of T cells. Notch signaling is crucial for not only early commitment to the T cell lineage, but together with other factors also regulates subsequent steps in T cell development (11).

T cell receptor (TCR) development

Thymic progenitors within the thymus go through several stages of maturation that are distinguishable by the expression of several cell surface markers. The development of a working TCR is a crucial stage in T cell maturation. Ultimately, each mature T cell has a distinct TCR that responds to a random pattern, enabling the immune system to distinguish a variety of pathogens. The majority of cells in the thymus give rise to TCRs, which possess α and β chains termed αβ T cells; however, approximately 5% bear the γ and δ TCR and are γδ T cells.

Checkpoint no. 1: TCR β-chain selection for TCR diversity

The earliest developing thymocytes lack expression of the co-receptors CD4 and CD8 and are thus termed double negative (DN) cells. There are four DN stages (DN1–DN4) distinguishable by expression of cell surface markers, CD44 and CD25.

A pivotal checkpoint in mammalian α/β T cell development, termed beta selection, occurs at the DN3 stage. At this stage, the T cells upregulate the recombination activating genes (RAGs) RAG1 and RAG2 and test variable (V)/diversity (D)/joining (J) segments rearrangement of their TCR beta genes. The diversity of TCR, and their capacity to engage with a wide variety of peptides, are both the result of this rearrangement.

The primary goal of β selection is to test whether thymocytes express the functional TCR β chain. This is accomplished not by rearranging the TCR α chain, but by pairing it with a surrogate alpha chain called pre-T cell receptor alpha (pTα), to produce pre-TCR. The pre-TCR tests the functionality of the recombined candidate β chain by undergoing antigen-independent activation and signal transduction. Successful engagement of signaling results in arrest of further rearrangement of β chain loci, DN cell proliferation, and further differentiation by up-regulation and expression of CD4 and CD8, these cells are termed double positive (DP) cells. Cells that do not undergo beta-

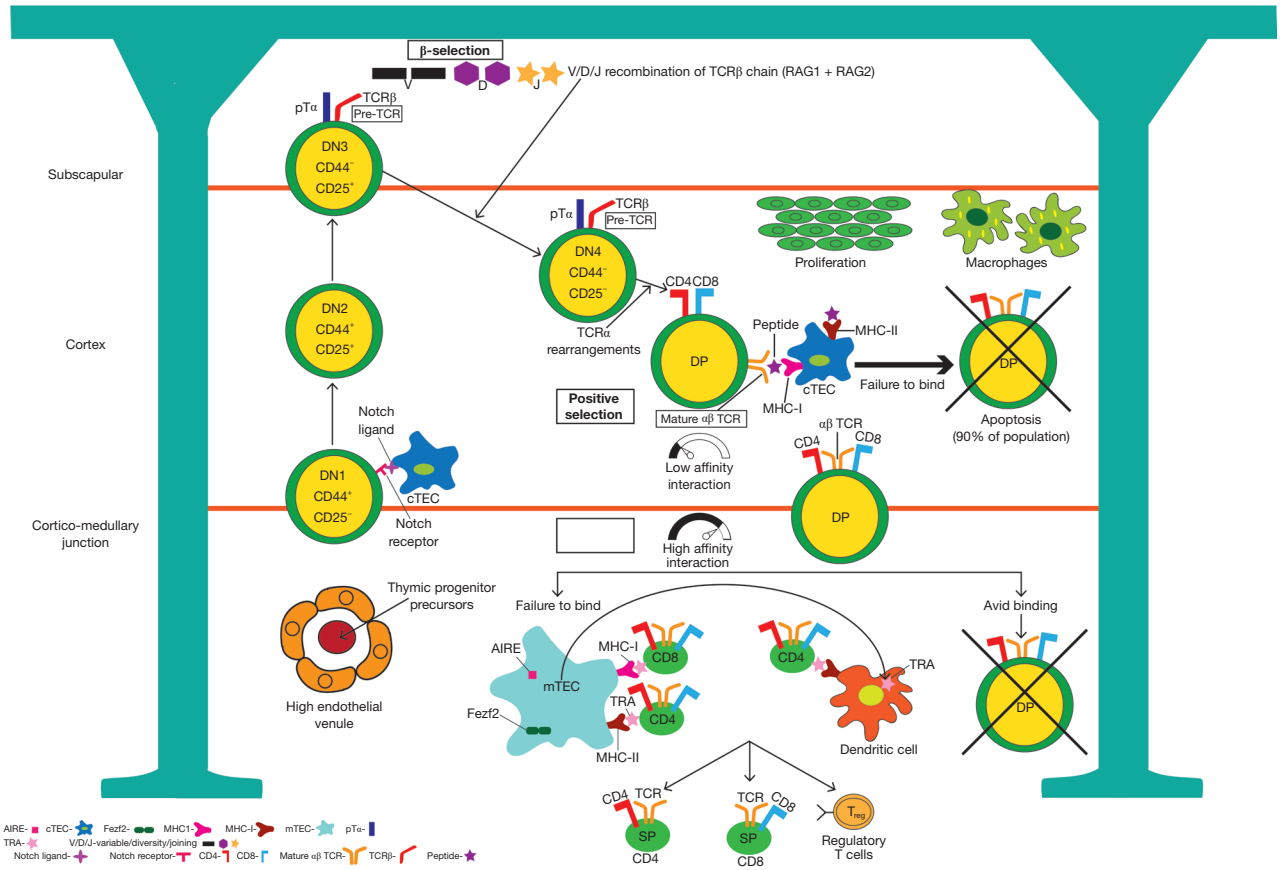

Figure 2 T cell development in thymus. Thymic progenitors within the thymus undergo different maturation phases that can be identified by the expression of several cell surface markers. After receiving Notch signaling from cTEC at the corticomedullary junction, DN thymocytes migrate outward in the thymic cortex. Positive selection occurs as DP thymocytes migrate back to the cortico-medullary interface and interact with MHC expressed on cTECs. Thymocytes that have been positively chosen move into the medulla. SP thymocytes are subjected to negative selection within the medulla by being evaluated for reactivity to tissue-restricted self-antigens expressed by mTECs or dendritic cells. Mature T cells leave the thymus through blood or lymph. pTα, pre-T cell receptor alpha; TCR, T cell receptor; V/D/J, variable/diversity/joining; RAG, recombination activating gene; DN, double negative; DP, double positive; cTEC, cortical thymic epithelial cells; MHC, major histocompatibility complex; AIRE, autoimmune regulator; mTEC, medullary thymic epithelial cell; Fezf2, forebrain embryonic zinc finger-like protein 2; TRA, tissue-restricted self-antigen; SP, single-positive; Treg, regulatory T cell.

selection die by apoptosis.

DP cells rearrange their TCR-α chain loci to produce a mature αβ-TCR. Subsequently, DP thymocytes test the functionality of the recombined α chain during two additional checkpoints of positive and negative selection to achieve signaling maturity.

Checkpoint no. 2: positive selection to promote development of foreign reactive T cells

Positive selection occurs in the cortex and determines whether V/J recombination of α chain pairs with β chain to produce a TCR that recognizes self-MHC, termed MHC restriction. TCR must bind to self-antigen-MHC expressed on cortical TECs with moderate affinity (confirming the ability to recognize self-MHC), but without a strong reaction to self-peptide. Only thymocytes that engage successfully with MHC will receive a vital "survival signal" and be able to respond to foreign antigens in a self-MHC-restricted manner. Thymocytes that do not react with MHC, representing 90% of the developing thymocytes, die from neglect.

Checkpoint no. 3: negative selection to eliminate self-reactive T cells

Thymocytes that survive positive selection are subjected to the final checkpoint of negative selection, which occurs in the thymic medulla and is supported by medullary TECs (mTECs) and dendritic cells. The purpose of negative selection is to remove TCR clones that recognize self-antigens, and constitutes the basis for central tolerance to prevent autoimmunity. Negative selection results from high-affinity interaction between developing T cells and self-peptides presented on MHC antigens (i.e., TCR recognizes self-peptide as well as MHC), compared to low-affinity interaction with self-peptide in positive selection. Negative selection is regulated by the transcription factor, autoimmune regulator (AIRE), which is expressed in the thymic medulla and controls the intrathymic expression of self-antigens. AIRE is down regulated by estrogen and upregulated by testosterone, possibly explaining the sex difference in the prevalence of young-onset MG. A new and crucial transcription factor in the negative selection process has recently been identified as the forebrain embryonic zinc finger-like protein 2 (Fezf2). Fezf2 regulates a large number of tissue-restricted antigens (TRAs); it is specifically expressed in mTECs and suppresses the initiation of an autoimmune response. With only limited overlap, Fezf2 and AIRE control the expression of various TRAs (12). Most autoreactive T cells are eliminated by apoptosis, but some differentiate into regulatory T cells (Tregs)—a process termed agonist selection.

Single positive T cells and thymic output

After negative selection, down-regulation of either co-receptors results in naive CD4 or CD8 single positive cells that leave the thymus and circulate in the periphery.

Peripheral tolerance (Figure 1)

T lymphocytes generated in the thymus are trained to be selective for a specific foreign antigen; self-reactive T cells are eliminated in the thymus via central tolerance. Self-reactive T cells that circumvent central tolerance are suppressed in the periphery (process termed peripheral tolerance) by several possible mechanisms: apoptosis, anergy (functional non-responsiveness due to lack of the co-stimulatory signal B7 on APCs), or by the action of Tregs, a subset of $CD4^+$ cells that are outsourced from the thymus gland.

Pathophysiology of MG

MG is an antibody-mediated disease with T cell driven immune pathogenesis and involves intricate interactions between $CD4^+$ T cells and B cells. Depending on the type of the underlying antibody present, the pathogenic mechanisms are further separated. Serum antibodies against the nicotinic AChR occur in 85% of patients, whereas antibodies against MuSK are found in 6% of patients. Seronegative MG accounts for less than 10% of patients, and refers to those who may have autoantibodies that are undetected by routine diagnostic tests for AChR and MuSK antibodies. Additional antibodies in this seronegative group, discovered utilizing cell-based assays, include those against low density lipoprotein receptor-related protein 4 (LRP4), agrin, collagen Q, titin, RYR, contactin, heat shock protein-70, matrix metalloproteinases, and voltage-gated potassium channel (Kv1.4); however, the pathogenic significance of these latter antibodies is still unknown (13).

Pathologic abnormalities in MG thymus

Heterogeneous findings in MG thymus include normal gland, thymic lymphocytic hyperplasia (TLH), thymic involution (atrophy), and thymoma.

TLH

While B cells are essentially nonexistent in the thymus under healthy conditions, the presence of B cell infiltrates defines TLH. Some of these infiltrates organize into germinal centers (GCs), which combined with other cells, most notably follicular dendritic cells, create lymphoid follicles, that are localized in the medulla or the perivascular areas. TLH is associated with numerous autoimmune diseases, including multiple sclerosis and Graves' disease. The GCs in the MG thymus differ from lymphoid follicles in peripheral lymphatic organs in several ways, including in their proximity to myoid cells that express AChR and their association with lymphangiogenesis and angioneogenesis (14). The GC number and serially measured AChR antibody levels show a positive association, indicating that the thymus is a source of anti-AChR antibodies. Furthermore, the finding that 80% of patients with TLH and GCs are young females, explains why young-onset MG (before age 40–50 years) is predominantly a female disease, while late-onset MG (LOMG) is frequently a male disease and is linked with thymic atrophy or thymoma. As mentioned above, the down-regulation of AIRE by estrogen may explain the sex

Table 2 Thymic pathologies associated with MG antibodies

MG type	Thymic follicular hyperplasia	Normal or atrophic thymus	Thymoma
AChR-MG	40%	50%	10%
MuSK-MG	Single cases	>95%	Single cases
LRP4-MG	30%	>70%	–
Seronegative-MG	+	+	Single cases

+, can be associated with either thymic follicular hyperplasia or normal/atrophic thymus. MG, myasthenia gravis; AChR, acetylcholine receptor; MuSK, muscle-specific kinase; LRP4, low density lipoprotein receptor-related protein 4.

difference in young-onset MG (15).

Abnormal diffuse enlargement of the thymus (besides its association with TLH) occurs in true thymic hyperplasia, which relates to an enlarged but normally organized thymus. True thymic hyperplasia is a reversible disorder that arises from physiological stresses such as chemotherapy, corticosteroid use, irradiation, or thermal burns, and is unrelated to autoimmune diseases (16).

Thymoma

Thymomas are slow-growing, locally invasive epithelial tumors consisting of transformed epithelial cells surrounded by maturing polyclonal T cells (17). Thymoma-associated MG (particularly type B2) accounts for around 15–20% of all MG patients; such cases are almost always AChR antibody positive and can be associated with other autoimmune and paraneoplastic syndromes [e.g., stiff person syndrome, neuromyelitis optica (NMO), Isaacs' syndrome]. Thymomatous MG occurs mainly in individuals >50 years of age; about 25% of individuals with thymoma have subclinical MG, which is defined as AChR antibody positive status but without symptoms (18).

Differentiating the underlying cause of an enlarged thymus is facilitated by its imaging features. Diffuse enlargement and a triangular shape of the gland suggest hyperplasia, whereas focal enlargement and a rounded shape indicate thymoma. Thymic hyperplasia and thymoma can additionally be distinguished using chemical shift (which detects microscopic fatty infiltration found in normal thymus and thymic hyperplasia) and diffusion-weighted sequences used in magnetic resonance imaging (MRI); restricted diffusion and a high chemical shift ratio favor thymic neoplasm over thymic hyperplasia (19,20).

Thymic involution/atrophy

From 10–20% of AChR+ MG cases, usually seen in patients over 40 years of age, have an atrophic thymus that consists predominantly of adipose tissue and calcifications. Although the amount of adipose tissue and epithelial space in an atrophic thymus is very similar to that seen in age-matched controls, the remaining islands of medullary parenchyma have a high density of infiltrating B cells, which in some cases form GCs, and show marked follicular hyperplasia; the disease in such cases, particularly in some elderly individuals, responds favorably to thymectomy (14,21).

MG, antibodies, and thymus gland (Table 2)

The thymus is implicated in the etiology of MG in individuals with AChR autoantibodies, but its role in seronegative patients and those with MuSK and other antibodies is yet unknown. The thymus of individuals with MuSK+ MG shows only minor histological changes, and the organ often matches that of age-matched controls. Seronegative patients, in varying percentages have hyperplastic changes (22,23). A large epidemiological study found that the LRP4-MG thymi were diverse, and that only 32% of patients had thymic abnormalities (24).

Pathophysiology of TLH related MG (Figure 3)

The central role of the chronic expression of interferon beta (IFN-β): MG, a thymic-restricted interferonopathy

Interferons type I (IFN-I) are major cytokines that are transiently produced in response to viral infections. However, the IFN-I particularly with the IFN-β signature is detectable in the MG thymus, even long after disease onset, suggesting an inadequate resolution of inflammation (25). Unlike other autoimmune disorders, such as systemic lupus erythematosus and dermatomyositis, that are characterized by the chronic overexpression of IFN-I in peripheral blood and target tissues, the IFN-I signature is specifically detected in the thymus, suggesting that MG could represent a thymus restricted interferonopathy (26).

To avoid chronic IFN-I production, the IFN-I signaling is tightly controlled by different retro control mechanisms,

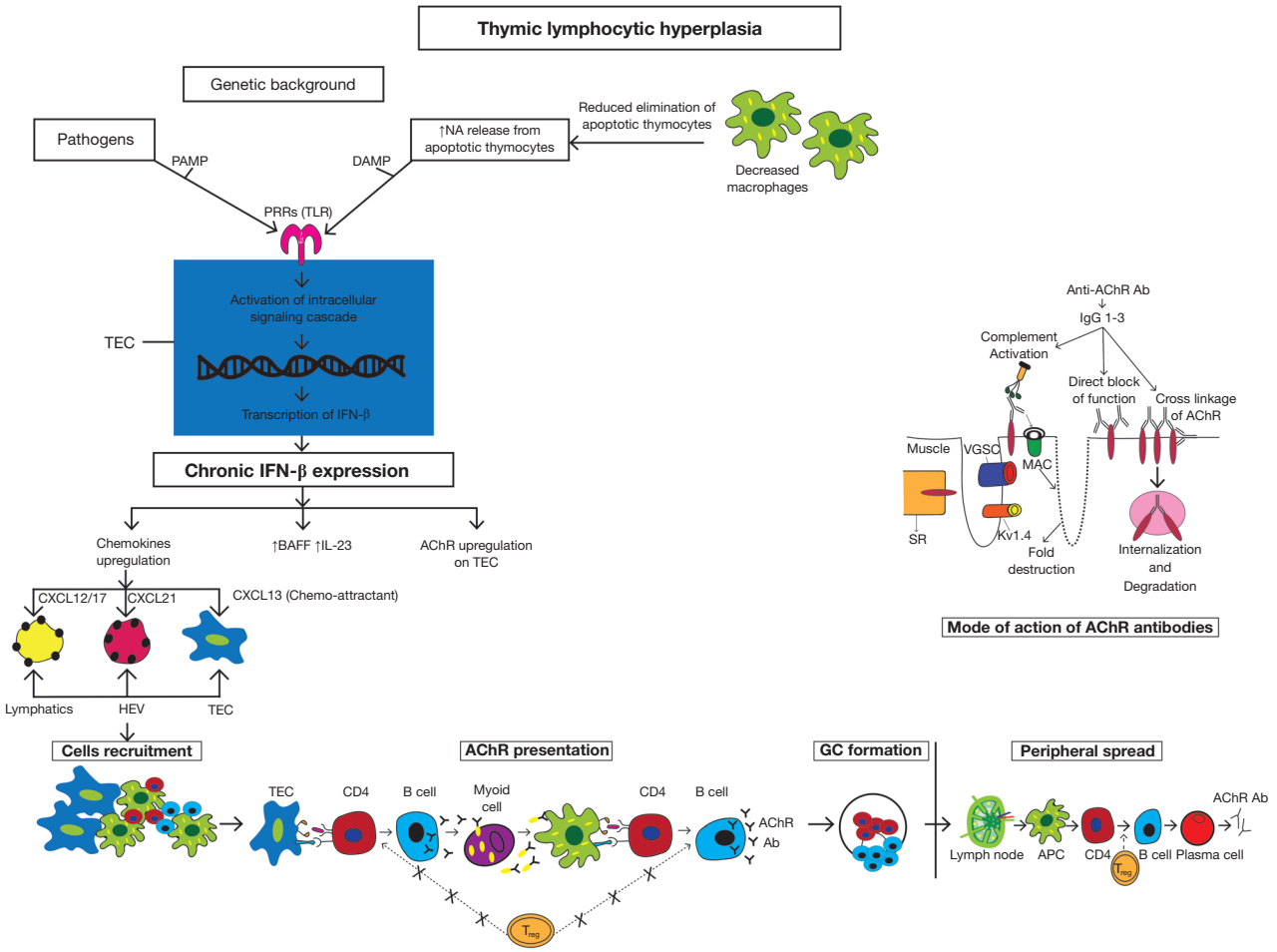

Figure 3 Pathogenesis of thymic lymphocytic hyperplasia related MG. Excessive NAs released from necrotic cells, exacerbated by impaired macrophage clearance in the thymus, as well as infections via TLRs on thymic epithelial cells, result in chronic over-expression of IFN-β. IFN-β upregulation is the primary orchestrator of thymic alterations: sensitization to AChR by selectively expressing α-AChR expression in TECs; promotes the expression of CXCL13 and CCL21 in the thymus, two chemokines involved in germinal center formation; causes BAFF overexpression; promotes the growth of pathogenic Th17 cells in the thymus. These modifications transform the thymus into a tertiary lymphoid organ with germinal center formation and the production of anti-AChR antibodies, resulting in neuromuscular junction failure. The autoimmune process triggered by the thymus can also disseminate to the periphery, explaining why disease activity persists even after thymectomy. PAMP, pathogen-associated molecular pattern; DAMP, damage-associated molecular pattern; PRRs, pattern recognition receptors; TLR, toll-like receptor; NA, nucleic acid; TEC, thymic epithelial cell; IFN-β, interferon beta; BAFF, B-cell activating factor; IL-23, interleukin 23; CXCL, chemokine family of ligands; HEV, high endothelial venule; AChR, acetylcholine receptor; Treg, regulatory T cell; GC, germinal center; APC, antigen presenting cell; IgG, immunoglobulin; VGSC, voltage-gated sodium channels; SR, sarcoplasmic reticulum; Kv1.4, voltage-gated potassium channel subfamily A member 4; MAC, membrane attack complex; MG, myasthenia gravis.

that include modulation by micro RNAs (miRNAs). miRNAs regulate post-transcriptional gene expression and are potent modulators of protein expression. Specific miRNAs are implicated in the MG thymic pathogenesis. MIR-146, which is engaged in retro-control of IFN-I signaling, is downregulated in the MG thymus; this deficiency may lead to prolonged innate immunological activation and inflammation (27,28).

The triggering factor

The inciting event leading to immune activation in MG

could be: (I) an infection: the thymus is a common target organ in infectious diseases. Even though no clear link with a pathogenic infection is yet established, there is evidence identified of certain infections including Epstein-Barr, polio, and West Nile viruses in MG thymi (29-31). (II) Endogenous nucleic acids (NAs) released from necrotic cells, including thymocytes, can induce IFN-β expression in the thymus. Thymocyte apoptosis not only occurs during thymocyte development (where about 95% of thymocytes are eliminated), but is also induced by acute stress. Under physiological circumstances, thymic homeostasis is maintained by removal of apoptotic cells by phagocytes, such as macrophages, through a process called efferocytosis. A decreased number of macrophages is seen in the thymus of patients with AChR+ MG. As a result, apoptotic thymocytes would be insufficiently eliminated, and progress to a secondary necrotic stage, release intracellular materials such as NAs, and promote the production of IFN-β in the thymus (32).

Activation of innate immune signaling pathways

Pathogen-associated molecular patterns (PAMPs) from pathogenic infections, and damage-associated molecular patterns (DAMPs) linked with the release of endogenous molecules such as NAs from injured or dying cells, are recognized by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). Such receptors are widely expressed on APCs, and partially on non-professional immune cells such as epithelial cells (33,34), and may thus become activated.

Aberrant activation of TLR pathways in the MG thymus activates intracellular signaling cascades, leading to the transcription of IFN-I subtypes. In AChR+ MG, a persistent IFN-I signature, particularly overexpression of IFN-β, seems to be the main orchestrator of changes seen in the thymus (25).

Formation of GCs in thymic follicular hyperplasia

GCs often occur in secondary lymphoid organs that produce B cells, such as lymph nodes. They are responsible for generating the humoral immune response that results in the production of antibodies and lasting memory B cells. The thymus does not contain GCs under healthy conditions; TLH is defined by their existence. These findings not only confirm the occurrence of thymic inflammation, but also suggest that the function of the thymus has changed from a repository for T cell maturation to one of the establishment of an adaptive immune response, making it a tertiary lymphoid tissue (35).

Steps involved in the generation of GCs

The following series of events is hypothesized in the development of tertiary lymphoid structures in the thymus of MG patients:

(I) Cellular recruitment

IFN-β induces the upregulation of non-functional unfolded AChR and chemokine family of ligands (CXCL). The latter includes upregulation of the chemoattractant CXCL13, particularly for B lymphocytes on TEC; and promotion of neogenesis of the lymphatic endothelial vessels by CXCL 21 and HEV by CXCL 12 and 17 in the thymus of MG patients, which favor the recruitment of peripheral cells (36). IFN-β also induces the overexpression of B-cell activating factor (BAFF; the pro-survival cytokine for B cells) (37) and induces pro-inflammatory cytokines such as interleukin (IL)-23, favoring the differentiation of naive T-cells into pro-inflammatory T helper (Th) 17 cells that produce IL-17 (38). Functional defects in Treg cells, which maintain immune homeostasis and self-tolerance and prevent autoimmune disease, are identified in MG (39). The combination of neogenesis and chemoattractant upregulation provides an extensive vascular network and an ideal inflammatory environment for peripheral APCs, B cells, and T cells to find their niche in the thymus.

(II) Sensitization to AChR and GC formation

The sensitization to the AChR involves a two-step model: (I) upon re-entry of AChR-reactive T cells from the blood to the thymus, the effector T cells get 'primed' by hyperplastic mTECs expressing MHC and non-functional, unfolded AChR subunits, leading to the production of low-affinity early AChR antibodies. (II) These early antibodies attack thymic myoid cells which express intact, folded AChRs. Due to the lack of MHC-II molecules, myoid cells are unable to present to T lymphocytes; instead, they activate complement and induce the release of AChR antibody complexes for processing by nearby APCs. Activated APCs then cross-present autoantigen-peptides to AChR-specific autoreactive CD4 T cells and B cells, which then organize into GCs, leading to the production of high-affinity late AChR antibodies and subsequent epitope diversification (40).

Altogether, these observations indicate that in a predisposing background [human leukocyte antigen (HLA) D-related genotype, sex hormones, vitamin D level, etc.], after the initial innate immune response is activated by either infection(s) or the release of NAs from necrotic thymocytes, TLR activation results in the persistent production of IFN-I by TECs. This provides a pro-

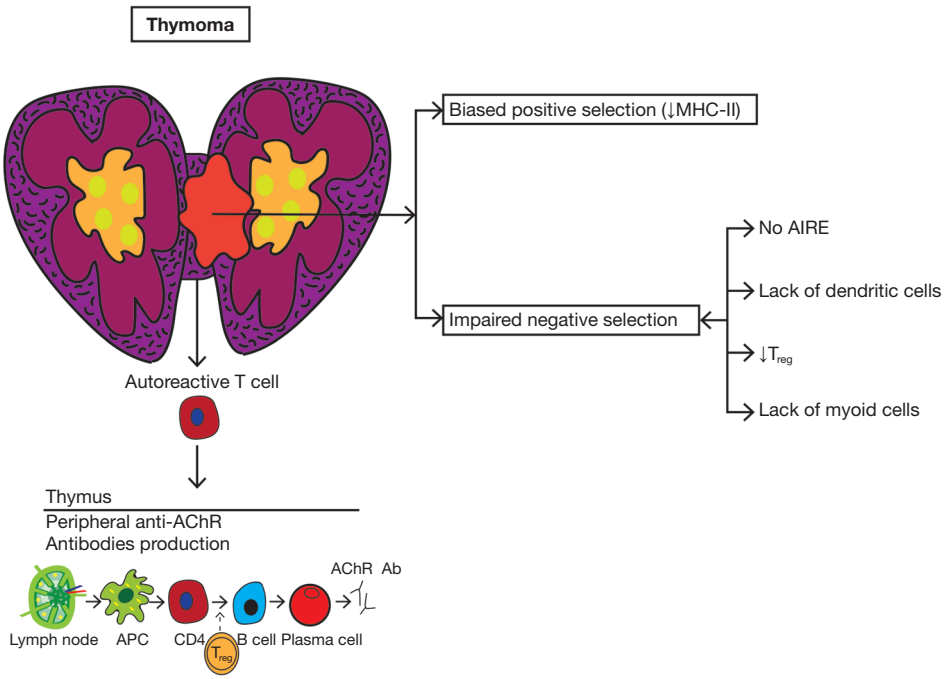

Figure 4 Pathogenesis of thymoma related MG. The absence of thymic architecture in thymoma, which is required for T-cell maturation and development, contributes to the formation of self-reactive T helper cells via biased positive selection and impaired negative selection. After being appropriately activated, self-reactive T helper cells results in the generation of autoantibodies against native AChR outside of the thymoma. MHC, major histocompatibility complex; AIRE, autoimmune regulator; Treg, regulatory T cell; AChR, acetylcholine receptor; APC, antigen presenting cell; MG, myasthenia gravis.

inflammatory environment for the induction of subsequent adaptive immune response, suggesting that IFN-I serves as an interface between innate and adaptive immunity.

Peripheral spread of thymus-initiated autoimmune process

The autoimmune process that began in the thymus later extends to the peripheral secondary lymphoid organs. This explains the ongoing disease activity detected even after thymectomy, which is likely mediated by autoantibody-producing B cells that have emigrated from the thymus, functionally defective Treg cells, and AChR antibodies produced at extra-thymic sites such as bone marrow and lymph nodes (41).

Mode of action of AChR-specific autoantibodies

AChR antibodies belong to the immunoglobulin (IgG)1 and IgG3 subclasses. They mediate tissue damage at the NMJ by multiple mechanisms: (I) antibody binding to AChRs leads to focal NMJ endplate lysis through complement activation and membrane attack complex formation; (II) cross-linking of adjacent AChRs by antibody leads to their internalization and degradation; and (III) further disruption of neuromuscular function is caused by antibody directly blocking the acetylcholine binding site (13).

Pathophysiology of thymoma-related MG (Figure 4)

Thymomas are closely associated with several immunological illnesses, including MG, because they lose thymic architecture that is necessary for T cell maturation and development. The following pathogenetic theories are proposed for thymoma-associated MG (8):

Biased positive selection

Neoplastic epithelial cells express epitopes of AChR subunits and titin, however MHC class II expression is low or absent in the neoplastic TECs, which is crucial for the T lymphocytes' positive selection. The TCR repertoire is altered by the reduced expression of MHC class II on

neoplastic epithelial cells. This results in the positive selection of Th cells with a stronger affinity for self-MHC-II molecules that should have been deleted, resulting in the subsequent emergence of T cell-dependent autoimmunity.

Impaired negative selection

Due to the lack of mature medullary structure required for negative selection, the self-reactive Th cells survive or are pre-primed *in-situ* by their target autoantigens. These factors include: (I) the absence of AIRE, which controls the expression of tissue-specific self-antigens; (II) lack of dendritic cells; (III) dysregulation of the master gene, forkhead box protein 3 (FoxP3). The FoxP3 gene is essential for Treg function; the latter keeps autoreactive effector T cells in check, thus affecting both central and peripheral tolerance; and (IV) lack of myoid cell-derived AChRs and titin, which are important for tolerogenic cross-presentation by APCs.

Peripheral anti-AChR antibody production

After evading central and peripheral tolerance, autoreactive mature Th cells enter the circulation, and after appropriate activation, stimulate the B cell response. Most often, this results in the generation of autoantibodies against native AChR outside of the thymoma. Only a small percentage of thymomas have intratumor lymphatic follicular hyperplasia and GCs. These ectopic GCs contribute to the local immune response and induction of antibody production against tumor-associated or self-antigens, thus increasing the risk of developing MG (42).

MG exacerbation post-thymectomy

The export of T cells from the thymus occurs years before a thymoma is diagnosed. Long-lived T cells may perpetuate anti-AChR antibody production at any time in the periphery (43). These data explain why some thymomatous MG patients after thymectomy may experience significantly higher mortality, lower remission rates, and less improvement than those who undergo thymectomy for nonthymomatous MG (44).

Pathophysiology of LOMG (Figure 5)

It has been hypothesized that age-related thymic involution contributes to immunosenescence (insufficiency) and inflammaging (overreaction), leading to the development of MG (45).

Immunosenescence

Immunosenescence is the term for age-related disruption in structural architecture and the functional components of the innate and adaptive immune systems. Immunosenescence causes thymic involution, which lowers the number of naive T cells while boosting the peripheral oligo-clonal growth of memory T cells. These events may lead to a decreased diversity in the overall TCR repertoire, leading to immunosenescence (immune insufficiency) (46).

Inflammaging

The current paradigm states that thymocytes are prone to negative selection if they express a TCR with a high affinity for self-peptides shown by MHC-II on mTECs. Age-related mTEC deficiencies include decreased AIRE and MHC-II expression. These factors reduce the ability to express the self-peptide-MHC-II ligand, which then modifies the intensity of TCR signaling (47,48).

Strong signaling, which results in negative selection and self-reactive elimination, swings either to weak signaling which releases self-reactive thymocytes, or to an intermediate level of signaling which supports the development of Treg cells. Normal Tregs suppress self-reactivity; however, aged Treg cells are unable to do so because of the loss of Treg TCR diversity (49).

The result of these changes is the generation of self-reactive T cells from an atrophic, myoid cell-deficient and AIRE-negative thymus, which upon activation in the periphery leads to the generation of pathogenic AChR antibodies and LOMG. After initiation, LOMG may become self-perpetuating due to stimulatory AChR/autoantibody complexes in muscle-draining lymph nodes, which may explain why thymectomy is ineffective in LOMG. Rarely, TLH can occur in older MG patients; in such cases, thymectomy can still be effective (21).

Evidence supporting role of thymectomy in MG

Thymomatous MG

Thymomas can spread locally and to distant sites, potentially causing compression in areas like the bronchi, lungs, or superior vena cava, leading to symptoms like superior vena cava syndrome. Therefore, regardless of whether the MG is ocular or generalized, thymectomy is indicated for definite tumor management. Thymomatous MG requires close observation and rigorous postoperative MG management since it is often more severe and responds less effectively to

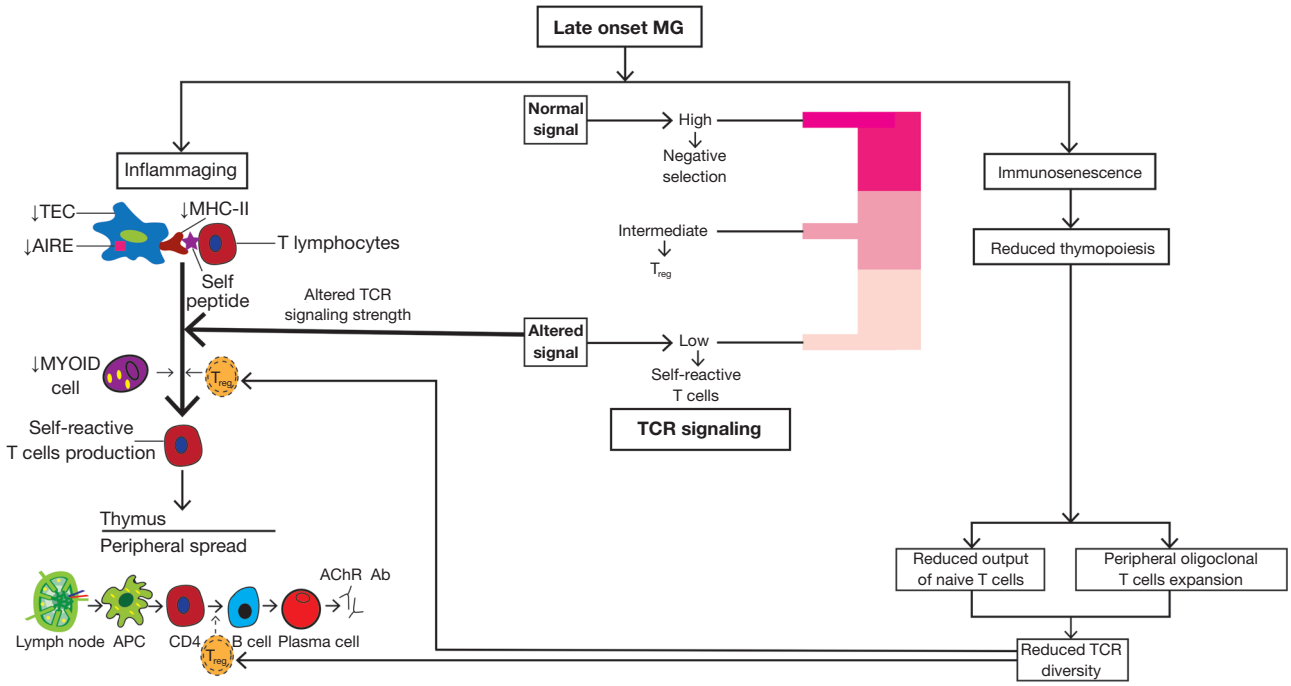

Figure 5 Pathogenesis of thymic Atrophy related MG. Inflammaging (because to defective negative selection and imbalanced generation of Treg TCR repertoire) and immunosenescence (due to diminished thymopoiesis and the proliferation of oligo-clonal T cells) both contribute to an increase in self-reactive T cells. These self-reactive T cells upon activation in the periphery leads to the generation of pathogenic AChR antibodies and late onset MG. MG, myasthenia gravis; TEC, thymic epithelial cell; MHC, major histocompatibility complex; AIRE, autoimmune regulator; Treg, regulatory T cell; TCR, T cell receptor; AChR, acetylcholine receptor; APC, antigen presenting cell.

thymectomy (please see section "*Pathophysiology of thymoma-related MG*" for details) (42-44).

Non-thymomatous MG

According to international consensus guidelines, thymectomy is advised for generalized nonthymomatous AChR+ MG patients aged 18 to 50 years in order to improve disease control and minimize immunotherapy needs while also reducing exacerbations and hospitalizations (50). This recommendation is supported by the following lines of evidence:

Randomized MGTX (Thymectomy Trial in Non-Thymomatous MG Patients) trial

The landmark MGTX multicenter, randomized trial demonstrated the superiority of prednisone and thymectomy, versus prednisone alone at 3-year follow-up; this observation was also supported by its 2-year extension study (total of 5-year follow-up) (3,51). The study compared various outcomes in these groups, including level of weakness and other symptoms related to MG, hospitalizations for exacerbations, and requirement for additional immunosuppression: within these and additional outcome measures, the thymectomy group demonstrated superiority. Further, these findings persisted at longer-term follow-up, though data were somewhat limited due to attrition of patient numbers.

Meta-analysis and systematic review

Various meta-analyses also support the conclusion that thymectomy is associated with improvement and even remission status in MG. One review, that included 22 retrospective studies, found the likelihood of achieving remission much higher among the surgical group compared to the conservative treatment alone group [odds ratio (OR) for improvement 2.44, 95% confidence interval (CI): 1.91–3.12] (52). These findings were further corroborated by a separate meta-analysis (53); however, these conclusions were somewhat limited due to multiple confounding factors,

observational study limitations, and heterogeneous methods among the included studies.

Evaluation of different predictors as well as short-term and long-term clinical response following thymectomy

A retrospective, single-center study (54) investigating short-term and sustained clinical response following thymectomy found that 72% of patients initially responded, but only half had a sustained clinical response on long-term follow-up at a median of 89.5 months. Thus, 28% of patients, therefore, never showed a sustained clinical response. Since a greater reduction in AChR levels was associated with a higher likelihood of achieving an initial clinical response, it has been suggested that AChR could represent a favorable prognostic marker. However, this study did not find any predictive value of sex, age at onset, disease subtype (thymomatous *vs.* non-thymomatous), thymus histology, delay to surgery after disease onset, surgical approach, and immunosuppressive treatment before surgery for reaching a sustained clinical response.

Conclusions from thymectomy studies

The following conclusions are drawn from these studies:

The advantage of thymectomy plus prednisone over prednisone alone suggests that in addition to the reduction of GCs with prednisone, thymectomy also eliminates molecules and cells that may contribute to disease pathogenesis (55,56).

Thymectomy may not be a curative procedure for MG, and the benefit may not last. This is due to the peripheral expansion of the autoimmune process from the thymus to the peripheral secondary lymphoid organs, which contributes to ongoing disease activity even after thymus removal and necessitates long-term immunosuppressive medications, possibly in a lower dose.

- The work by Rath *et al.* and other studies (54,57) show the effectiveness of minimally invasive, particularly robotic thymectomy, as compared to the extended trans-sternal method used in the MGTX trial to achieve removal of the entire thymus.
- The fact that clinical and demographic factors cannot accurately predict outcomes after thymectomy suggests that further investigation into miRNAs, particularly miR-150-5p, and the use of specific MRI techniques, could be employed as objective indicators for mechanism-based tailored treatment (see section "*Pathologic abnormalities in MG thymus*" for details) (58).

Thymectomy in sub-populations of MG

Ocular MG (OMG)

Thymectomy is recommended in thymoma-associated OMG patients; however, its role in non-thymomatous OMG remains controversial due to a lack of prospective trials.

Case series and meta-analysis

Remission rate

A number of case studies and meta-analyses have demonstrated that the remission rate of 57% to 71% over more than 5 years after thymectomy in OMG and generalized MG (gMG) is comparable (59,60).

Reduction in progression to gMG

No patients in two series of 96 total patients, and only 1 in a series of 61 patients, developed gMG after thymectomy (60-62). This suggests that thymectomy may delay the development of gMG, as the projected generalization rate throughout this time period was 50%. However, the significance of these findings is limited by the heterogeneity among trials.

Additional factors

- Histology: thymomatous MG patients with pathology revealing subtype B2/B3 thymoma had a higher risk of conversion to gMG compared to those with AB/B1 subtype or hyperplasia (63).
- Age and race: complete remission was higher in children and subjects from Western countries, than in adults and in the Asian population with OMG (64).

Recommendation

Thymectomy is not currently recommended as first-line treatment for OMG, but it may be offered in AChR+ non-thymomatous OMG patients, not responding to immunosuppressive medications or acetylcholinesterase inhibitors, or in those who have contraindications to taking immunosuppressive medications or who are unable to tolerate them (50).

Age—elderly/juvenile MG patients

Adults beyond the age of 50 years

There is limited data on the role of thymectomy in elderly patients. The MGTX trial allowed patients to participate up to the age of 65 years; however, the median age of the thymectomy arm was 32 years (range, 18 to 63 years), and neither arm had many patients above the age of 50 years (3).

In general, thymic atrophy is more prevalent in older

persons. This results in the generation of self-reactive T cells and the production of self-perpetuating pathogenic AChR antibodies outside the thymus, thus explaining the relative lack of effectiveness of thymectomy in LOMG (see section "*Pathophysiology of LOMG*") (45-49).

A single-centre, retrospective study involving 43 MG patients older than 60 years at onset, who underwent robotic thymectomy, identified thymic atrophy to be the most prevalent pathology (seen in 86%). However, thymectomy in this study seemed to be safe (1 perioperative death due to aortic dissection) and effective as 20% had a good outcome, which was defined as minimal disease manifestations or better, and with a statistically significant steroid-sparing effect (65).

Although there is no set age limit for thymectomy, most experts advise against surgery for most patients >60 years of age, based on a concern that the risks of thymectomy outweigh the potential benefits at this age. Others, however, disagree and advocate a customized strategy based on each patient's risk and benefit analysis, believing that older age is not always an excluding factor.

Juvenile MG

Juvenile MG involves the same pathophysiology as adult-onset disease. Thymectomy is a widely accepted option for peripubertal and postpubertal children with AChR+ gMG. In a review of various studies that included 588 patients, thymectomy was associated with improvement in clinical status and reduced need for medical therapy in 77% of patients. Within this group >12 years of age, increased likelihood for remission and more favorable outcomes were seen in those who underwent surgery within 1 year of onset of symptoms (66). These findings were also seen in previous reviews (67), suggesting a role for earlier intervention with thymectomy.

Antibody status: AChR, MuSK and seronegative MG

To-date there are a few studies that have examined outcomes related to antibody status in MG; however, some trends are evident (63,66-70). One study of OMG patients found a significant positive association between AChR –ve (AChR negative) MG status and complete remission following thymectomy (63). In contrast, when examining juvenile MG patients, Heng *et al*. (68) found an improved response in children with AChR+ MG, whereas Tracy *et al.* (67) did not find a significant difference.

MuSK+ MG patients, who often present with significant bulbar and facial involvement, remain difficult for long-term management given their often challenging and treatment-resistant clinical course (69,70). Assessment of outcomes in these patients following thymectomy remains mixed and additional data are needed. Most MuSK+ MG patients often have normal thymus histology, although a few show thymic hyperplasia (71). Analyses in a review examining the relationship between MuSK antibody and MG status found lack of improvement in clinical outcomes following thymectomy for MuSK+ patients; further, there was no difference in the need for immunosuppressive agents between the surgical and non-surgical groups (71,72). However, a study examining a small subset of MuSK+ patients in Thailand found favorable responses to thymectomy in several patients, including complete remission in three of seven and the ability to decrease immunosuppressant amount in four (72). Interestingly, the complete response appeared following a longer interval (up to 3 years), suggesting longer follow-ups are needed. Similarly, a separate retrospective study examining various treatment options reported favorable response at 3 years to thymectomy in 39% of the MuSK+ cohort, though notably most of these patients were also on immunosuppressants (71).

Despite the fact that thymectomy is an option for those with seronegative MG, including those with LRP4 antibodies, there are little data to support its use in this group. This is in large part because seronegative MG patients were ineligible for the MGTX trial, and in general make up a small proportion (6% to 12%) of all MG patients.

Risk of other autoimmune disorders post thymectomy

There is a wealth of evidence suggesting a relationship between MG and increased risk for developing other autoimmune diseases. While thymectomy has become a standard treatment in MG, there is also growing evidence of an increased rate of autoimmunity following this procedure (73). Although removal of the thymus can decrease Th cell populations and activity, it may lead to increased T cell suppressor activity, thus upsetting the T cell homeostasis (73).

In a study by Lin *et al.* (73) that examined the emergence of autoimmune diseases post-thymectomy, the incidence of any autoimmune disease was 2.68 times higher in the post-thymectomy group (MG and non-MG) compared to the non-thymectomy group. The hazard ratio for any autoimmune disease was 2.65 in the post-thymectomy

Table 3 Perioperative management

Preoperative
• Continue baseline myasthenia-related drug management to optimize disease control
• Risk stratify postop respiratory failure
• Minimize sedation
• Optimize lung function and comorbidities
• Rule out cardiac dysfunction
• Large substernal thymoma—evaluate for airway/cardiac collapse
• Minimize steroid dose as able
• Consider IVIg *vs.* plasmapheresis in the weeks prior to planned resection
Intraoperative
• Mechanical ventilation (with lung isolation if thoracoscopic approach)
• Minimize muscle relaxant use
• Sugammadex to reverse muscle relaxants
Postoperative
• Adequate pain control
• Avoid sedative/opioids
• Pulmonary toilet with breathing exercises/incentive spirometry
• Aggressive treatment with medication/IVIg/plasmapheresis if disease worsens
• Consider stress dose steroids depending on preoperative dose
• Avoid medications that can exacerbate MG (magnesium, beta blockers etc.)
• Review clinically for need for resumption of anticholinesterase drugs

IVIg, intravenous immune globulin; MG, myasthenia gravis.

group, after adjustment for age and sex; this finding remained after analyzing for organ-specific and systemic autoimmune diseases (73). Similarly, a single center cohort study from Beijing observed a higher occurrence of autoimmune diseases in MG patients post-thymectomy (4.3%) compared to those without thymectomy (1.98%); however, this difference could have been confounded by a higher proportion of females in the thymectomy group (74). There have also been case reports on patients with MG following thymectomy who develop NMO, another autoimmune disorder, though more work is needed to clarify this relationship (75).

Thymectomy: perioperative management

The reported rates of myasthenic crisis after surgeries, notably thymectomy, range from 2% to 25% in various series (76). To prevent this potentially fatal complication, MG patients undergoing thymectomy are best managed by a multidisciplinary team comprising the surgeon, anesthesiologist, and neurologist, with a presurgical customized plan to formulate management during the preoperative, intraoperative, and postoperative phases (*Table 3*).

Preoperative

Thymectomy in MG is an elective procedure, typically advised within the first three years of the diagnosis. It is advisable that MG symptoms are optimally controlled such that patients have minimal to no respiratory or bulbar manifestations (minimal disease defined per MG Foundation of America disease severity grading) (50). In real practice, this can be quite difficult to achieve given treatment resistance and disease severity, and at times, patients undergo the procedure despite ongoing symptoms in an effort to curtail disease activity. Since MG patients can be quite sensitive to the discontinuation of their medications, the use of symptomatic anticholinesterase medication (e.g., pyridostigmine) and immunotherapy should be continued through the perioperative period. It is also important to recognize that anticholinesterase drugs may not only alter the response to both depolarizing and nondepolarizing neuromuscular blocking agents (NMBAs), but also that NMBA reversal may be unpredictable or insufficient if sugammadex is not used for NMBA reversal. While corticosteroids may help with disease-induced muscle weakness, it is likely advantageous to taper the steroids to as low a dose as possible as the clinical condition allows to reduce the likelihood of postoperative infections and problems with wound healing.

Intravenous immune globulin (IVIg) or plasmapheresis should be used in patients with mild persistent residual respiratory or bulbar dysfunction. To ensure that the benefits of the fast therapy peak and last during the perioperative phase, these treatments should finish one week before surgery. This gives the coagulation factors eliminated by the exchange in the event of plasmapheresis

Table 4 Patient related factors predisposing to respiratory failure

Factors	OR (95% CI)
History of myasthenic crisis	4.13 (3.08, 5.54)
Bulbar symptoms	3.71 (2.54, 5.42)
Osserman stage (IIB + III + IV)	11.15 (6.88, 18.08)
Pyridostigmine dose (>750 mg/day)	3.53 (2.47, 5.03)
Elevated serum acetylcholine receptor antibody level	8.74 (3.31, 23.08)
Decreased vital capacity	5.71 (3.11, 10.48)
Coexisting disease	33.78 (10.57, 107.96)
Disease duration (>2 years)	5.94 (1.12, 31.48)

OR, odds ratio; CI, confidence interval.

Table 5 Surgical factors predisposing to respiratory failure

Factors	OR (95% CI)
Open *vs.* minimally invasive	5.88 (2.06, 16.80)
Blood loss (>1,000 mL)	15.03 (3.50, 64.50)

OR, odds ratio; CI, confidence interval.

Table 6 Scoring system to predict respiratory failure after surgery

Variables	Points
Osserman stage	
Stage I–IIA	0
Stage IIB	1
Stage III–IV	3
Duration of myasthenia gravis (years)	
<1	0
1–2	1
>2	2
Lung resection	
No	0
Yes	2.5
BMI (kg/m^2)	
<28	0
≥28	1

Total points (range, 0.0–8.5). BMI, body mass index.

time to recover.

Based on a variety of preoperative characteristics, patients should be risk stratified for the likelihood of the occurrence of postoperative respiratory failure and hence to anticipate the need for intensive care unit (ICU) care post-surgery (*Table 4*) (77).

Intraoperative (Table 3)

A range of techniques, including inhalation agents and intravenous anesthetics, is utilized for inducing and maintaining anesthesia for MG patients. The main objectives are to avoid anesthetic medications that can have lingering effects on the respiratory and bulbar muscles, and thus to facilitate a quick recovery after surgery. This is accomplished by maintaining body temperature, avoiding long-acting sedatives including opioids, and minimizing the use of non-depolarizing muscle relaxants. The lingering effects of anesthesia are best reversed with use of sugammadex and a twitch monitor, with the aim of shortening recovery time.

When using a thoracoscopic approach, mechanical ventilation uses a lung isolation technique with advanced airway devices like a double-lumen endotracheal tube or a bronchial blocker. Only ventilating the non-operative side during the procedure will ensure the lung is out of the field for the procedure. Since the lungs are not in the operating field during procedures requiring sternotomy, lung isolation is not required.

Surgical factors predisposing to respiratory failure must also be assessed (*Table 5*) (77).

Postoperative (Table 3)

Appropriate postoperative management includes pulmonary toilet and utilization of optimal pain management using multimodal analgesia that minimizes the use of opioids and sedation, as weak and ineffective cough can risk respiratory compromise and infection. Following extubation, patients need vigilant monitoring, early continuous positive airway pressure therapy, or IVIg or plasma exchange treatment to prevent reintubation.

Leuzzi *et al.* have proposed a simplified scoring system to predict respiratory failure after thymectomy in MG patients (*Table 6*). A score of <2.5 has less than a 10% chance of

respiratory failure and need for ICU admission, versus more than a 50% chance if the score is >4 (78).

Surgical methods

The goal of thymectomy in MG is to remove the thymus and as much of the surrounding mediastinal and cervical fat, which contains varying levels of ectopic thymic tissue, without endangering the recurrent laryngeal, left vagus and phrenic nerves (79).

There are four major methods for surgical approaches to thymectomy: open transsternal, transcervical, combined transcervical-transsternal, and minimally invasive (video- or robot-assisted) (80-82).

For many years, transsternal thymectomy (which was employed in the MGTX trial) has been the acknowledged standard surgical technique. It permits a thorough examination of the anterior superior mediastinum and the total removal of all thymic tissue and related fat. Since the MGTX trial, less invasive thymectomy techniques have become more common. Comparing non-randomized trials, these techniques produce outcomes that are comparable to those after aggressive surgeries. These less invasive methods have shorter recovery and hospitalization times, lower morbidity, and seem to be just as successful as open thymectomy. A recent systematic review (which included patients with thymomas, mediastinal masses, and thymectomies for MG) compared robot-assisted thoracic surgery (RATS) *vs.* video-assisted thoracoscopic surgery (VATS) *vs.* open thymectomy and found no significant differences between VATS and RATS approaches. RATS compared to an open approach had fewer complications and shorter length of stay in the hospital (83).

The thoracoscopic approach may be unilateral (right or left), bilateral thoracoscopic, or sub-xiphoid. With regard to unilateral thoracoscopic thymectomy there is no consensus as to which side (right *vs.* left) is more likely to achieve total thymectomy (84). Some have advocated for a subxiphoid thoracoscopic approach rather than right or unilateral thoracoscopic approach, with less pain and higher rates of total thymectomy noted, though this approach is not widely employed (85,86).

A key distinction between VATS and RATS, is that the former involves the surgeon holding the tools, while the latter allows the surgeon to operate the unique wristed instruments directly from a console, managing every aspect of their movement with a greater degree of freedom instead of having to handle "straight stick" instruments directly. The number and size of the incisions are usually similar when comparing VATS and RATS approaches. While there are no randomized trials comparing RATS *vs.* VATS approaches for thymectomy, one retrospective cohort study did show greater rates of remission with a 42-month follow-up after robotic resection (39.25% *vs.* 20.3%, P=0.01) with similar operative time (87). Another more recent retrospective cohort study showed RATS technique was an independent predictor of remission, with a trend toward greater remission after RATS *vs.* VATS (26% *vs.* 18%, P=0.06) (88). *Table* 7 provides a comparison of the pros and cons of these techniques.

Conclusions

The thymus is crucial for the development and maturation of T cells and the establishment of central tolerance. Different thymic pathologies including TLH, thymoma and thymic atrophy, use diverse pathways to contribute to the development and maintenance of autoimmunity in MG. A deeper understanding of these pathophysiological processes will not only shed more light on the role of thymectomy with specific pathologies, but will also explain why the prognosis is different with various thymic pathologies.

Minimally invasive thymectomy is now increasingly utilized for both non-thymomatous and thymomatous MG. The effectiveness and long-term outcomes of thymectomy in children, geriatric patients, and in those with ocular, MuSK+, and seronegative MG must be determined by

Table 7 Approaches in thymectomy

Factors	Transsternal	Extended cervical	Minimally invasive
Use	Standard approach	1st described surgical approach—extended approach by Cooper (introduced in 1988) most commonly used cervical approach	Increasingly utilized
Surgical access	Standard median sternotomy (midline chest incision from 2 cm below the sternal notch to the xiphoid process)	Transverse curvilinear incision made 2 cm above the sternal notch between the sternocleidomastoid muscles	VATS *vs.* RATS—access via 3–4 small ports (may be left, right, bilateral, or subxiphoid approach)
Major advantage	Excellent exposure of the anterior mediastinum and thymus	No significant advantage—often used by surgeons trained in this technique. Less pain associated with recovery	Minimally invasive, general advantages of video-assisted/robotic-assisted surgery
Limitations	Extended restrictions to allow for healing of sternum	Controversial and not widely accepted due to lack of familiarity, inadequate thymus exposure, and concern for incomplete resection. More limited visualization of the gland	Requires careful patient selection. Requires tolerance of single lung ventilation, can have difficulty visualizing contralateral phrenic nerve Increased cost with robotic
Indication	Large tumors and tumors invading adjacent structures	Limited to treatment of nonthymomatous myasthenia gravis	Stage I to II thymomas, thymic carcinomas <5 cm, nonthymomatous myasthenia gravis—increasing experience with larger tumors
Conversion rate	–	0–19% to transsternal approach—some may require sternotomy to control bleeding	0–7% to transsternal approach
Perioperative course	Longer hospitalization, postoperative pain from sternotomy, complications related sternotomy including infections and mediastinitis, rare perioperative death	Brief hospitalization (often 1 night or even none), operative major complication rate <1%	Shorter hospitalization, lower operative blood loss, decreased postoperative pain, rare perioperative death
Complications	Pulmonary: respiratory failure and prolonged intubation often associated with patients with myasthenia gravis—otherwise pleural effusion, pneumonia, atelectasis, pneumothorax		
	Nerve injury: phrenic nerve (<1% with transsternal approach, 7% with VATS, extremely rare though possible with RATS—leading to diaphragmatic dysfunction); left recurrent laryngeal nerve (with dissection of the aorticopulmonary window leading to vocal cord paralysis)		
	Infection/mediastinitis: overall rare—mediastinitis is more likely with sternotomy		

VATS, robot-assisted thoracic surgery; RATS, robotic-assisted thoracic surgery.

randomized controlled studies.

Acknowledgments

The authors gratefully acknowledge the assistance of Mrs. Molly Partelow in the preparation and formatting of the manuscript, and in the creation of figures.
Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://med.amegroups.com/article/view/10.21037/med-23-43/rc

Peer Review File: Available at https://med.amegroups.com/article/view/10.21037/med-23-43/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-23-43/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work have been investigated and resolved.

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doi: 10.21037/med-23-43
Cite this article as: Waheed W, Bacopulos A, Seyam M, Kooperkamp H, Moin M, Malik T, Tandan R. Physiological and pathological roles of the thymus and value of thymectomy in myasthenia gravis: a narrative review. Mediastinum 2024;8:31.