Peer Review File

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Reviewer A

This is a very well written review about the current evidence of thymectomy in juvenile myasthenia gravis. The topic is currently of high importance due to the recent publication of health consequences of thymectomy in NEJM (https://pubmed.ncbi.nlm.nih.gov/37530823/).

Comment 1: I would recommend to shorten the paragraph of open thymectomy (line 226-237 can be removed). Same accounts for the paragraph for thoracoscopic thymectomy.

Reply 1:

We appreciate this feedback. The description of the surgical approach to open and thoracoscopic thymectomy have been removed as requested.

Changes in the text:

Removal of lines 228-237 and 280-295

Comment 2: I would rather add a paragraph about the discussion and current evidence of age at thymectomy and its long-term side effects, especially in regard to premature immunosenescence.

Reply 2:

We appreciate the importance of this topic. In the "Surgical Candidacy" section, we have further expanded upon this discussion.

Changes in the text:

Still, there remains significant controversy surrounding the appropriate age and timing from symptom onset to thymectomy. Delaying thymectomy affords a chance for spontaneous remission, an event which occurs as often as 20-29% of the time in children [39]. Furthermore, the thymus is critical in the growth and development of a child's immune system; therefore, many argue that surgery should be postponed due to concern that removing the thymus while the immune system is still in development will have negative consequences later in life [22, 40-42]. As such, a study performed by Popperud et al. confirmed that thymectomy for JMG performed at median (range) age at thymectomy of 17 (2-33) years can lead to premature immunosenescence, including a reduced number of B cells, naive cytotoxic T cells and helper T cells and increased memory T cells at median (interquartile range) 12 (7-26) years after thymectomy was performed. However, these findings were not related to age at thymectomy nor with any discernible clinical consequence [43]. However, it is necessary to mention a 2023 case-control study in adults with MG who are five years or more post-thymectomy found

thymectomized patients have not only decreased production of CD4+ and CD8+ lymphocytes and higher levels of proinflammatory cytokines but also a higher incidence of cancer and all-cause mortality compared to their non-thymectomized counterparts [44].

There is controversy regarding the impact of age and timing from symptom onset on the efficacy of thymectomy. A study with 31% CSR and 62% symptom improvement rates following thymectomy in 13 patients with mean (range) age at thymectomy of 10.8 (1.4-18.6) years and mean (range) time from disease onset of 9.2 (0.6-33.0) months found that time from onset to surgery was a mean 199 days longer in those who did not respond to thymectomy [25]. In a study performed on 141 patients with JMG with median (range) age at onset of 6 (1-18) years who underwent open transsternal resection at median (range) age of 12 (3-18) years found improved CSR rates when surgery was performed when patients are at least 12 years old [36]. However, the same study demonstrated improved postsurgical outcomes when thymectomy was performed within 12 months of onset of generalized symptoms [36]. Conversely, a study by Kim et al. including 50 patients with JMG who underwent thoracoscopic thymectomy at mean (standard deviation, SD) age of 10.5 (0.8) years and mean (SD) time to thymectomy of 19.6 (4.2) months with 51.0% of patients with thymectomy within one year of disease onset found no difference in outcome when evaluating age or timing of thymectomy relative to symptom onset [47]. A systematic review including 17 articles published between 1997 and 2020 encompassing 588 JMG patients who underwent thymectomy concluded that improved surgical outcomes may be associated with both early intervention and post-pubertal intervention [22]. Moreover, by performing surgery early, children avoid growth failure, delay in bone aging and detrimental metabolic effects experienced by JMG patients who require prolonged glucocorticoids [46]. Overall, there may be benefit to performing surgery early relative to symptom onset, particularly for patients who are post-pubertal or with severe disease requiring prolonged use of high-dose steroids.

Reviewer B

Thank you for the opportunity to review this interesting narrative review regarding thymectomy for JMG. JMG is rare and the disease's pathophysiology is complicated. Therefore, there have been limited data available on surgical management of JMG. A couple of comments are listed below for the authors' consideration.

Comment 1: The authors state that "there remains controversy surrounding the appropriate age and timing from symptom onset to thymectomy." We understand the risk of immunological consequence of thymectomy in children. In clinical practice, when was thymectomy performed for JMG? Please explain in more detail, presenting the age, the period of illness, symptoms, radiological findings, medication and indication in previous studies.

Reply 1:

We agree on the importance of such issues when considering surgical management of JMG. As such, we have dedicated a large portion of our manuscript to these topics as detailed below.

Regarding medical therapy:

There are no prospective studies which compare complete stable remission (CSR), disease improvement, or change in medication requirement for thymectomy relative to medical management for JMG, such as the MGTX trial did for MG; however, we identified four retrospective studies (Table 2) and two systematic reviews (Table 3) which evaluate thymectomy and compare it to medical management for JMG. Available data consist of small and heterogeneous populations limiting cohort comparisons; however, patients who undergo thymectomy have less postoperative corticosteroid and cholinesterase inhibitor use in addition to comparable if not higher rates of CSR [4, 24, 25]. Furthermore, thymectomy has been shown to decrease the number of days spent intubated, in the intensive care unit and hospitalized [25]. An analysis of the KID database demonstrated between 2003 and 2012 there was stability in the number of thymectomies performed in children for JMG [26]. However, data estimating the number of pediatric thymectomies performed before and after the publication of the MGTX trial in 2016 is not available at present.

Regarding indications for surgery, symptoms and imaging:

While thymoma is rare in children, affecting just over 2% of children with JMG, thymomatous JMG is always surgical [22, 27-29]. As such, after diagnosis of JMG, either magnetic resonance imaging or computed tomography is performed to evaluate for the presence of thymic enlargement or thymoma [30]. When imaging suggests non-thymomatous disease, there is lack of consensus regarding the indications for surgical management. This is perpetuated by a lack of standardized classification system between existing pediatric studies. Likewise, available evidence regarding the role of thymectomy for patients with ocular vs generalized disease, pre- vs post-pubertal age at surgery, and seropositive vs seronegative antibody status remain insufficient [24].

The first categorization system developed, the Osserman Score, was introduced in 1958 [31]. Ranging from Class I to IV based on symptom severity and progression, Class I involves only the ocular muscles while Classes II-IV represent progressive and increasing severity of generalized muscle involvement [31]. Hans Oosterhuis published his scoring system in the 1980s after observing more than 400 patients with MG. Scores of 1-4 represent increasing degree of disability while 0 represents complete remission and 5 mechanical ventilatory dependence [32]. In 2000, the Myasthenia Gravis Foundation of America (MGFA) published the Quantitative MG Score (QMG) intended as the first objective system based on a patient's strength when performing specified actions [33]. This system was utilized in the MGTX trial; however, it has not been

adopted widely by pediatric studies which continued to use the Osserman or Oosterhuis classifications for grading preoperative disease severity [22]. However, the QMG was modified for pediatric patients by eliminating the grip strength test and incorporating a straw for bulbar strength evaluation to create the first JMG-specific scoring system that is both more developmentally appropriate and less impacted by a child's cooperability [34].

Despite this heterogeneity, most JMG cohorts are described as to whether disease is pure ocular or with generalized involvement. Although pure ocular disease is more common, nearly two-thirds of children who undergo thymectomy have generalized JMG [29]. In addition, there is a trend in some studies toward greater response to thymectomy for those with generalized and/or more severe disease than those with pure ocular type [22]. However, this was not found across all studies [22, 35, 36].

Approximately 80% and 3.5% of JMG patients have anti-AChR and anti-muscle specific tyrosine kinase (anti-MuSK) antibodies, respectively [22, 29]. Overall, data regarding the influence of seropositivity on response to surgery is insufficient [24]. The presence of anti-AChR antibodies has been shown to correlate with greater surgical response; therefore, anti-AChR seropositivity often contributes to the determination to pursue thymectomy [22, 37]. However, some patients who are anti-AChR negative respond to thymectomy; therefore, the role of surgery remains ambiguous for those with anti-MuSK antibodies or who are seronegative [22, 38].

Regarding age at surgery and duration of illness:

We have expanded upon this discussion significantly as you will find below. In addition, we have added the measures for age at thymectomy and duration of illness prior to thymectomy to the studies reported in Tables 2 and 4.

Changes in the text:

There is controversy regarding the impact of age and timing from symptom onset on the efficacy of thymectomy. A study with 31% CSR and 62% symptom improvement rates following thymectomy in 13 patients with mean (range) age at thymectomy of 10.8 (1.4-18.6) years and mean (range) time from disease onset of 9.2 (0.6-33.0) months found that time from onset to surgery was a mean 199 days longer in those who did not respond to thymectomy [25]. In a study performed on 141 patients with JMG with median (range) age at onset of 6 (1-18) years who underwent open transsternal resection at median (range) age of 12 (3-18) years found improved CSR rates when surgery was performed when patients are at least 12 years old [36]. However, the same study, demonstrated improved postsurgical outcomes when thymectomy was performed within 12 months of onset of generalized symptoms [36]. Conversely, a study by Kim et al. including 50 patients with JMG who underwent thoracoscopic thymectomy at mean (standard deviation, SD) age of 10.5 (0.8) years and mean (SD) time to thymectomy of 19.6 (4.2) months with 51.0% of patients with thymectomy within one year of disease

onset found no difference in outcome when evaluating age or timing of thymectomy relative to symptom onset [47]. A systematic review including 17 articles published between 1997 and 2020 encompassing 588 JMG patients who underwent thymectomy concluded that improved surgical outcomes may be associated with early intervention and post-pubertal intervention [22]. Moreover, by performing surgery early, children avoid growth failure, delay in bone aging and detrimental metabolic effects experienced by JMG patients who require prolonged glucocorticoids [46]. Overall, there may be benefit to performing surgery early relative to symptom onset, particularly for patients who are post-pubertal or with severe disease requiring prolonged use of high-dose steroids.

Cohort age at thymectomy and duration of illness prior to thymectomy have been added to Tables 2 and 4.

Comment 2: In previous studies, did thymectomy for JMG cause immunological consequence? In addition, did thymectomy cause any restriction on patients in short or long term? I wonder that patients who underwent thymectomy cannot receive bone marrow transplantation to treat leukemia.

Reply 2:
The immunological consequences of thymectomy for JMG has been expanded upon in the section "Surgical Candidacy". However, as surgeons, discussing the role of bone marrow transplant for post-thymectomy patients who develop leukemia is outside of the scope of our expertise and likewise this review; therefore, this has not been included in our narrative review.

Changes in the text:
Delaying thymectomy affords a chance for spontaneous remission, an event which occurs as often as 20-29% of the time in children [39]. Furthermore, the thymus is critical in the growth and development of a child's immune system; therefore, many argue that surgery should be postponed due to concern that removing the thymus while the immune system is still in development will have negative consequences later in life [22, 40-42]. As such, a study performed by Popperud et al. confirmed that thymectomy for JMG performed at median (range) age at thymectomy of 17 (2-33) years can lead to premature immunosenescence, including a reduced number of B cells, naive cytotoxic T cells and helper T cells and increased memory T cells at median (interquartile range) 12 (7-26) years after thymectomy was performed. However, these findings were not related to age at thymectomy nor with any discernible clinical consequence [43]. However, it is necessary to mention a 2023 case-control study in adults with MG who are five years or more post-thymectomy found thymectomized patients have not only decreased production of CD4+ and CD8+ lymphocytes and higher levels of proinflammatory cytokines but also a higher incidence of cancer and all-cause mortality compared to their non-thymectomized counterparts [44] .

Comment 3: I would like the authors to discuss the prognosis of patients who underwent thymectomy during childhood.

Reply 3:
The complete stable remission (CSR) rates and disease improvement rates are discussed for each surgical approach in their corresponding sections.

For open thymectomy:

When performed in children, disease improvement rates as high as 90-100% have been reported alongside CSR rates of 25-66% [36, 37, 54, 55].

For thoracoscopic thymectomy:

Small noncomparative studies evaluating outcomes following right and left thoracoscopic approaches demonstrate 50-100% disease improvement rates with minimal to no postoperative complications [47, 62, 65-69]. As mentioned, critics have argued that thoracoscopic thymectomy results in incomplete clearance of thymic tissue and is associated with lower remission rates compared to open thymectomy [3, 70-75]. However, retrospective studies comparing thoracoscopic and open thymectomy for JMG have found thoracoscopic thymectomy to have less operative blood loss, shorter postoperative length of stay, improved cosmesis and either a comparable or lower postoperative complication rate with no difference in postoperative disease control [22, 24, 34, 55, 76-78]. However, and notably, one study has identified incomplete resection with thoracoscopy [3, 24].

For robotic thymectomy:

When compared to non-operative management, patients who underwent robotic thymectomy for JMG had a higher 5-year cumulative CSR rate as well as reduced daily dose of cholinesterase inhibitors and corticosteroids; however, with a 19.1% postoperative complication rate. Although studies have not yet compared robotic-assisted thymectomy to other surgical approaches for JMG, studies completed in adults, including comparisons between robotic-assisted and thoracoscopic thymectomy, have demonstrated its safety alongside comparable clinical outcomes relative to sternotomy and superior outcomes compared to thoracoscopy [14, 80, 83].

Furthermore, in Tables 3 and 4, the post-surgical improvement rates and CSR rates are listed for all studies where this outcome was reported. However, as requested, this discussion has been furthered in regard to immunologic prognosis following thymectomy and factors which may result in an improved prognosis as outlined above.

Changes in the text:
As above for Comments 1 and 2.

Comment 4: In thymectomy for JMG, how much of the thymus should be removed? Is there any difference between children and adult regarding the area of the thymus that should be removed? Please also provide additional explanation regarding the extent of thymus that should be resected in thymomatous JMG.

Reply 4:
For optimized outcomes for both thymomatous and non-thymomatous MG and JMG, complete thymic resection is necessary. As requested, this has been expanded upon in the manuscript.

Changes in the text:
However, as incomplete clearance of thymic tissue is associated with reduced remission rates, complete thymic resection in both thymomatous and non-thymomatous JMG is critical. As such, experts have voiced concern that MIS approaches provide inadequate visualization, and therefore, incomplete extirpation of mediastinal fat and ectopic foci of thymic tissue [48-51].