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Practice advisory: Thymectomy for Myasthenia Gravis (Practice Parameter Update)

Report by:

Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

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Presentation Objectives

- To present updated evidence regarding the effectiveness of thymectomy for treating patients with myasthenia gravis (MG)
- To present practice recommendations regarding thymectomy treatment for patients with acetylcholine receptor antibody– positive generalized MG.

Overview

- Introduction
- Clinical question
- AAN guideline process
- Methods
- Conclusion
- Practice recommendations

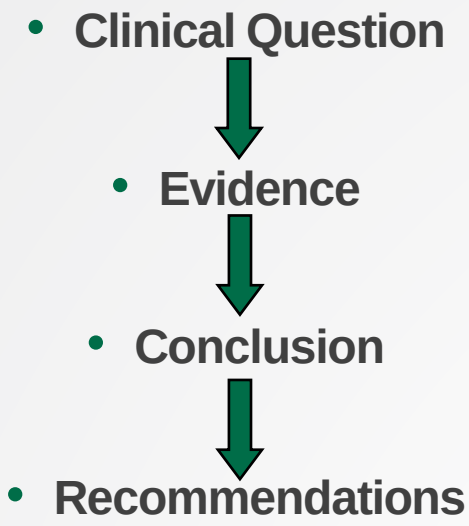
Introduction

- Reports of remission following thymectomy in patients with MG suggested a therapeutic benefit for patients with MG.[1]
- However, a practice guideline regarding the efficacy of thymectomy for MG treatment published by the AAN in 2000 concluded that it was impossible to determine "whether the observed association between thymectomy and improved MG outcome was a result of a thymectomy benefit or was merely a result of the multiple differences in baseline characteristics between the surgical and nonsurgical groups."[2] A randomized controlled trial was recommended.
- The results of a randomized trial of thymectomy in MG were published in 2016.[3]

Clinical Question

- This guideline addresses the following question:
  - For patients with generalized MG, is thymectomy, compared with medical therapy alone, effective in improving patient-relevant outcomes?

AAN Guideline Process*



*Guideline developed using the 2011 *AAN Clinical Practice Guideline Process Manual*, as amended.

Literature Search/Review

Rigorous, Comprehensive, Transparent

58 abstracts

1 included article

MEDLINE and the Cochrane Databases of Systematic Reviews and Controlled Clinical trials were searched for relevant articles March 1, 1998, to October 7, 2016; the search was updated January 16, 2019; March 24, 2019; and October 12, 2019.

Inclusion criteria:

- Patients (any age) with autoimmune MG observed a minimum of six months
- Random or pseudorandom allocation to therapeutic groups
- Any patient-relevant outcomes that were compared between thymectomy and nonthymectomy treatment groups
- Masked outcome assessment

Exclusion criteria:

- Case reports and case series
- Studies in which outcome assessment was not masked

Class I

A clinical RCT of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences.

The following are also required:
a. Concealed allocation
b. No more than two primary outcomes specified
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias.

e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following characteristics are also required*:

i. The authors explicitly state the clinically meaningful difference to be excluded by defining the threshold for equivalence or noninferiority.
ii. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective).
iii. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are comparable to those of previous studies establishing efficacy of the standard treatment.
iv. The interpretation of the study results is based upon a per-protocol analysis that accounts for dropouts or crossovers.

f. For crossover trials, both period and carryover effects examined and statistical adjustments performed, if appropriate.

* Note that numbers i to iii in Class Ie are required for Class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to Class III.

Class II
An RCT of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criteria a–e (see Class I) or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets items b–e (see Class I).
(Alternatively, a randomized crossover trial missing one of the following two characteristics: period and carryover effects described or baseline characteristics of treatment order groups presented.)
All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences.

AAN Classification of Evidence (2011)

Therapeutic Scheme

Class III	Class IV
• All other controlled trials (including studies with external controls such as well-defined natural history controls). • (Alternatively, a crossover trial missing both of the following two criteria: period and carryover effects described or baseline characteristics of treatment order groups presented.) • A description of major confounding differences between treatment groups that could affect outcome.** Outcome assessment is masked, objective, or performed by someone who is not a member of the treatment team.	• Studies that (1) did not include patients with the disease, (2) did not include patients receiving different interventions, (3) had undefined or unaccepted interventions or outcomes measures, or (4) had no measures of effectiveness or statistical precision presented or calculable.

**Objective outcome measurement: an outcome measure that is unlikely to be affected by an observer's (patient, treating physician, investigator) expectation or bias (e.g., blood tests, administrative outcome data).

Clinical Question

For patients with generalized MG, is thymectomy, compared with medical therapy alone, effective in improving patient-relevant outcomes?

Conclusion

- For patients with AChR ab+ generalized MG, treatment with thymectomy plus prednisone is probably more effective than treatment with prednisone alone for increasing the chance of attaining minimal manifestation status (MMS; risk difference at 36 months, 20%; 95% CI 1.6%−37%) and improving other MG-related outcomes, including decreased use of azathioprine or IV immunoglobulin rescue therapy and reduced number of hospitalizations for MG exacerbations (one Class I study, moderate confidence in the evidence; see figure e-2, table 1).

Table 1: Selected Secondary Outcomes in the MGTX Trial

Secondary outcome	Prednisone alone	Prednisone plus thymectomy	Mean difference (95% CI)
	Mean ± SD or N, (%)		
MG-ADL, 12 mo	3.33 ± 3.40	1.92 ± 2.73	1.42 (0.28 to 2.55)
MG-ADL, 24 mo	3.11 ± 2.93	2.02 ± 2.78	1.1 (0.03 to 2.17)
MG-ADL, 36 mo	2.69 ± 2.80	2.14 ± 2.92	0.55 (-0.53 to 1.63)
Azathioprine use	28/58 (48%)	11/65 (17%)	31.4% (15.6% to 47%)
Plasma exchange use	9/58 (16%)	10/65 (15%)	0.1% (-12.7% to 12.9%)
IV immunoglobulin use	23/58 (40%)	11/65 (17%)	22.7% (7% to 38%)
Hospitalization for MG exacerbation, 0–36 mo	22/60 (37%)	6/66 (9%)	19.2% (5.9% to 32.6%)

Abbreviation: MG-ADL = Myasthenia Gravis-specific Activities of Daily Living scale

Practice Recommendations

Recommendation 1

Rationale

- Thymectomy leads to meaningful benefits for patients with AChR ab+ generalized MG. In addition, transsternal thymectomy appears to be safe.[5]
- Because of the moderate benefits of thymectomy and the need for a major surgical procedure with its attendant discomforts and costs, there is likely to be considerable variability in patient preferences relative to undergoing thymectomy. However, the panel anticipates that most patients would want to be aware of the availability of thymectomy as a treatment option.

Practice Recommendations

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Recommendation Statement 1:

- Clinicians should discuss thymectomy with patients who have AChR ab+ generalized MG and are 18–65 years of age. The discussion should clearly indicate the anticipated benefits and risks of the procedures and uncertainties surrounding the magnitude of these benefits and risks (**Level B**).

Practice Recommendations

Recommendation 2

Rationale

- There are several surgical methods of thymectomy, with the goal of removing as much thymic tissue as possible safely while preserving phrenic, left vagus, and recurrent laryngeal nerve function. The classical method of thymectomy is an external transsternal thymectomy, facilitating complete removal of thymic tissue and fat. A transcervical approach uses smaller incisions but is rarely used alone because of inadequate visualization of the thymus; it may be combined with the transsternal approach. Minimally invasive techniques include video-assisted thoracoscopic thymectomy (VATS) or robotic-assisted thoracoscopic surgery, both with potentially higher risk for leaving residual thymic tissue.[10]

Practice Recommendations

Recommendation 2

Rationale, cont.

- It is uncertain whether the results of a thymectomy study using an extended transsternal approach can be generalized to minimally invasive thymectomy techniques that do not involve a median sternotomy. A randomized trial with unblinded outcome assessment comparing VATS with transsternal thymectomy demonstrated reduced blood loss, surgical times, intensive care unit stay, and hospitalization length for patients undergoing VATS but was underpowered to detect significant differences in MG clinical outcomes.[11] It seems likely, if otherwise equally efficacious in removing all thymic tissue, that patients with MG would prefer minimally invasive thymectomy techniques without a median sternotomy.

Practice Recommendations

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Recommendation Statement 2:

- **Recommendation 2:** Clinicians should counsel patients with AChR ab+ generalized MG considering minimally invasive thymectomy techniques that it is uncertain whether the benefit attained by extended transsternal thymectomy will also be attained by minimally invasive approaches (**Level B**).

Suggestions for Future Research

- It seems unlikely that future adequately powered randomized controlled trials with blinded outcome assessment of thymectomy will be completed given the logistical challenges and costs associated with the recently completed trial.
- Much can be learned, however, from prospective cohort studies designed to identify characteristics that predict which patients with MG benefit from thymectomy.
  - Such studies could also include pediatric and older patients with muscle-specific tyrosine kinase–positive, seronegative, and ocular types of MG.
- In addition, there is a need for well-designed observational studies comparing outcomes of minimally invasive thymectomy techniques with transsternal approaches.
- Finally, it will be informative to have registries of patients undergoing these procedures with long-term outcome assessments using both clinician- and patient-reported outcome measures

References

References cited here can be found in the practice guideline article. To locate this material, please visit AAN.com/guidelines.

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Questions?