A systematic review of diagnostic studies in myasthenia gravis
Benatar M

CRD summary
This review found that the accuracy of tests for the diagnosis of myasthenia gravis should be interpreted with caution, owing to the methodological limitations of the included studies. Although these conclusions appear appropriately cautious, they should be interpreted with extreme caution given the likelihood that relevant studies have been missed by the limited search conducted.

Authors’ objectives
To determine the accuracy of tests used for the diagnosis of myasthenia gravis.

Searching
MEDLINE was searched (years not reported). The search terms, which were reported, included a diagnostic filter. The references of retrieved articles were screened for additional relevant studies.

Study selection
Study designs of evaluations included in the review
Inclusion criteria were not defined in terms of the study design. The included studies used both a diagnostic cohort and case-control design.

Specific interventions included in the review
Inclusion criteria were not defined in terms of the intervention, but it appears that studies of any test for the diagnosis of myasthenia gravis were eligible for inclusion. The included studies assessed the ice test, rest test, Tensilon test, acetylcholine receptor antibodies, repetitive nerve stimulation and single-fibre electromyography (EMG).

Reference standard test against which the new test was compared
Studies had to specifically define the reference standard to be included in the review. The reference standards used by the included studies were one or more of the following: Gestalt, prestigmine test or EMG, anti-acetylcholine receptor antibodies, single-fibre EMG, Tensilon test, repetitive nerve stimulation decrement, EDX (not defined), response to therapy and extra-ocular/eyelid weakness.

Participants included in the review
Inclusion criteria were not defined in terms of the participants.

Outcomes assessed in the review
Studies had to report sufficient data to enable the calculation of the sensitivity and specificity. The outcomes reported in the review were the sensitivity, specificity and likelihood ratios (LRs).

How were decisions on the relevance of primary studies made?
The author did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Studies were assessed for methodological quality using the following criteria: prospective or retrospective study design; inclusion of a consecutive patient sample; diagnostic cohort or case-control design; interpretation of index test blinded to the results of the reference standard and vice versa; absence of incorporation bias. The author did not state how many reviewers performed the validity assessment.

Data extraction
Data were extracted separately for the diagnosis of ocular and generalised myasthenia; unless explicitly stated it was assumed that the patients had generalised myasthenia. The data were extracted as 2x2 tables, with 0.5 added to each cell to account for cells containing a value of zero. The sensitivity, specificity and LRs were calculated for each study. The
The author did not state how many reviewers performed the data extraction.

**Methods of synthesis**

**How were the studies combined?**

The pooled sensitivity and specificity were calculated, weighted for sample size. Pooled estimates were used to calculate summary LRs, which were then used to transform estimates of pre-test probability of disease to give estimates of post-test probability.

**How were differences between studies investigated?**

Separate analyses were conducted for studies evaluating ocular and generalised myasthenia, and for case-control and cohort studies.

**Results of the review**

The author stated that 20 studies were included. However, study details and results tables included data for 22 studies (number of participants not reported).

A diagnostic case-control design was used in 15 studies; the other 7 studies used a diagnostic cohort design. Data collection was prospective in 7 studies, consecutive patients were enrolled in 7 studies, 18 studies avoided incorporation bias, and blinding was reported in 5 studies.

**Ice test (7 case-control studies).**

Ocular myasthenia (3 studies): the sensitivity ranged from 93 to 97% and the specificity from 97 to 98%. The pooled sensitivity and specificity were 94% (95% confidence interval, CI: 90, 99) and 97% (95% CI: 94, 100), respectively. Generalised myasthenia (5 studies): the sensitivity ranged from 77 to 92% and the specificity from 97 to 98%. The pooled sensitivity and specificity were 82% (95% CI: 75, 89) and 96% (95% CI: 93, 100), respectively.

**Sleep/rest test (2 case-control tests).**

One study reported a sensitivity of 99% and a specificity of 91% for the diagnosis of ocular myasthenia. The other reported a sensitivity of 50% and a specificity of 97% for the diagnosis of generalised myasthenia.

**Anti-acetylcholine receptor antibodies (7 studies: 3 cohort studies, 4 case-control studies).**

Ocular myasthenia (6 studies): the sensitivity ranged from 39 to 71% and the specificity from 95 to 100%. The pooled sensitivity was 66% (95% CI: 63, 69) for the case-control studies and 44% (95% CI: 37, 52) for the cohort studies, while the pooled specificity was 99% (95% CI: 98, 100) and 98% (95% CI: 95, 100), respectively. Generalised myasthenia (6 studies): the sensitivity ranged from 87 to 98% and the specificity from 98 to 100%. The pooled sensitivity was 90% (95% CI: 88, 91) for the case-control studies and 96% (95% CI: 93, 99) for the cohort studies, while the pooled specificity was 99% (95% CI: 98, 100) and 99% (95% CI: 97, 100), respectively.

**Tensilon test (1 cohort study).**

The single study reported a sensitivity of 92% for ocular myasthenia and 88% for generalised myasthenia. Specificity was 97% for both types of myasthenia.

**Repetitive nerve stimulation (7 studies: 4 cohort studies, 3 case-control studies).**

Ocular myasthenia (5 studies): the sensitivity ranged from 11 to 39% and the specificity from 89 to 98%. The pooled sensitivity and specificity were 29% (95% CI: 22, 36) and 94% (95% CI: 91, 98), respectively. Generalised myasthenia (5 studies): the sensitivity ranged from 32 to 98% and the specificity from 95 to 98%. The pooled sensitivity and specificity were 79% (95% CI: 74, 84) and 97% (95% CI: 95, 99), respectively.

**Single-fibre EMG (6 cohort studies).**
Ocular myasthenia (6 studies): the sensitivity ranged from 62 to 99% and the specificity from 66 to 98%. Since the studies assessed different muscles, overall pooled estimates were not reported. Generalised myasthenia (2 studies): the sensitivity was 75% and 98%, and the specificity was 96% and 98%.

**Authors' conclusions**
The accuracy of tests for the diagnosis of myasthenia gravis should be interpreted with caution, owing to the methodological limitations of the included studies.

**CRD commentary**
The review addressed a very broad objective and inclusion criteria were only defined in terms of the reference standard and outcome. The literature search was limited to one database and included a diagnostic filter, and there were no attempts to locate unpublished studies. It is therefore highly likely that relevant studies have been missed and that the review may be subject to publication bias. A formal validity assessment was undertaken using relevant criteria, and the results of this were reported clearly and considered in the synthesis of data. The author did not report the number of reviewers involved at each stage of the review process, so it is not possible to determine whether appropriate steps were taken to minimise bias and error.

Some study details were reported in the tables, but there were no details about the participants in the included studies; this makes it difficult to determine the generalisability of the review findings. There appears to be some confusion regarding the number of studies included: the author stated clearly in the ‘Abstract’ and ‘Results’ that 20 studies were included, yet reported the results of 22 studies in the tables and provided references for these. The methods used to pool the studies were acceptable but the use of more statistically robust methods would have been preferable. Given the heterogeneity between the studies, pooling was only carried out within certain subgroups of patients and this resulted in a large number of pooled estimates which were somewhat confusing to interpret. Although subgroup analyses are appropriate to investigate heterogeneity, in some cases these subgroup analyses were unnecessary as pooled estimates were almost identical between subgroups. The author's cautious conclusions appear appropriate in light of the data, but should be interpreted with extreme caution given the likelihood that relevant studies have been missed by the limited search.

**Implications of the review for practice and research**
Practice: The author stated that the accuracy of tests commonly used for the diagnosis of myasthenia gravis may be poorer than previously supposed.

Research: The author stated that further studies of the accuracy of each of the tests investigated are required. The study populations in which these studies are carried out should be similar to the population in which the test will be used in practice, and should also include prospectively enrolled consecutive patients.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.