Does this patient have myasthenia gravis?
Scherer K, Bedlack R S, Simel D L

CRD summary
The review assessed the diagnostic accuracy of signs, symptoms and simple tests for myasthenia gravis. The authors concluded that some symptoms (speech becoming unintelligible after prolonged periods) and signs (peek sign) may be useful to confirm the diagnosis of myasthenia gravis, while the results of some tests (ice test, sleep test, response to anticholinesterase agents) may be useful to rule-in or rule-out the condition. The authors highlighted deficiencies in the methodology of the review and the primary studies, thus the results should be interpreted cautiously.

Authors' objectives
To determine whether elements of history and examination, or simple clinical test results, change the likelihood of a diagnosis of myasthenia gravis.

Searching
MEDLINE was searched from 1966 to January 2005 for articles in English; the search terms were reported. Additional studies were sought by scanning the bibliographies of retrieved articles.

Study selection
Study designs of evaluations included in the review
All of the included studies were diagnostic case-control studies. Studies based on a small number of patients were not excluded.

Specific interventions included in the review
Studies evaluating a specified sign or symptom were eligible for inclusion. Studies requiring sophisticated equipment or subspecialty-trained physicians were excluded. The signs and symptoms evaluated by the included studies were food in mouth after swallowing, unintelligible speech after prolonged speaking, peek sign and quiver eye movements. The simple tests evaluated by the included studies were ice test, anticholinesterase test, rest test and sleep test.

Reference standard test against which the new test was compared
No inclusion criteria for the reference standard were specified. All of the included studies were diagnostic case-control studies that compared the presence or absence of a sign or test result in patients with myasthenia gravis with its presence or absence in a control group. Where stated, the method of diagnosing myasthenia gravis was acetylcholine receptor antibody, acetylcholine esterase inhibitor, electromyography, repetitive nerve stimulation, edrophonium or neostigmine tests, or overall clinical impression.

Participants included in the review
The studies were required to include both patients with myasthenia gravis and controls.

Outcomes assessed in the review
No inclusion criteria for the outcome measure were specified. The review reported positive and negative likelihood ratios (LRs).

How were decisions on the relevance of primary studies made?
One author identified potentially relevant articles by screening titles and abstracts, while two authors independently reviewed the retrieved articles. Articles were included if it was agreed that the study met the inclusion criteria.

Assessment of study quality
The primary studies were graded on a 5-point level of evidence scale, with level one the highest. This assessed a number
of aspects of methodological quality relevant to diagnostic studies, e.g. participant selection and spectrum, use of an appropriate reference standard, blinding of comparisons, and study design (case-control or diagnostic cohort). Two authors independently assessed study quality.

Data extraction
Two authors independently extracted the data using a standardised instrument.

Methods of synthesis
How were the studies combined?
Positive and negative LRs, with 95% confidence intervals (CIs), were presented for each data set reported. For tests that were evaluated by more than one study (ice test and anticholinesterase test), summary LRs were estimated using a random-effects method.

How were differences between studies investigated?
The authors did not report a method for assessing between-study heterogeneity, but stated that the results across studies for the ice test and anticholinesterase tests were homogeneous.

Results of the review
Fifteen studies with a total of 896 participants (358 myasthenia gravis patients) were included. The proportion of participants with a diagnosis of myasthenia gravis ranged from 9 to 75%.

The majority of the studies included in the review (12 of the 15) were graded as evidence level four or five. No study in the review was rated as evidence level one.

Simple tests.

Based on the results of 7 studies, the pooled positive LR for the ice test was 24.0 (95% CI: 8.5, 67.0) and the pooled negative LR was 0.16 (95% CI: 0.09, 0.27). Also based on 7 studies, the pooled positive and negative LRs for the anticholinesterase test were 15.0 (95% CI: 7.5, 31.0) and 0.11 (95% CI: 0.06, 0.21), respectively.

The rest test and the sleep test were each evaluated by one study. The positive LR reported for the rest test was 16.0 (95% CI: 0.98, 261.0) and the negative LR was 0.52 (95% CI: 0.29, 0.95). For the sleep test, the reported positive and negative LRs were 53.0 (95% CI: 3.4, 832.0) and 0.01 (95% CI: 0.00, 0.16), respectively.

Symptoms.

'Food in mouth after swallowing' and 'unintelligible speech after prolonged speaking' were each evaluated by one study. The positive LR reported for 'food in mouth after swallowing' was 13.0 (95% CI: 0.85, 212.0) and the negative LR was 0.70 (95% CI: 0.58, 0.84). For 'unintelligible speech after prolonged speaking', the reported positive and negative LRs were 4.5 (95% CI: 1.2, 17.0) and 0.61 (95% CI: 0.46, 0.80), respectively.

Signs.

The peek sign and quiver eye movements were each evaluated by one study. The positive LR reported for the peek sign was 30.0 (95% CI: 3.2, 278.0) and the negative LR was 0.88 (95% CI: 0.76, 1.0). For 'quiver eye movements', the reported positive and negative LRs were 4.1 (95% CI: 0.22, 75.0) and 0.82 (95% CI: 0.57, 1.2), respectively.

Authors' conclusions
Items in the history and physical examination, along with some simple tests (ice test, sleep test, anticholinesterase test), are useful in predicting the presence of myasthenia gravis. The authors stated that these results should be interpreted with caution given the high prevalence of myasthenia gravis in the included study populations, and that further research is needed.
CRD commentary
This review addressed a clearly stated question. The inclusion criteria were, however, poorly defined; the use of broad inclusion criteria may have reflected the paucity of literature in this area and, as such, could be considered appropriate. The search was restricted to English language studies indexed in MEDLINE and those identified from their bibliographies, and this might have resulted in the incomplete retrieval of the available dataset. No attempt to identify unpublished material was reported and publication bias was not assessed. Appropriate steps were taken to minimise the potential for bias in the study selection process, data extraction and quality assessment processes. The methodological quality of the primary studies was assessed using a grading system appropriate to diagnostic studies, and the results were reported. In addition, the authors discussed the potential impact of aspects of methodological quality on the results of the review.

The description of the statistical or pooling methods used in the review was minimal, thus it was difficult to assess whether or not the approach taken was appropriate. The authors’ conclusions were suitably cautious given the limitations mentioned already and in their discussion.

Implications of the review for practice and research
Practice: The authors stated that the presence of certain symptoms (speech becoming unintelligible after prolonged periods) and signs (peek sign) may be useful in confirming the diagnosis of myasthenia gravis, but their absence does not rule it out. The ice test, sleep test, and response to anticholinesterase agents are useful in confirming and in ruling out the diagnosis. A positive test should prompt referral for confirmatory testing (acetylcholine receptor antibody testing, electrophysiologic tests), and should help confirm the diagnosis in patients who have negative results for the acetylcholine receptor antibody panel. Owing to the uncertainty surrounding sensitivity estimates, symptomatic patients with normal examination findings should be referred for specialist diagnosis.

Research: The authors stated that further research is needed to evaluate these and other, as yet unassessed, signs and symptoms that may be predictive of myasthenia gravis. Future studies need to evaluate intra-observer variability and agreement between experts and non-experts.

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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.