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A reappraisal of diagnostic tests for myasthenia gravis in a large Asian cohort☆

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ABSTRACT

Background: Myasthenia gravis (MG) is a chronic autoimmune neuromuscular disease characterized by weakness of bodily skeletal muscles. Office-based diagnostic tests such as repetitive nerve stimulation (RNS), single fiber electromyography (SFEMG), and the ice test, are used to refine the differential clinical diagnosis of this disease. Evaluating the clinical sensitivity and specificity of these tests, however, may be confounded by lack of a gold standard, non-blinding, incorporation bias, use of non-representative populations and retrospective data.
Objective: In this study comprising a large Asian cohort of 127 patients recruited from a Neuro-ophthalmology clinic, we minimized aforementioned confounders and tested the diagnostic value of 3 office-based tests against 2 reference standards of MG by virtue of clinical features, antibody assay and response to treatment.
Results: Regardless of the reference standard used, the ice and SFEMG tests displayed a higher sensitivity (86.0 to 97.3%) compared to the RNS test (21.3 to 30.6%). Conversely, the specificity of the ice (31.3%) and SFEMG (21.7% and 17.2%) tests were reduced compared to the RNS test (82.6% and 84.4%). The combined use of the ice test and SFEMG, improved the specificity of MG diagnosis to 63.6% and 64.3%, without affecting the sensitivity of those tests.
Conclusion: Our findings indicate, in an Asian population, high sensitivity of the SFEMG test and suggest the ice test as a valid, affordable and less technically demanding approach to diagnose MG with ocular involvement. Both ice test and SFEMG alone, however, yielded poor specificity. We suggest that the combination of SFEMG and ice test provides a more reliable diagnosis of MG.

1. Introduction

Myasthenia gravis (MG) is a relatively common neurological disorder resulting from an antibody-mediated neuromuscular transmission defect. The majority of patients present initially with ocular symptoms of fatigable ptosis and diplopia (ocular MG or OMG), and some progress to involve extraocular areas (generalized MG or GMG).

The diagnosis of MG has been discussed extensively, both in terms of sensitivity and specificity. Acetylcholine receptor and anti-MUSK antibodies are more often positive in GMG than OMG [1], and this may limit their usage in the latter presentation. For example, up to 70% of patients with OMG may be tested negative for acetylcholine receptor antibody; conversely, at least 70% of patients with GMG are positive for this antibody. Repetitive nerve stimulation (RNS) has a lower sensitivity than single fiber electromyography (SFEMG) [2]. However, SFEMG findings can be influenced by many co-existent factors, including presence of diabetes mellitus, neuropathy, myopathy and previous local trauma and surgery. The edrophonium test is less well-tolerated, but may not be easily interpretable when fatigability is not obvious.

Therefore, clinical information often remains the 'reference or gold standard' utilized in studies of this nature. A detailed critique of previous diagnostic studies by Benatar [3] found that confounding factors

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include non-blinding, incorporation bias, and use of a study population not representative of the actual clinical spectrum of MG.

In patients with ocular involvement, the ice test or ice pack test is a simple and well-tolerated office procedure [4]. However, its clinical value has not been ascertained in large studies. Considering all these elaborated issues, we sought to reappraise the value of electrodiagnostic investigations and the ice test in diagnosing MG in an Asian population.

2. Methods

A total of 127 Asian patients (66 men; mean age: 58.2; age range: 18 to 84 years; 89% ethnic-Chinese; 21 GMG and 106 OMG patients) were consecutively included in this study from a large Neuro-ophthalmological clinic, based on referrals for evaluation of ocular and/or neuromuscular complaints suggestive of MG. All patients had initial ocular symptoms and were followed up for a minimum of 2 years, as conversion to GMG may occur later in some patients. Ethics committee approval was obtained prior to the start of the study.

OMG was suspected in patients with variable, fatiguable ptosis and/or demonstrable variable ophthalmoplegia. Exclusion criteria included prior strabismus surgery as well as any other cause of paralytic strabismus. GMG was defined clinically as OMG patients presenting with or progressing onto having motor weakness, causing one of the following: dysphagia, dysarthria, dyspnea, or remote motor weakness, involving the neck or the extremities. Therefore, the reference standard for "possible" MG was based on presence of clinical features of OMG or GMG in association with at least one of the following clinical investigations: 1) positive acetylcholine receptor antibodies (AChR-Abs), 2) positive clinical response to treatment with pyridostigmine, corticosteroids or other immunomodulation therapy. These are used to form reference standards 1 and 2 below for the purposes of this study, against which all 3 investigations (ice test, RNS and SFEMG) are compared.

2.1. Ice test

The ice pack test is a clinically simple, safe, and affordable procedure, which can be performed in a clinical office or at the bedside, evaluating the effect of ice application on the ptosis. A standardized ice pack test was performed in seventy patients, in procedural agreement with previous studies [4]. The test was performed by an experienced neuro-ophthalmologist, who was blinded to the results of other investigations. After digital suppression of the action of the frontalis muscle, the interpalpebral distance was recorded vertically in both eyes, in the primary gaze, at the level of pupils' centers, using a millimeter ruler. After a baseline measurement of the interpalpebral fissure, the ice pack was applied bilaterally, during 2 min, followed by a new measurement within 10s after removal. An ice-induced enlargement of the palpebral fissure by >2 mm was considered a positive test. Since the pure ocular form of MG is frequently not detected by the traditional paraclinical tests, the ice test is an attractive diagnostic method for OMG, or MG patients with ocular presentation.

2.2. RNS

A health care technician blinded to the clinical features and to the SFEMG findings of each patient performed RNS in 103 patients. This was achieved with a Dantec 9013L0221 bipolar electrode held in place by a fixation strap for surface stimulation. Surface recordings (belly-tendon configuration) were made with disposable adhesive electrodes (Medtronic 9013S0211Medtronic, Skovlunde, Denmark). Studies were performed on a Dantec Keypoint EMG machine with amplifier filter frequencies set at 3 Hz and 5 kHz. Ten single square-wave pulses of 0.3-ms duration were used for each stimulation run at 3 Hz. Surface temperature was kept at 32 °C to 34 °C. Automated decrement calculations of baseline to negative peak amplitude and of negative peak area between the first and fourth supramaximal compound muscle action potentials (CMAP) were obtained. Each patient and control subject underwent five runs testing the abductor digiti minimi muscle aiming to record a mean percentage decrement. After a 5-min period of rest, the patient was instructed to maintain a maximal muscle contraction for 20 s. Immediate postexercise stimulation was performed to exclude the presence of an incremental response, defined as 100% increase in negative peak amplitude. Thereafter, similar 3-Hz stimulations were applied at 1, 2, and 3-min intervals. RNS recordings were made on the abductor digiti minimi muscle. A decremental response above 10% in any muscle recordings was regarded as a positive RNS result [5,6].

2.3. SFEMG

Ninety-nine patients underwent stimulated SFEMG of the orbicularis oculi [7]. This involved the use of disposable adhesive surface electrodes (TECA, Old Woking, United Kingdom) placed 2.5 cm away from the edge of the orbicularis oculi. Stimulation pulses of 0.1 ms at 10 Hz and 5 to 12 mA were administered. A 40-mm 9013K0872 needle electrode (Dantec, Skovlunde, Denmark) was inserted at the edge of the muscle for single-fiber recordings. Filter settings were maintained at 500 kHz to 10 kHz. Single-fiber responses were selected on the basis of short rise times (<300 μs), clear separation from other discharges and stability of waveform. Mean jitter was calculated from 20 accepted single-fiber responses. All SFEMG assessments were performed on a Dantec Keypoint EMG machine. The upper limit for normality for mean jitter was 23 μs. The examination was classified as abnormal if mean jitter exceeded this value and at least 2 of 20 responses had jitter values above 30 μs. The electrophysiologist performing SFEMG was blinded to the clinical findings and result of other tests.

2.4. Workflow

At initial presentation, patients were evaluated by a clinician and routed to separate facilities to undergo the ice test, RNS, and SFEMG. Treatment was initiated based on clinical impression and results of the ice test, given that the outcomes of the other investigations were only available a few weeks after the initial presentation. Patients were also investigated for presence of AChR-Abs. Assays were performed at an offsite facility. These results were available 20 weeks post initial presentation. Each patient had treatment escalation based on clinical response, which was collectively decided by the patient and managing physician. Non-responders were considered on an individual basis by the attending physician after all results were available, at or after 20 weeks. Blinding of personnel performing investigations was ensured in this standardized work flow (Fig. 1).

Patients with suspected OMG were offered a treatment if their fluctuating ocular signs (ptosis, diplopia) were associated with at least one of the following: 1) positive AChR-Abs 2) positive ice test 3) positive RNS or SFEMG, corroborating the clinical diagnosis. In OMG patients with isolated ptosis, the first line treatment was oral pyridostigmine for at least a 4 week period. Over the follow-up period, oral steroids (0.5 to 1 mg/kg/day over 8 weeks) were added if a patient developed additional symptoms and signs of GMG.

2.5. Statistical analysis

Two reference standards were used in this study to reflect the presence of MG in a patient.

2.5.1. Reference standard 1

A patient was considered as having MG if he presented with clinical complaints of OMG and/or GMG, and if he fulfilled at least one of the following two criteria: 1/positive AChR-Abs test or 2/showed improvement in response to treatment. This was to ascertain as accurately as possible a diagnosis of MG in view of a lack of internationally accepted gold standard, by incorporating both antibody positivity and clinical