ICE PACK TEST IN THE DIAGNOSIS OF MYASTHENIA GRAVIS

Diogo Fraxino de Almeida¹, Rafael de Figueiredo Radaeli², Aluisio Cláudio Mentor Neves Couto Melo Jr³

Myasthenia gravis (MG) is the most frequent neuromuscular transmission disorder with incidence of 2-20 patients per million. Its pathophysiology is autoimmune, with acetylcholine receptors (AChR) autoantibodies damaging the post-synaptic fold at the muscle membrane. MG often presents with isolated ocular symptoms, including diplopia and ptosis, at least at the onset. Even in patients with generalized symptoms, ocular signs occur in almost all patients in some point during the course of the disease. In up to 15% of the patients the disease remains confined to the eyes¹. Other clinical features include bulbar symptoms (dysphagia, dysarthria), proximal limb muscles weakness and fatigue. Unusual presentations as distal limb muscles weakness can also be found in a minority of cases²,³. The main characteristic of the MG is the fluctuating weakness during the day, being milder during the morning and more severe at the evening. Physical activity usually worsens the weakness. The diagnostic confirmation of MG is often challenging. The tests usually performed to confirm the diagnosis of MG are the edrophonium test (Tensilon⁶), repetitive nerve stimulation (RNS), single fiber EMG and serum acetylcholine receptors (AchR) antibodies. The most traditional bedside diagnostic test for myasthenia gravis is the edrophonium test. It has been considered diagnostic of MG in the past, however false-positive results have been reported in other neurologic disorders like amyotrophic lateral sclerosis, botulism and brain tumor⁴,⁵. Furthermore, it carries a risk of serious cardiac adverse reactions. Its sensitivity is about 86% in pure ocular disease⁶. Unfortunately it is not easily available in Brazil. Another bedside test that can be done is the sleep test, however this test is time consuming and probably not practical for the busy physician, since the patient has to take a nap of 15 to 20 minutes in a dark room for clinical comparison⁷. The other complementary tests have variable sensitivity and specificity. The diagnostic field of the RNS and AchR antibodies for pure ocular disease is quite low. The AchR antibodies are the most specific test for myasthenia gravis, however the sensitivity varies from 56% in pure ocular myasthenia according to Tabassi et al.⁸ to 70% in Oh et al.⁹ study. The repetitive nerve stimulation has even lesser sensitivity, varying from 35% in distal muscles to 45% in proximal muscles¹⁰. The most sensitive test for ocular myasthenia is single fiber EMG, reaching up to 80% in pure ocular cases and 95% in generalized disease⁹, however its specificity is low, the test is expensive, technically demanding and not widely available.

The ice pack test is a very simple, safe and cheap procedure that can be performed by the physician at the bedside¹⁰. Moreover, the ice pack test does not require medications or expensive equipment and is free of adverse effects¹¹. It consists of the application of an ice pack on the patient symptomatic eye for 3 to 5 minutes. The response is positive when there is improvement of the diplopia or ptosis (increase in at least 2 mm of the palpebral fissure from before to after the test). Considering that the pure ocular form of MG is frequently not detected by the traditional tests available, the ice pack test is an attractive diagnostic method for MG. We describe two cases where the ice pack test was done at the bedside for the diagnosis of MG and reviewed the literature about this test. Both patients have signed an informed consent authorizing the publication of the cases and photos showed in this article.

CASES

Case 1

A 35-year-old woman with history of diplopia, ptosis and fatigue for the last 7 years was first evaluated in another hospital and a diagnosis of MG was made based on clinical findings and a decremental response on the repetitive nerve stimulation test only on the accessory nerve (results not available). She was started on pyridostigmine 60 mg every 4 hours and in-
termittent courses of prednisone at the dose of 1 mg/kg/day. In spite of a partial response to the treatment, the symptoms were not adequately controlled. She was then referred to our clinic for a second opinion. She had a prominent left eye ptosis and diplopia with definite ophthalmoparesis. There were no other abnormalities on the neurologic examination. The AChR antibodies test was negative and the RNS test in facial, accessory and ulnar nerves was performed again in our laboratory with normal results. She was then submitted to the ice pack test on the left eye (Fig 1).

Case 2

A 35-year-old man complained of diplopia and ptosis in the last 3 months before the first evaluation at our EMG laboratory. The symptoms were fluctuating with worsening in the end of the day. There were no other complaints and no history of other diseases. The neurologic examination showed only left eye ptosis and mild ophthalmoparesis. The limbs strength was 5 on the MRC scale. The AChR antibodies were negative. He was then referred to our clinic to further evaluation. The RNS test showed more than 10% decremental response at 2, 3 and 5 Hz stimulation on the facial nerve with recording electrodes in the orbicularis oculi muscle. There was no decremental response on the accessory and ulnar nerves. The ice pack test was then performed to confirm the diagnosis (Fig 2).

**DISCUSSION**

Clinical and laboratorial experiences showed an important correlation between temperature and myasthenia gravis. It is widely known that warm temperatures worsen MG symptoms and cooling is able to ameliorate them. The improvement of MG with cooling probably occurs by lesser acetylcholinesterase activity in temperatures below 28°C, providing increasing amount of ACh molecules in the synaptic cleft. Based on this evidence, orbital cooling (ice pack test) has been developed as a simple, safe and reliable procedure for the diagnosis of ocular myasthenia.

The ice pack test seems to be both sensitive and specific when compared with the edrophonium test, although there are no randomized and controlled studies to validate it. The sensitivity in ocular myasthenia with ptosis associated or not with generalized symptoms is high varying from 80 to 100%. The ice pack is applied directly to the eyelid levator muscle and an objective improvement is observed. Golnik et al. concluded that the sensitivity of the test is lesser when complete ptosis is present. In the other hand, the specificity of the ice pack test is very high considering that it is not positive in other diseases that can simulate MG such as oculomotor nerve palsy, oculopharingeal muscular dystrophy and mitochondrial myopathies. False-positive results were virtually not seen. In a large study with 156 patients comparing ice pack test with the edrophonium test, the ice test had sensitivity and specificity of 100%. In such study, all cases with positive edrophonium test had positive ice test whereas none of the cases with negative edrophonium test had positive ice test. Therefore, the confidence of the test in the diagnosis of the MG is very good, supporting its use in the diagnosis of MG.

Some authors contest the theory that cooling is the responsible by the improvement of the ptosis in the ice pack test. Movaghar and Slavin compared the eyelid response after application of heat versus ice packs to a ptotic eyelid in patients with confirmed myasthenia gravis. They concluded that both heat and cold pack were able to cause improvement of the ptosis in all four tested patients. All their patients were then submitted to a modified sleep test, where the patients were asked to close the eyes for 15 minutes and keep resting. As all patients showed clear improvement, they concluded that neither cold nor heat were responsible by the improvement, stating that rest seems to be the relevant factor of ptosis improvement. In other study, Kubis et al. found that in myasthenic subjects the median improvement of the ptosis with ice was statistically significant when compared with rest alone. They concluded that eyelid elevation after the ice pack test is in part caused by rest, however the ice test significantly improves ptosis more than rest alone does. Although cooling is able to improve the muscle strength in myasthenic patients, decrease the muscle temperature below 22°C is not recommended because it can cause decrease the muscle fiber contraction force, rather than improve the neuromuscular transmission.

The reliability of the ice test in patients with mild ophthalmoplegia and diplopia without ptosis is probably lesser, because the findings are subjective. Saavedra et al. have not found any definite effect on ocular movements after the ice pack test, although Larner and Thomas stated clear subjective and objective effect of the ice pack.
test on eye movements. Except for this finding, further investigations and treatment provided no other evidence of MG in their case, making diagnosis uncertain. They recommended caution in making MG diagnosis based only on the ice pack test for patients with isolated diplopia and mild ophthalmoparesis, without any ptosis.

Electrophysiological improvement was also documented with the ice-pack test. Odabasi et al.27 documented a definite clinical and decremental response improvement in the RNS test in the facial nerves in three patients submitted to the ice pack test.

Benatar28 highlights that the majority of the literature studies about ice pack test in MG has employed a case-control design, in which patients with previous diagnosis of MG were compared to a control group. Usually these studies have a tendency to overestimate both sensitivity and specificity29. These methodological limitations need to be considered during the ice test interpretation.

In conclusion, the ice pack test is an easy, safe, cheap and reliable test to be used at bedside in the MG suspected patients with ptosis. It is safer and can replace the edrophonium test in MG with ptosis, since the specificity and sensitivity is 100% when compared with the edrophonium test30. It is useful even in patients with normal RNS and negative serum AChR antibodies. Caution should be taken on the interpretation of the ice test in patients with isolated diplopia without ptosis, mainly when there is no definite ophthalmoplegia. The major disadvantage of the ice test is that it is only applicable when ptosis is present. Thus it is not helpful in patients with isolated proximal limb weakness.

REFERENCES