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Letter to the Editor

Orthoptic measurements should not be used as a primary diagnostic tool for myasthenia gravis

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We read with interest the article by Keene *et al*. about 39 patients with myasthenia gravis seropositive for acetyl-choline receptor antibodies who underwent three orthoptic measurements (maximal eye duction angle, eye deviation between the eyes, and fatigability using standard Hess charts) to assess whether such examinations of extra-ocular eye muscles (EOMs) can be helpful in diagnosing myasthenia gravis [1]. The area under the curve (AUC) was found to be 0.73 comparing myasthenia to healthy controls, and 0.69 comparing myasthenia to disease controls for duction angles, 0.89 comparing myasthenia to healthy controls and 0.54 comparing myasthenia to disease controls for the outer field of the Hess chart, and 0.93 comparing myasthenia to healthy controls or disease controls for drift [1]. It was concluded that orthoptic measurements can be used to diagnose myasthenia gravis by quantifying EOM weakness and fatigability, and that drift during sustained gaze on a Hess chart is specific to myasthenia gravis and could be used for diagnostic purposes [1]. The study is appealing, but raises concerns that warrant further discussion.

The first limitation of the study is that the wording is ambiguous [1]. The term "ocular myasthenia gravis" is inappropriate [1]. It is either "ocular myasthenia'" or "myasthenia gravis" (generalised myasthenia). Included were 39 patients with myasthenia gravis, suggesting they had generalised myasthenia [1]. Therefore, the argument for orthoptic measurements that antibodies are negative in 50% of ocular myasthenias is not valid. Antibody testing is commonly negative in supposed "ocular myasthenia" when in fact it is mitochondrial progressive external ophthalmoplegia or other differentials of ophthalmoparesis.

The second limitation of the study is that the current anti-myasthenia medication, the latency between taking cholinergics and orthoptic measurements, adherence to that medication, current infections, co-medication, comorbidities, the time of day, prior physical activity, and whether the patient underwent thymectomy or not, were not standardised and included in the evaluation. All these factors strongly influence the degree of bulb movements and thus the results of orthoptic measurements. As long as these factors are not included in the evaluation, the study cohort examined is completely inhomogeneous and the results will therefore vary greatly and are therefore not suitable for drawing general conclusions. We therefore, disagree with the statement that myasthenia gravis can be diagnosed by orthoptic measurements [1]. Myasthenia is still diagnosed based on history, symptoms, signs, antibody testing, repetitive nerve stimulation, tensilon testing, and computed tomography (CT) of the mediastinum, which may or may not reveal a thymoma or thymic hyperplasia.

The third limitation is that the disease control group was very heterogeneous and therefore inhomogeneous. This cohort should not be used as a disease control group. Causes and pathophysiology of EOM weakness vary significantly between patients with Graves' orbitopathy, progressive external ophthalmoplegia, and patients with oculo-pharyngeal muscular dystrophy. We should also know whether the 14 patients with seronegative myasthenia gravis were positive for muscle tyrosine-kinase (MUSK) antibodies, LRP4 antibodies, or antibodies against titin.

Overall, the study carries obvious limitations that require re-evaluation and discussion. Clarifying these weaknesses would strengthen the conclusions and could improve the study. Before orthoptic measurements are recommended in myasthenia diagnostics, the recommended methods should be applied to homogenous study groups in order to generate reliable results.

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