Original Article

Myasthenia Gravis

Repetitive Nerve Stimulation Test, An Investigation that Helps in Confirming Diagnosis in Seronegative Myasthenia Gravis

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ABSTRACT

Objective: To assess the effectiveness of Repetitive Nerve Stimulation Test in the diagnosis of Seronegative Myasthenia Gravis.

Study Design: Descriptive Observational.

Place and Duration of Study: This study was conducted at Dow University of Health Sciences and Jinnah Postgraduate Medical Centre during the period of three years from 2010 to 2013.

Materials and Methods: A total 129 cases, both out patients as well as inpatients, who were diagnosed as a case of Myasthenia Gravis clinically and by other investigations including, Edrophonium Test, Chest Radiology, and Acetylcholine Receptor antibodies were studied.

Results: Out of 129 cases, of Myasthenia Gravis, who were admitted or came in outpatient department, 55 subjects are male. On Repetitive Nerve Stimulation study at 3Hz, significant decrement was found in trapezius in 16 (88%) patients who are seronegative and in 90 (81%) seropositive patients.

Conclusion: Repetitive Nerve Stimulation Test is a promising tool in the diagnosis of Myasthenia Gravis and should be a part of investigations used to diagnose this neuromuscular junction disorder especially in seronegative cases, for confirming the diagnosis.

Key Words: Nerve Stimulation Test, Seronegative Myasthenia Gravis, neuromuscular junction

INTRODUCTION

Myasthenia Gravis is a chronic autoimmune neuromuscular disease characterized by varying degrees of fatigue of the skeletal muscles of the body. The hallmark of this disease is muscle fatigue that increases during periods of activity and improves after periods of rest. As it is an autoimmune disorder the antibodies are either directed against the muscle nicotinic acetylcholine receptors (nAChR) itself or against other post synaptic targets such as the muscle specific kinase (MuSK) that indirectly reduce nAChR numbers. [1,2] Myasthenia Gravis can begin at any age, but onset in the first decade is relatively rare (10%). The peak age of onset is between 20 -30 years in female and between 50-60 years in male.[3] The incidence in female is higher under the age of 40 years whereas in later life it is higher in males. The initial symptoms or signs of Myasthenia Gravis are ptosis or extra ocular muscle weakness in up to 65% of patients. While increasing muscle fatigue, bulbar and proximal limb weakness occurs in generalized Myasthenia Gravis. Some patients may present with neuromuscular respiratory failure from the onset.[4] In addition to history and examination, various modalities are used for the diagnosis of Myasthenia Gravis including pharmacologic (Edrophonium Test)[5], electro diagnostic (Repetitive Nerve Stimulation & Single Fiber EMG)[6,7,8,9] and immunologic methods (Anti AChR Antibodies & Anti MuSK Antibodies).[10,11,12] The thymus has been implicated as having a central role in the pathogenesis of MG and thymic abnormalities such as thymic hyperplasia and thymoma are present in a large percentage of MG patients.[13,14] It has an association with thymic abnormalities, imaging (CT scan) of chest for detection of anterior mediastinum mass is also an important prelude especially when thymectomy is considered, in addition to pharmacological treatment both symptomatic and immune modulating.[15,16,17]

The term seronegative myasthenia gravis (SNMG) refers to the generalized disease without detectable anti-acetylcholine receptor (anti-AChR) antibodies. In these patients, 70 % cases have IgG antibodies against the muscle-specific kinase (MuSK) have been described[9,10].

MATERIALS AND METHODS

Hundred twenty nine consecutive patients (55 men and 74 women; mean age 40 years in seropositive and 33 years in seronegative patients) with generalized Myasthenia Gravis, seen at Dow University of Health Sciences and Jinnah Postgraduate Medical Centre, were studied during the period of 3 years from 2010 to 2013. For diagnosis of generalized Myasthenia Gravis, we required involvement of Neck and proximal muscles

weakness, Ocular symptoms for example Ptosis, Diplopia, Bulbar muscles involvement for example Dysphagia, Respiratory muscles weakness. With history of Episodic generalized body weakness and reduced exercise tolerance. These patients have positive response to edrophonium injection, electrophysiological evidence of a defect in neuromuscular transmission decrement on repetitive nerve stimulation test, or positive acetylcholine receptor or MuSK antibodies. Edrophonium was injected intravenously. Initially 2 mg was given as a test dose. If this was tolerated and no definite improvement in strength occurred after 30 seconds another 8 mg was injected. A positive test consisted of obvious improvement in blepharo-ptosis and/or muscle strength, and equivocal improvement was regarded as negative. Patients with Sensory symptoms, History of sphincter involvement, upper or lower motor neuron signs, with Pupillary Involvement and with Constant weakness, were excluded from the study.

Patients' clinical disabilities were evaluated using the Osserman's Scale[18] and Myasthenia Gravis Foundation of America (MGFA) clinical classification.[19] In patients receiving anticholinesterase medication, this medication was withdrawn 24 hours before the electrophysiological examination.

Electrophysiology: Repetitive nerve stimulation was performed in patients by using the Neuro-pack electro diagnostic machine by Nihon Kohdan. The recording was done on proximal, distal and facial muscles (in case of Ocular Myasthenia) on either side at 34 degree Celsius skin temperature. Repetitive nerve stimulation test was carried out at 3 Hz in abductor digiti minimi, trapezius, orbicularis oculi, and nasalis by stimulating ulnar nerve at wrist, spinal accessory at Erb's point and facial nerve respectively. Ten supramaximal stimuli were delivered at 3 Hz, at rest, 10 sec and the consecutively for 3 min after 1 minute of maximal voluntary contraction of the target muscle. A decrement exceeding 10% in the baseline to peak amplitudes in nasalis muscles and 15% or more in trapezius and abductor digiti minmi, between first and fifth response was considered significant (fig.1).

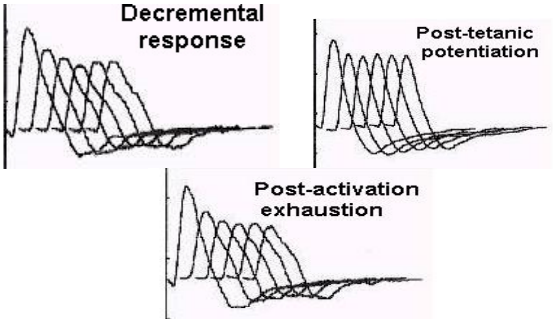

Figure No.1:

When no decrement was obtained from the muscle at rest, a one minute voluntary exercise was given and RNS repeated after two and four minute. The distal compound muscle action potential was recorded and when found to be ambiguous; a 10 sec post exercise response was recorded to rule out any increment due to a presynaptic neuromuscular defect.

Antibody Assays: AChR antibodies were measured by a standard radioimmunoprecipitation assay using human adult type AChR as antigen.

RESULTS

In this study the effectiveness of Repetitive nerve Stimulation study (RNS), in seropositive and seronegative myasthenia gravis is compared. The Seropositive and seronegative groups were compared with regard to significant decrement on repetitive nerve stimulation at 3 Hz. Out of 129 patients with Myasthenia Gravis, 18 appeared to be seronegative (13.9%).

Table No.1: Age Distribution (n=129)

Age in years	Frequency/Percent
Under 15	0
19-29	27
30-40	40
41-50	36
51-60	18
60 & above	08

Table No.2: Clinical and laboratory data of the patients with Myasthenia Gravis:

	Seropositive (n= 111)	**Seronegative (n = 18)**
Age in Years, (Mean)	19-64 (40.35)	22-48 (32.9)
Male:Female	48:63	7:11
Positive Edrophonium Test	90%	64%
Thymoma	1%	0%
Thymic Hyperplasia	10%	5%

Table No.3: Significant Decrement on Repetitive Nerve Stimulation Test in patients with Myasthenia Gravis:

	Seropositive (n= 111)	**Seronegative (n = 18)**
Nasalis	70 (63%)	13 (72%)
Trapezius	90 (81%)	16 (88%)
Abductor Digiti minimi	75 (67%)	14 (77%)

According to age distribution chart most common age of presentation of Myasthenia Gravis is between 30 to 40 years (Table 1). In seropositive patients it is about 40 years and in seronegative patient the mean age of onset in around 32 years.

Positive edrophonium test is found in 90 % of seropositive and 64 and 46% in seronegative. Thymoma is found in only 1 % seropositive patient. While 10% seropositive cases have thymic hyperplasia. Thymoma was not seen in Seronegative, patients, but 5% of them have thymic hyperplasia. (Table 2).

When comparing Repetitive Nerve Stimulation test with a frequency of 3 Hz in Trapezius muscle both in Seropositive and seronegative patients', it was found that 88% patients who were seronegative have significant decrement, which was nearest to the decrement response in seropositive patients. This response can also be seen in abductor digiti minimi muscle (Table 3), and it reflects the significance of Repetitive Nerve Stimulation test in confirming diagnosis of Seronegative Myasthenia gravis.

DISCUSSION

In this study, the effectiveness of Repetitive Nerve Stimulation Study in Seronegative as well as seropositive Myasthenia Gravis is evaluated. Myasthenia Gravis is a chronic autoimmune neuromuscular disease characterized by varying degrees of weakness of the skeletal muscles of the body. In more than 80% patients antibodies to acetylcholine receptor are detected by serology[2,10]. Approximately, 12% to 17% of patients with generalized Myasthenia Gravis lack demonstrable serum Acetylcholine receptor antibodies, and they are referred to as the seronegative myasthenia gravis[11,12]. In our study 13.9% patients were seronegative.

The change in muscle response to repetitive nerve stimulation has become the most commonly used test for the diagnosis of Myasthenia Gravis. It has shown to be a useful diagnostic technique provided it is used correctly and to its full capability. It has also given additional knowledge about Myasthenia gravis[7,8].

There is normally no change in size of the responses to paired or repetitive shocks delivered to the motor nerve at rates of up to 10 Hz or in the response to single shocks delivered before and after maximum voluntary activity or tetanic stimulation. In myasthenia gravis, a progressive decrement in the response may occur with repetitive stimulation (especially at 2 to 3 Hz), or an initial decrement may be followed by a leveling off of the response at a reduced size. Abnormalities are more likely to be found in proximal rather than distal limb muscles and in facial rather than limb muscles. Repetitive nerve stimulation at 3 Hz is positive in about 75% of patients with generalized Myasthenia Gravis.[20] Repetitive Nerve Stimulation Test is found in significantly higher number of Seronegative Myasthenic Patients[21].

In contrary to the study (D.E. Stickler) that conclude the insignificant electrophysiological results in seronegative patients, we have found a considerably good percentage of Seronegative patients who have significant decrement on Repetitively Nerve Stimulation Test [22].

One study suggests that, for individual patients with an atypical picture of Myasthenia Gravis by dissociation between a severe clinical pattern and no definite neurophysiological findings on conventional tests, repetitive nerve stimulation and/or stimulated single-fibre EMG with an increasing stimulation rate may be helpful[23].

Another study showed that Repetitive nerve stimulation (RNS) abnormalities were observed in 86% of Muscle Specific Kinase antibody-positive and 82% of Acetylcholine Receptor antibody positive patients[24].

In our study it is found that 77.7% patients with seronegative myasthenia gravis have significant decrement on repetitive nerve stimulation at 3Hz which is nearest to decrement found in seropositive patients.

CONCLUSION

This study reports the result of Repetitive Nerve Stimulation study in seronegative as well as seropositive myasthenia gravis. This brings about the usefulness of this simple diagnostic tool in the evaluation of patients with myasthenia. This test proved its effectiveness equally in seropositive as well as in seronegative myasthenia gravis and for the confirmation of Seronegative Myasthenia Gravis where the diagnosis is in doubt.

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