ASSESSMENT OF NEUROMUSCULAR JUNCTION INTEGRITY IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Diabetes Mellitus produces long-term damage and failure of various tissues, in particular, diabetes-induced neural damage. Changes of neuromuscular transmission would contribute to the progressive weakness in diabetic patients; Electrophysiological studies are of recognized use in the confirmation of alterations of neuromuscular transmission and helping to differentiate them from other conditions.

The current study was performed to evaluate the integrity of neuromuscular junction (NMJ) in patients with type 2 diabetes using repetitive nerve stimulation (RNS) technique and assessment of acetylcholine receptors antibodies in the serum.

Patients and Methods: This cross-sectional study involved 103 patients with type 2 diabetes mellitus. The entire subjects met certain inclusion and exclusion criteria to exclude other possible contributing factors of neuropathy. All subjects completed a pre-requested questionnaire, then physical and neurological examinations were done, routine nerve conduction study, repetitive nerve stimulation and assessment of acetylcholine receptors antibodies were performed.

Results: Among 103 patients with type 2 DM patients 56 of them were diagnosed as peripheral polyneuropathy however, the rest (47) their NCS result were normal, 11 (10.7%) of them showed positive decrement test, All those with positive decrement test they have also peripheral polyneuropathy, serum acetylcholine receptor antibody test was negative in all the participants (those with positive and negative decrement test).

Conclusions: This preliminary study implies that type 2 diabetes contributes to the neuromuscular junction dysfunction. Further studies are indicated to explain the pathophysiology and mechanisms responsible for positive decrement test in type 2 diabetic patients.

Keywords: Diabetes Mellitus, Neuromuscular Junction Dysfunction, Repetitive Nerve Stimulation.

Hyperglycemia associated with diabetes mellitus (DM) produces long-term damage and failure of various tissues. In particular, diabetes-induced neural damage is a predominant form of neuropathy. Changes of neuromuscular transmission would contribute to the progressive muscle weakness in diabetics. Therefore, the goal of this study was to further explore the effects of diabetes on the neuromuscular junction (NMJ).

Neuromuscular junction (NMJ) disorders are characterized by fluctuating muscle weakness, depending on the site of neuromuscular transmission failure, NMJ disorders have been classified as: (A) presynaptic (e.g., Lambert-Eaton myasthenic syndrome), (B) synaptic (e.g., cholinesterase inhibitor toxicity), and (C) post-synaptic (e.g., myasthenia gravis).

Electrophysiological studies are of recognized use in the confirmation of
alterations in neuromuscular transmission and helping to differentiate them from other conditions\(^5\).

Electrodiagnostic techniques used for investigation of NMJ disorders include repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG)\(^6\). Recent literature widely explores the use of SFEMG in the diagnosis and monitoring of myasthenia gravis, but this technique is time consuming and has a lesser role in the daily clinical practice\(^7\). RNS is the most widely used electrodiagnostic method in the evaluation of suspected neuromuscular transmission disorders. RNS is technically easier and does not require special technical training and skill as SFEMG\(^7,8\).

The technique of RNS is similar to that used in conventional nerve conduction studies, differing only in the application of stimuli trains or paired stimuli, the use of conditioning exercise, and the careful immobilization of the limb to reduce movement artifact. A decrement of more than 10\% on slow RNS (2 or 3 Hz) is characteristically seen in patients with postsynaptic disorder, while increments usually exceeding 50-200\% of the baseline value in amplitude seen in presynaptic disorder, marker of synaptic efficacy\(^9\).

**MATERIALS AND METHODS**

This cross-sectional study was conducted at the Department of Medical Physiology, College of Medicine, University of Sulaimania and Sulaimania Diabetes Center, from December 2017 – July 2018. The study included one hundred three patients diagnosed as type 2 diabetes mellitus (T2DM), (80 female, 23 male), with an age ranging from 38 to 72 years (mean ± SE =55.14 ± 0.67 years). Patients diagnosed as type 2 diabetes mellitus regardless of the duration of the illness were included in the study. However, Patients with the following conditions were excluded: rheumatoid arthritis, thyroid disease, alcoholism, liver and kidney disease, drugs known to cause neuropathy or myopathy, pregnancy, positive family history of neuropathy or myopathy. All patients gave their informed consent; the study has been approved by Ethical Committee of College of Medicine.

Physical examinations were performed to assess knee and ankle jerk, muscle power and perception to vibration. Nerve Conduction Study examinations were performed according to the standard method recommended by the American Diabetes Association\(^10\), using Neurowerk EMG/EP measuring machine (4 channel, Germany) at 20 to 25°C room temperature. The following nerves were examined: a- Motor nerve conduction study of posterior tibial, peroneal, femoral, median, ulnar and musculocutaneous nerves, b- Median, ulnar, radial and sural sensory nerve conduction study, c- F waves minimum latency (Fmin) of posterior tibial, peroneal, median and ulnar nerves.

Standard methods and techniques for assessment and evaluation of neuromuscular junction integrity by RNS were performed\(^11,12,13,14\). Serum acetylcholine receptors antibodies were assessed using EUROIMMUN ELISA (IgG) kit.

**RESULTS**

Among the 103 patients with type 2 DM, routine NCS showed that 56 of the participant have peripheral
polyneuropathy; however, the rest (47) their NCS result were normal (Figure 1).

RNS including both increment and decrement tests were performed for the entire participant, 92 (89.3%) of patients showed negative decrement test (Table 1), and (Figures 2, 3),

11 (10.7%) of them showed positive decrement test (Figure 2). As demonstrated in Table 2, and 3.
Table 3: Shows Positive Decrement Test in One Diabetic Patient Showing 30% Decrease of CMAP Amplitude Before Exertion and 13% after Exertion.

<table>
<thead>
<tr>
<th>Sequence Accessory nerve 3 Hz</th>
<th>Before exertion (base line)</th>
<th>Immediately after 10 second of exercise (post exercise facilitation)</th>
<th>2 minutes after 60 seconds of exercise (post exercise exhaustion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampl. 1 [mV]</td>
<td>11.6</td>
<td>12.5</td>
<td>11.3</td>
</tr>
<tr>
<td>Ampl. 4 [mV]</td>
<td>8.1</td>
<td>10.8</td>
<td>7.5</td>
</tr>
<tr>
<td>Dec [%]</td>
<td>-30</td>
<td>-13</td>
<td>-35</td>
</tr>
<tr>
<td>Stim. [mA]</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
</tbody>
</table>

Also, Figure 4 and 5 significant decrements (more than 10%) of compound muscle action potential amplitude between the first and fourth motor response were observed. Increment test was negative in all participants.

Estimation of serum acetylcholine receptor antibodies was done for all the patients and the results were negative in all the participants (those with positive and negative decrement test).

DISCUSSION

Target organ complications secondary to diabetes are one of the most important medical concerns. A clear example is diabetic neurological complication, which is the most common and early complication of diabetes affecting up to 60% of diabetic patients.

Several studies have been carried out to examine the effect of type 1 diabetes on neuromuscular junction and association between myasthenia gravis and the occurrence of type 2 diabetic as a consequence of high dose of steroid therapy. To the best of the researcher’s knowledge, limited investigations have examined the impact of type 2 diabetes on NMJ function, in present study we assessed neurophysiological assessment of normal RNS, the gender distribution among those with positive decrement test were 7 females and 4 males.
impact of neuromuscular junction function in 103 patients with type 2 diabetes, 11 of them show significant decremental response and all of these patient have coexisting diabetic polyneuropathy, a finding consistent with experimental studies conducted by Marques and Santo\textsuperscript{17} and Souayah et al\textsuperscript{18} on streptozotocin-induced type 1 diabetic mice, they found that diabetic neuropathy is associated with functional and morphological changes of the neuromuscular junction (NMJ), in addition to that current results may explain the clinical aspects of an experimental study on type 1 induced diabetic mice performed by Garcia et al\textsuperscript{19}, they showed that NMJ undergoes dramatic changes of function, morphology and the reduction of muscle end-plate cholinesterase (AchE) that may contribute to endplate pathology and subsequent muscle weakness during diabetes.

In present study serum acetylcholine receptor antibody was negative in all diabetic patients with polyneuropathy including those with positive decrement test, these findings are in accordance to that reported by Wakat et al\textsuperscript{20} that type 2 diabetes associated neuromuscular junction dysfunction have no organ specific autoantibody to neuromuscular junction.

Current preliminary findings indicate that type 2 diabetes contributes to neuromuscular junction dysfunction. Further extensive investigations are recommended to elucidate the mechanism responsible for this dysfunction and positive decrement test in type 2 diabetic patient with peripheral polyneuropathy.

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ASSESSMENT OF NEUROMUSCULAR JUNCTION INTEGRITY IN PATIENTS

Introduction:

Neuromuscular junction integrity is assessed in patients with various neurological disorders, including myasthenia gravis. The assessment of neuromuscular junction integrity helps in evaluating the function of the neuromuscular junction and identifying potential abnormalities that may lead to muscular weakness and fatigue.

Methodology:

The assessment of neuromuscular junction integrity involves the use of electrophysiological techniques such as repetitive nerve stimulation and incremental dose of curare. These techniques help in determining the integrity of the neuromuscular junction by observing the response of muscle fibers to nerve stimulation.

Results:

The results of the assessment of neuromuscular junction integrity in patients with myasthenia gravis showed a significant reduction in the response of muscle fibers to nerve stimulation, indicating a decrease in the number of functioning neuromuscular junctions.

Conclusion:

The assessment of neuromuscular junction integrity is a valuable tool in the diagnosis and management of neurological disorders, particularly myasthenia gravis. It helps in monitoring the progression of the disease and the effectiveness of the treatment regimen.

References:


The conclusion of the assessment of neuromuscular junction integrity in patients with myasthenia gravis is that the neuromuscular junction integrity is significantly reduced, indicating the need for further investigation and intervention to improve the quality of life and prevent complications.
تقييم سلامة الاتصال العصبي العضلي لدى مرضى النوع الثاني من داء السكري

الخلفية والأهداف: يؤدي داء السكري إلى أضرار طويلة الأمد وفشل الأنسجة المختلفة، وعلى وجه الخصوص، الأضرار العصبية الناجمة عن مرض السكري. التغيرات في انتقال العصبي العضلي يمكن أن تساهم في ضعف الترديجي للعضلات خلال مرض السكري. تعتبر الدراسات الفيزيولوجية الكهربية ذات استخدام معتمد في تأكيد تغييرات الانتقال العصبي العضلي وتساعد على تمييزها عن الحالات الأخرى.

تم إجراء الدراسة الحالية لتقديم وظيفة الاتصال العصبي العضلي في المرضى الذين يعانون من مرض السكري النوع 2 باستخدام تقنية تفتيش العصب المتكرر وتقسيم الأجسام المضادة لمستقبلات الأسيتيل كولين في المصل.

الموضوعات وطرق البحث: شملت هذه الدراسة المستعمرة 103 مريض يعانون من داء السكري من النوع الثاني. استمرت الدراسة جميع معايير تضمين واستبعاد معينة لاستبعاد العوامل الأخرى المحتملة التي تساهم في الاعتلال العصبي.

النتائج: من بين 103 مريضا، قد يكون 56 منهم باعتلال الأعصاب المحيطة أمازيجية (47%) كانت نتيجة طبيعية، أظهر 11 (10.7%) منهم اختبار تناقص إيجابي، وكل أولئك الذين لديهم اختبار تناقص إيجابي لديهم أيضا اعتجال الأعصاب المحيطة، وكان اختبار الأجسام المضادة لمستقبلات الأسيتيل كولين ساسي في جميع المشاركين (أولئك الذين لديهم اختبار تناقص إيجابي وساسي).

الاستنتاجات: تشير هذه الدراسة الأولية إلى أن مرضى السكري من النوع الثاني يساهم في ضعف الاتصال العصبي العضلي، وتحتاج إلى دراسات أوسع لبيان الفيزيولوجيا المرضية والآليات المسؤولة عن اختبار تناقص إيجابي في مرضى السكري من النوع الثاني.