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Review

6MWT can identify type 3 SMA patients with neuromuscular junction dysfunction

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Abstract

The aim of the study was to establish if the decrease in gait velocity on the 6 minute walk test relates to signs of neuromuscular junction dysfunction in spinal muscular atrophy type 3 patients. 6 minute walk test and low-rate repetitive nerve stimulation test were performed in fifteen ambulant patients with spinal muscular atrophy type 3 of age between 9 and 66 years. The 6 minute walk distance ranged between 66 and 575 m. The difference between the first and the 6th minute ranged between 0 and −69%. The low-rate repetitive nerve stimulation test measured in % of loss ranged between −31.7% to +4.2% to the axillary nerve. The correlation between 6 minute walk test changes and low-rate repetitive nerve stimulation test changes was 0.86. Our data suggest that the 6 minute walk test can identify fatigue in the ambulant type 3 patients who have a concurrent neuromuscular junction dysfunction. The identification of fatigue with a simple clinical test may help to target patients who may benefit from drugs that facilitate neuromuscular transmission.

Keywords: Spinal muscular atrophy; 6 minute walk test; Low-rate nerve stimulation; Fatigue; Neuromuscular junction; Neuromuscular disorders

1. Introduction

Spinal muscular atrophy is a neuromuscular disease characterized by degeneration of α-motor neurons in the spinal cord due to homozygous functional loss of the survival motor neuron 1 gene [1].

There has been increasing evidence that, in addition to muscle weakness, SMA patients may also experience fatigue and signs of impaired neuromuscular junction [2–6].

Using low-rate repetitive nerve stimulation (LRNS) in SMA patients, abnormal decrement response was found in 49% of them [5]. This was thought to be due to marked developmental abnormalities in the anatomy of the neuromuscular junction.

Other studies, using the 6 minute walk test (6MWT) in ambulant type 3 SMA reported a decrease in gait velocity during successive minutes, suggesting that the 6MWT could be used to measure fatigue in these patients [3].

In both neurophysiological [5] and clinical studies [2] the signs of fatigue were not consistent across all the ambulant type 3 patients examined. So far no systematic study has been performed to establish a possible correlation between the two measures.

The aim of our study was to establish if the decrease in gait velocity dysfunction on the 6MWT relates to signs of neuromuscular junction dysfunction on LRNS in ambulant type 3 patients.

2. Methods

Fifteen ambulant type 3 SMA patients (7 type 3a with onset before 3 years, 8 type 3b) were asked to participate in this study. All patients had a genetically confirmed diagnosis of SMA. The Ethics committee of our institution approved the protocol and

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written consent was obtained from all participants or their guardians.

2.1. 6MWT

6MWT was performed according to the ATS guidelines. Participants were instructed to walk as fast as possible along a 25-m linear marked course for 6 minutes. The use of assistive devices such as ankle foot orthoses was not permitted during the assessments.

Distance walked each minute was recorded, noting both the total distance covered in 6 minutes (6MWD) and the difference between the first and the 6th minute expressed in % change.

2.2. Repetitive nerve stimulation

LRNS test was performed registering from deltoid (axillary nerve) in all patients and, when possible, if patients agreed, also from abductor digiti minimi (ulnar nerve), and orbicularis oculis (facial nerve) following the protocol routinely used in our lab [7]. Supramaximal stimulation was given at Erb's point, wrist, and mastoid, respectively. The peak-to-peak amplitude of the compound muscle action potential (CMAP) was measured. A decrement ≥10% was taken as the cutoff point to identify neuromuscular junction dysfunction.

2.3. Statistical analysis

The changes on both measures were correlated.

Sensitivity and specificity of the 6MWT to identify neuromuscular junction dysfunction on repetitive nerve stimulation were also used.

3. Results

3.1. 6MWT

The total 6MWD ranged between 66 and 575 m. Fig. 1 and Table 1 provide individual details of the distances achieved at each minute during the 6MWT. The difference between the first and the 6th minute ranged between 0 and −69%. In 11 of the 15, the changes were more than −10% (Table 1). These were found in 7 patients with type 3a and in 4 with type 3b.

3.2. Repetitive nerve stimulation

Regarding axillary nerve the LRNS % loss ranged between +4.2% to −31.7%. Nine of the 15 had values beyond the cutoff point of more than −10%. These were found in 6/7 patients with type 3a and in 3/8 with type 3b. (Table 1). LRNS were normal from ulnar nerve and facial nerve when examined.

4. Statistical analysis

The correlation between 6MWT changes and LRNS changes was 0.86 (Fig. 2).

Sensitivity was 1 and specificity was .67. Positive predictive value was .81 and negative predictive value was 1.

5. Discussion

Our results confirmed previous findings [2–4,8] that signs of fatigue on the 6MWT, expressed as a decrease in gait velocity between the first and the last minute, are common (73.3%) in type 3 SMA patients. This cannot be attributed to weakness as patients with other neuromuscular disorders, such as Duchenne muscular dystrophy, have a more regular pace and do not show

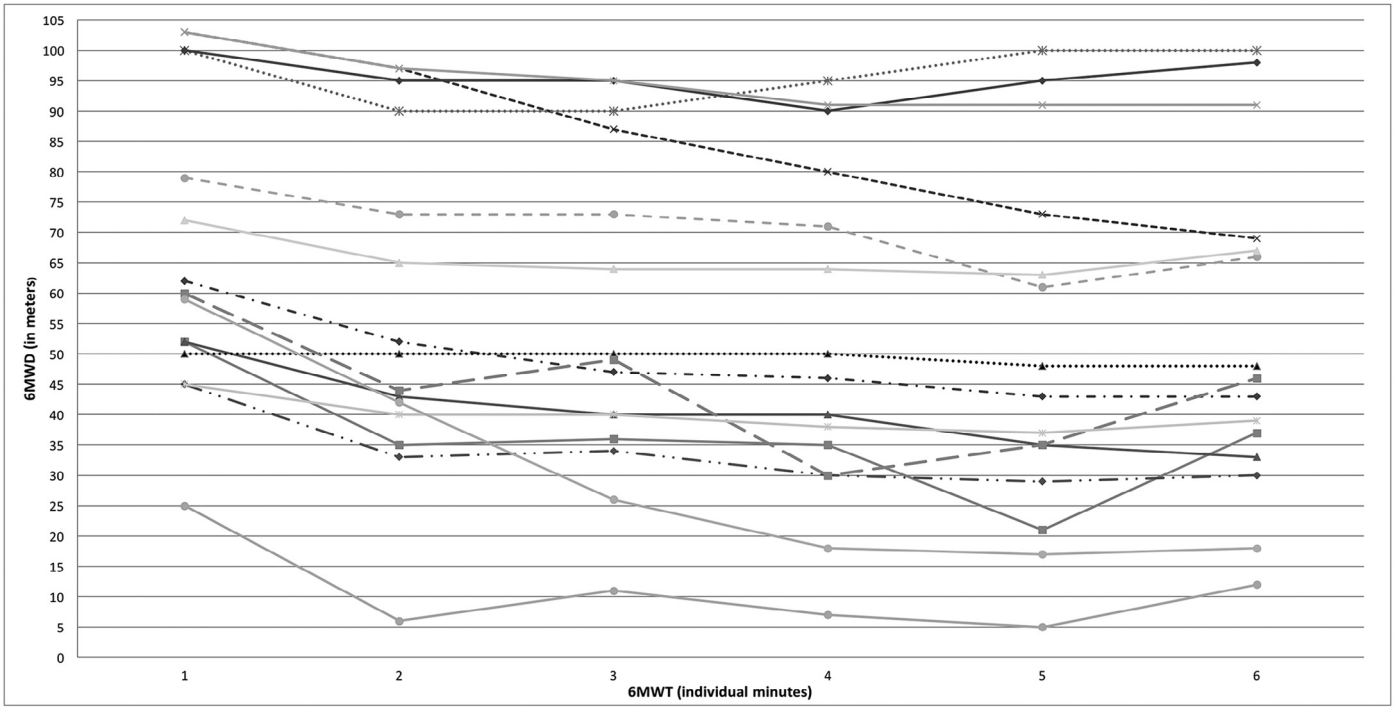

Fig. 1. Individual details of the distance achieved at each of the 6 minutes during the 6MWT.