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Exercise role in neuromuscular disorders: A brief review and future directions

Since Rehabilitation in neuromuscular disorders is a complex activity due to the interplay of many aspects from different pathologic findings to different needs of each patient regarding their participation in social environments, we will therefore focus on the exercise role in neuromuscular disorders.

In this context we will make a review of what has been published as well as the recent advances in normal, athletes, older ages and NMD, followed by our own experience in ALS

The positive effects of exercise are, in general, well known and were demonstrated at different systems and organs as well as at cellular and molecular level, but then again the complexity of this effect becomes difficult to systematize, especially due to the lack of standardized approaches as used by many authors.

It is usually recommended to general normal population, however it imposes risks and that those risks increase with age, intensity of exercise, the presence of cardiorespiratory diseases or other co-morbidities. Thus, its prescription challenges the physician to increase benefits and to reduce the risks and prevent the resulting poor outcomes from inactivity in terms of health and quality of life

On the other hand the negative effects of inactivity increase with ageing due to a reduced number of motor units with a predominance of Type I muscle fibres and a gradual loss of muscle strength up to 40-50%, progressive decay of pulmonary ventilation, gas exchanges and aerobic or work capacity. Given this full picture that is also likely to occur both in slowly or rapidly progressive neuromuscular disorders[1,2] it would be expected better results with aerobic exercise with low resistance or negative results from progressive strengthening exercises in this ageing population. However two important

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studies have shown evidence of the opposite. Fiaterone *et al.*,[3] in a randomised placebo-controlled trial of 100 people older than 65 years with progressive increased resistance, were able to verify an improved muscle strength and size without adverse effects, Concluding that muscle fibre have the ability to adapt to effort with plastic changes. Still in normal populations De Lateur[4], evaluated the fatigue role in exercise, as determinative of effectiveness of the physical training. She conducted a study design specifically to evaluate the effect of fatigue using two protocols of exercise (continuous vs intermittent) in each individual with the same intensity in left and right quadriceps to fatigue but, in one side with a rest interval of 2-3 minutes, and the other without any interval until fatigue she noticed that the quadriceps trained to fatigue without any rest periods achieved better results in terms of strengthening and in a shorter time, calling the attention to the fatigue role in designing exercise programs.

However Strength training or aerobic exercise programmes that might maximise muscle and cardio respiratory function and prevent additional disuse atrophy in patients with muscle disease, with the exception of very few studies have not been properly and fully addressed in neuromuscular disorders and, on the other hand it is commonly believed that over-exerting might cause more rapid disease progression. To assess efficacy and safety of strength training and aerobic exercise training in patients with muscle diseases, very recently a systematic Cochrane review has searched the evidence and has concluded from only two studies fulfilling criteria that moderate-intensity strength training appears not to do harm but there is insufficient evidence to establish that it offers benefit. Limitations in the design of studies in other muscle diseases prevent general conclusions in these disorders[5].

So it is much needed further investigation in this field with well designed randomised trials, carefully evaluating outcome measures such as for strength training: primary outcomes such as static or dynamic muscle strength (endurance or fatigue) and secondary outcomes such as functional assessments, quality of life evaluations, muscle membrane permeability, pain, and fatigue. For aerobic exercise training the primary outcomes should include aerobic capacity expressed as work capacity and secondary outcomes aerobic capacity (oxygen consumption, parameters of cardiac or respiratory function), functional assessments, quality of life, muscle membrane permeability, pain, and fatigue.

Since it is general accepted that clinical studies and investigation must depend on appropriate rationales and it often is in the basic science that one can find them, we will now give a very brief summary of the important breakthroughs in exercise physiology

The observation that continuous residence at moderate heights (2000-2500 m with relative hypoxia) Improves oxygen transport capacity, increase in erythropoietin, increase in hemoglobin concentration, increase in VO2 max, and increase in exercise performance [6] led these authors to evaluate the role of hypoxia in exercise in a RCT with four groups trained 5x/week/6wk, being two groups

under hypoxia and the other two in normoxia also with two intensity levels (High and Low), he found the relative increase VO2 max and Wmax in the hypoxia groups especially in those working at high intensities with increased mRNA for HIF1, mioglobin, and VEGF in the hypoxia group and concluded that exercise under hypoxia elicit specific and stable effects at molecular level, configuring a condition described as long-term potentiation or facilitation. In fact, Vogt *et al.*, found the molecular basis of exercise and attributed the difficulties of normoxia low intensity training to the failure in the intensity of stimuli to activate transcription enough to generate an increase in mRNA content that could persist until the next bout of training. However Vogt did not evaluate for how long these results were stable.

From the first two studies, above mentioned, together with the study of Vogt what can we learn to apply in exercise in neuromuscular disorders. It seems we need to evaluate a strengthening exercise program till fatigue and in hypoxia conditions. However in NMD rapidly progressing like ALS in which respiratory insufficiency is the most likely terminal event, hypoxia may in fact contribute to the deleterious and known effects as the produced in those chronically living in the Himalayas[7] with reduced aerobic capacity, muscle size and strength.

Since stability is another major goal in Rehabilitation, to obtain results with persistent effects in order to translate them into the daily life, it is obvious that long-term potentiation should be a focus in Rehabilitation but it is far from being recognized.

In general, LTP is a long-term increase in the size of the postsynaptic response to synaptic transmission, at the moment it is the best paradigm to explain plasticity, it is well accepted as the cellular explanation for memory in which the activation of genes and new protein synthesis is likely the cause of these longer changes. In fact, Vogt recognized the increased activation of a transcriptor factor the HIF 1that binds to the promoters of gene expression of erythropoietin, FBGF, mioglobin, VEGF, and these genes are known for the critical role in haemoglobin transport capacity, vascular permeability and muscle hypertrophy.

From animal experiences it is recognized that LTP is induced by electric stimulation acting simultaneously upon pre and post synaptic membrane, it is also induced by enriched environment or different stimulus timely sequenced[8, 9] so we know that added stimuli may help neural adaptation and muscle hypertrophy and it is the explanation to the frequent use in Rehabilitation settings of added and multiple stimuli (Electric, Mechanical, Chemical, Proprioceptive,Visual, Auditory), increasing the feedback. However results may not be sustained beyond exercise application

In fact, there is no known exercise program with sustained efficacy which is why AHA still advises the exercise practising ½ hour 3x/week. Until Human Performance Research will increase knowledge of molecular and cell signalling to control transcription factors or translational pathways.

Until then rehabilitation approaches will have to focus on the type of exercise, in-

tensity, duration, specificity, and safety stressing the need of multiple stimuli.
The role of exercise in amyotrophic lateral sclerosis, a controversial issue in advanced disease stages[10] Sanjak et al, have shown a reduced work capacity, and a reduced maximal O2 consume at any given work level. On the other hand, fatigue is of uncertain origin as investigated by different authors[11-14], casting doubts on the mechanisms weather due to central fatigue or to deficits in excitation-contraction coupling with obvious implications on designing a strengthening exercise program to fatigue and since hypoxia may be an early sign with poor prognosis, as shown by Velasco *et al,* 2003 and Pinto *et al,* 2003[15, 16] and there is recent evidence of increased incidence of ALS in normal population carrying low levels of VEGF gene[17], with increase fragility to hypoxic sates, as shown in rats VEGF gene carrying deficits[18] it is indeed assumed that exercise under hypoxia conditions determine negative effects on ALS patients at advanced disease stages. These evidence, taken together may explain the positive effects of the exercise program in ALS patients with respiratory insufficiency or poor effort tolerance that our group performed[19].
We have undertaken a prospective, comparative controlled trial, 20 consecutive patients distributed in two groups selected upon geographic residence, With global, partial RI or intolerance to effort with pulse dessaturations, Group 2 was exercised in a treadmill with assisted ventilation (BIPAP STD-30®), All patients were followed-up for 12 months each 3 months, Norris bulbar and spinal score, FIM score, RFT each 6 months

Table I. Efficacy outcome[1]

Group	Diff	95%	CI p
Sc. Spinal	9,591	2,908 - 16,274	0,005
FIM	27,483	9,997 - 44,969	0,002

In fact, progressive resisted exercise in ALS may not be harmful even in advanced disease stages, reduced motor decline (as measured by spinal Norris score) and improved function (as measured by Functional Independency and Mobility scale) (Table I), as long as simultaneously performed with NIV, with exercise intensity control through pulse.
In line with recent research (possible VEGF defective gene) this methodology agrees with etiologic mechanisms, but further studies should validate this work and we are currently replicating our own results, with a newly designed study (RCT), To evaluate efficacy of a progressive resistance exercise within the aerobic capacity limits through Gas exchanges analysis, ECG, Pulse oximetry, evaluating: strength, VO2 max, timed-walking measures, functional and QoL parameters.
In Conclusion, a few studies have addressed the exercise role in muscular and neuromuscular disorders, aerobic and strengthening exercise seems to be an relevant therapy, requiring increased levels of evidence, exercise is an exciting area of investigation together with increased knowledge in molecular biology, and in Rehabilitation field therapeutic attitudes should point towards LTP or facilitation.

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