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Address reprint requests to

Lisa S. Krivickas, MD  
Spaulding Rehabilitation Hospital  
125 Nashua St  
Boston, MA 02114

## THE ROLE OF EXERCISE IN NEUROMUSCULAR DISEASE

David D. Kilmer, MD

In the past several decades, the real benefits of regular physical exercise for the able-bodied population have been shown, including improved strength and endurance for daily activities as well as modification of risk factors for cardiac disease. However, research is clearly lacking in determining whether persons with such disabilities as hereditary neuromuscular disease (NMD) respond to exercise training in a similar beneficial manner, and, if so, whether the adaptations augment their ability to perform work and enjoy avocational activities.

Although it has been presumed to be caused by their weakness and fatigability, recent work suggests that persons with NMD usually have a sedentary lifestyle.<sup>33</sup> Reasons for this are complex; it cannot simply be ascribed to the primary disease. First, habitual exercise patterns and interest in sporting activities often occur during the school years, where these people may not even participate in physical education. Well-meaning parents, teachers, and physicians, concerned that exercise may actually be detrimental, caution the child or adolescent against physical exertion. The result is a sedentary adult who suffers not only from weakness due to loss of muscle fibers, but from the additional component of disuse weakness. This is frequently compounded by lack of the foundation of motor skills in typical sports and games first learned by others during childhood and adolescence. Finally, persons with NMD

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From the Department of Physical Medicine and Rehabilitation, University of California, Davis Medical Center, Sacramento, California

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have lower levels of employment, resulting in limited financial resources to join fitness clubs, purchase equipment, and travel to events.<sup>14</sup>

The main questions this article seeks to address are: (1) how does the person with NMD respond to strengthening and aerobic (endurance) exercise; (2) what evidence exists that exercise may actually be harmful; and (3) how do we encourage this population to participate in physical activity and sport?

## RESPONSE TO STRENGTHENING EXERCISE

The response of intact skeletal muscle to strengthening (resistance) exercise is well delineated. With muscle overload, there is an initial catabolic response with some disruption of muscle fibers. The muscle adapts by synthesizing new myofibrillar proteins, with little change in the oxygen transport system or mitochondrial density. The result of increased myofibril size and number is greater cross-sectional muscle fiber area, resulting in muscle hypertrophy, with the ability to resist higher loads. The response is thought to be highly specific to the type of resistance exercise. Some debate exists about the capacity for human muscle fiber hyperplasia,<sup>27</sup> but the general belief is that there is very limited if any ability in an adult to increase the number of muscle fibers with training.

Although muscle hypertrophy appears to be the dominant mechanism for strength gains with long-term training,<sup>37</sup> it has been shown clearly that strength improvements occur shortly after starting a strengthening program, before hypertrophy can possibly occur. These strength gains without structural changes in muscle are likely due to neural adaptations, primarily relating to more efficient motor unit recruitment from improved coordination, learning, and activation of prime movers.<sup>10</sup>

Muscle weakness is the final outcome of all neuromuscular disease. Individual NMD frequently are identified by their pattern of weakness and family history; however, electromyographic findings and microscopic pathology may be quite similar among slowly progressive myopathic or neuropathic disorders. This, along with the relative rarity of the diseases, requires researchers frequently to group the disorders together when investigating responses to training and giving recommendations.

Along with loss of skeletal muscle fibers, atrophy of disuse is thought to be frequent in persons with NMD.<sup>45</sup> Disused muscle fibers lose myofibril size, resulting in reduced fiber cross-sectional area, less force production, and reduced muscle endurance.<sup>2</sup> Thus, the response to strengthening exercise may include an element of reversing the effects of disuse as well as altering the natural history of the NMD itself.

## Overwork Weakness

First identified with patients recovering from polio, weakness associated with excessive physical activity is a major concern among patients and clinicians with NMD.<sup>15, 45</sup> There are descriptions of prolonged increased weakness following strengthening exercise in ALS,<sup>28</sup> peripheral nerve lesions,<sup>18</sup> and Duchenne muscular dystrophy.<sup>5</sup> The dominant upper limb has been found to be weaker in persons with facioscapulo-humeral muscular dystrophy than the nondominant with heavy upper extremity use, providing circumstantial evidence for overwork.<sup>21, 23</sup> A single subject with scapuloperoneal dystrophy had a reversal of rapid strength decline after reducing daily physical activity.<sup>46</sup> It should be noted that these are all case reports, and overwork weakness has not been demonstrated in a controlled prospective study using exercise regimens.

## Methods of Evaluating Strength

Although the clinician typically uses the manual muscle test (MMT) during strength assessment of these patients, this evaluation has a limited role in understanding the progression of disease.<sup>22, 32</sup> Quantitative muscle testing is necessary to evaluate the response to an exercise intervention. This limits the usefulness of early intervention studies using MMT in NMD subjects.<sup>19, 47</sup>

The simplest means of quantitative muscle testing is to measure static, isometric contractions using cable tensiometers or dynamometers.<sup>13, 26</sup> These devices provide reliable data, but measure strength at only one joint angle, thus limiting real-world application. Another method involves the maximal amount of weight the subject can lift one time. More recently, elegant devices to determine isokinetic strength by measuring maximal force at a preset velocity have been used with NMD patients; these have provided information on both shortening (concentric) and lengthening (eccentric) contractions.<sup>23</sup> Good reliability has been shown in this population using both types of data, particularly for uniplanar joints such as the knee and elbow. Strength of the shoulder, wrist, and ankle musculature in specific motions, although important functionally, is more difficult to isolate, making these dynamometers and measurements less reliable. Strength testing at these joints may be better suited to the hand-held myometer, which can be used in the clinic.<sup>26</sup>

Measures of fatigue and endurance, for example using the number of contractions at a given submaximal resistance level, are less well studied and are not likely to be nearly as reliable. This is unfortunate because muscular endurance is more likely to be relevant to performance of daily activities than any measurement of maximal strength.

Regardless of method, impressive strength gains usually are measured over the first several weeks of a training protocol. Since physio-

logic changes cannot occur at the muscle fiber level this quickly, these gains are presumed to be due to improved motor planning and synchronization of motor unit firing with learning. Actual strength gains from muscle fiber hypertrophy occur after several weeks.

### **Strengthening Exercise: Rapidly Progressive Disorders**

In Duchenne muscular dystrophy (DMD), there is a rapid progression of strength loss both qualitatively and quantitatively.<sup>34</sup> The child typically requires a wheelchair for mobility between the ages of 8 and 12. Because of this rapid progression, these children usually cannot participate with their peers in the normal physical activities involved in play and exploration of their environment, often leading to isolation and lack of social development.<sup>25</sup> A desirable role for strengthening exercise is to slow the rate of progression of weakness, allowing more natural development. Because of the rapid progression, a control group is a desirable but rarely obtained component of intervention studies.

Strengthening intervention studies with DMD patients generally have shown maintenance of strength or even mild improvement in strength over the period of the investigation. However, these studies are limited by use of primarily nonquantitative measures,<sup>44</sup> lack of a control group,<sup>39</sup> and use of the opposite limb as a control without considering the effects of cross-training.<sup>7</sup> Other problems include variations in the type and intensity of resistance training and duration of follow-up. Interestingly, no systematic studies using this population have shown any deleterious effects of resistance exercise. Thus, based on limited data one may conclude that resistance training can maintain one-repetition strength in DMD patients. However, owing to the relative paucity of investigations, it is prudent to recommend a submaximal strengthening program. A great concern is how to incorporate these activities effectively into the daily routine of the child, avoiding use of mundane and tedious regimens that employ resistive weights and pulleys.<sup>25</sup>

With the advances in molecular genetics and possible identification of abnormal gene products, more rational and specific approaches should be taken in designing exercise protocols and understanding potential deleterious effects. As an example, it is now known that DMD patients lack a structural protein of the muscle cell membrane called dystrophin.<sup>20</sup> This protein appears to be essential to maintain the cytoskeletal framework of the muscle fiber during muscle contraction.<sup>11</sup> Muscle actions known to stress the cytoskeletal elements of the fiber, such as strong eccentric contractions, are likely to enhance breakdown of the muscle fiber.<sup>16</sup> With this knowledge, future resistance exercise regimens will need to assess carefully the amount of such contractions being performed. Indeed, Edwards et al<sup>9</sup> proposed that routine eccentric

contractions occurring during gait are a likely source of the pattern of weakness typically seen in myopathies.

The other rapidly progressive NMD to consider is ALS. However, because of its variable progression and bulbar involvement, systematic strengthening exercise intervention studies have not been performed with these patients. Clinicians generally recommend a submaximal strengthening program for patients who are motivated to engage in these activities in the hope of attenuating strength loss.

### **Strengthening Exercise: Slowly Progressive Disorders**

In slowly progressive hereditary neuromuscular disorders, the goal of strengthening intervention studies has been to improve patient strength rather than simply to retard strength loss. Because of the rarity of these diseases, most studies have grouped different NMDs together in order to obtain adequate numbers for analysis. A presumption of these studies is that improving strength gives patients more reserve to perform daily tasks—a yet-untested hypothesis.

Vignos<sup>44</sup> used high-resistance exercise in both rapidly and slowly progressive NMD, and found greater strength improvements in the less severe disorders. This tendency toward greater improvement with stronger patients also was found by Milner-Brown and colleagues, who reported that high-resistance weight training produced improvement in strength measured isometrically, generally in muscles with more than 10% of normal strength.<sup>35</sup> McCartney and associates demonstrated substantial increases in strength of subjects with slowly progressive NMD using a carefully controlled regimen over 9 weeks.<sup>31</sup>

To ensure safety, only supervised strengthening programs in this population have been advocated.<sup>45</sup> In order to test the effects of a less supervised approach, a moderate resistance home exercise program was devised that demonstrated similar strength gains in both patients and normal control subjects without evidence of overwork weakness.<sup>1</sup> Based on this encouraging result, the home program was advanced to high-resistance training in similar subjects without apparent additive beneficial effects; in fact, eccentrically measured elbow flexor strength actually decreased significantly.<sup>23</sup>

Limitations of the above studies include lack of a disease control group and inclusion of subjects with a variety of slowly progressive disorders, each with unique pathophysiologic characteristics. Recently a Dutch group limited their investigation to myotonic muscular dystrophy (MMD) and hereditary motor and sensory neuropathy (HMSN), using nonexercising controls; they demonstrated modest gains in both strength and function of the HMSN group but no improvements in the MMD group.<sup>30</sup> Of note, no untoward effects were demonstrated in either group. The design of this study, using measures of functional performance as well as static strength, should be a model for future investiga-





