



# THE NMDINFO



## NEWS

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*The mission of the Research and Training Center is to improve the lives of individuals with neuromuscular diseases by developing and evaluating new strategies that address lifelong needs for research-based medical care and counseling, psychosocial well-being, education, and independent living.*

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## Review of Neuromuscular Diseases and Current Research

In this and subsequent newsletters, this section will review the clinical and laboratory characterization, genetics, pathophysiology, management and current research of some of the major neuromuscular diseases. This issue will review Facioscapulohumeral muscular dystrophy (FSHD). The last issue of this newsletter reviewed Duchenne and Becker muscular dystrophies.

Facioscapulohumeral muscular dystrophy (FSHD) is one of several disorders in the “facioscapulohumeral syndrome”, which also includes individuals with various limb-girdle, spinal muscular atrophy, and congenital myopathy syndromes who have coexistent mild facial weakness. It is the third most common dystrophy after myotonic dystrophy and Duchenne dystrophy.

FSHD is an inherited autosomal dominant disease and these disorders are transmitted to sons or daughters from either the mother or father and, unless it is a new mutation, the parent usually also has the disease. The probability that an affected individual will transmit the disease to an offspring is 50 percent with each pregnancy, unless both parents have the disease. In that case, all children will inherit the disorder. The gene location is 4q35.

FSHD is characterized by a pattern of muscle weakness involving the face, scapula, upper arm, hip girdle, and foot dorsi-flexors. Asymmetry of weakness is common. Progression is usually slow and continuous and severity is highly variable. Progression and severity tend to correlate inversely with age of onset. Many patients describe an up-and-down course with periods of rapid deterioration. In some families, progressive hearing loss, retinal abnormalities of the eye and cardiac involvement are present. In the absence of significant bulbar, respiratory, and cardiac involvement, life expectancy is normal. A comprehensive review of the clinical manifestations, prognosis, management, genetics and pathophysiology has recently been published.<sup>1</sup>

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## Facioscapulohumeral Muscular Dystrophy

**Disease:** Landouzy and Dejerine dystrophy. Facioscapulohumeral dystrophy (FSHD).

**Inheritance Type:** Autosomal Dominant. Expression in either sex. Occasionally, apparent sex limitations in some families. Abortive or mildly affected cases are quite common.

**Protein:** Unknown

**Gene Location:** 4q35

**Incidence:** The relatively high incidence of 1 in 15,000 to 1 in 20,000 makes FSHD the third most common form of muscular dystrophy. This can be attributed to its autosomal dominant mode of inheritance (occurs in every generation), and the high frequency of new mutations, which account for approximately 10% of all new cases.

**Onset of Symptoms:** Insidious and indolent in most cases occurs in early childhood to adult life. Ninety-five percent of affected individuals show signs by age 20. Presentation in early onset FSHD ("Coates syndrome") occurs in infancy. As many as 30% of affected individuals (by laboratory testing) remain clinically asymptomatic. An early age of onset is associated with greater weakness.

**Rate of Progression and Severity of Weakness:** Usually very benign, slow and steady progression, but with considerable variation from one family to another and even within the same family. While a study conducted by our Rehabilitation Research and Training Center (RRTC) of 53 individuals with FSHD<sup>2</sup> showed a decline of only -0.22 manual muscle test (MMT) units per decade of age, some subjects had a relapsing-progressive course. Weak-

ness, in general, was relatively mild, with an overall mean MMT score of 3.7 units (normal strength is 5). An early age of onset is associated with greater likelihood of more severe and progressive weakness.

**Distribution and Description of Weakness:** Clinically heterogeneous, typical FSHD is defined by a descending sequence of progression with initial weakness and atrophy in the facial and shoulder girdle muscles, especially the shoulder fixators, followed by variable involvement of the foot dorsi-flexor and hip girdle musculature. Some individuals, however, present with difficulty walking from foot-drop or hip-girdle weakness. There is usually unilateral asymmetric weakness.

Neck flexor muscles are relatively spared compared to the neck extensors. Shoulder appearance includes straight clavicles (collar bones), as well as forward sloping and rounding of the shoulders. Chest pectoral muscles are atrophied resulting in creases in arm pit. Shoulder blades are laterally displaced, and winging is evident, especially with attempted forward arm flexion or abduction. Preferential wasting of the lower trapezius muscles results in an upward jutting of the shoulder blades. Upper arm biceps and triceps muscles are involved with sparing of the shoulder deltoid muscles, resulting in a "Popeye" arm appearance. Except for wrist extensors, forearm and hand muscles are spared. Abdominal muscle weakness results in a protuberant abdomen and exaggeration of the lumbar lordosis. Preferential weakness of lower abdominal muscles results in upward movement of the umbilicus on attempted neck flexion (Beavor's sign),

specific for FSHD. While there is foot dorsiflexor weakness, the calf plantar flexor muscles are spared.

The face is unlined with a pouting appearance of lips and a transverse smile. There is an inability to purse the lips or bury the eyelashes. Extraocular, eyelid, and bulbar\* muscles are usually spared. With advanced weakness individuals may be unable to pronounce labials and often have indistinct speech.

**Other Clinical Characteristics:** Asymmetry of upper extremity musculature with greater weakness of muscles (especially grip strength) on the dominant side supports the theory of chronic overwork weakness (see Focus for description of overwork weakness). Muscle stretch reflexes are depressed, but sensory examination is normal. Functional evaluation shows inability to whistle, blow up a balloon, drink through a straw, difficulty climbing a rope or doing pushups.

**Secondary Conditions:** There is severe scapular winging and loss of shoulder function in some individuals and severe hyperlordosis in some cases. Contractures are rare or mild. Some individuals have cardiac involvement represented by a relatively high susceptibility to induced atrial flutter or fibrillation. In severe FSHD, there may be symptomatic respiratory impairment. Pain is common and may be difficult to control.

**Associated Conditions:** Sensorineural\* hearing deficit was originally observed in "Coates syndrome," a myopathy that presents in infancy. With this disease progression is rapid, and a progressive exudative telangiectasia\* of the retina is also present. Many individuals with later onset also have impaired hearing function. In a few individuals with

early onset FSHD, mental retardation and seizures have been reported.

**Prognosis:** In the absence of significant bulbar\*, respiratory, and cardiac involvement, life expectancy is normal. Progression is usually steady and slow, although many individuals report a relapsing-progressive course with long periods of quiescence, interrupted by rapid deterioration. About 20% become wheelchair ambulatory. In early onset FSHD, however, most individuals become wheelchair reliant by the late second or third decade.

**Differential Diagnosis:** Must be distinguished from some limb-girdle dystrophy and spinal muscular atrophy variants; congenital myopathy syndromes, as well as Emery-Dreifuss dystrophy, polymyositis (some FSHD cases have a significant muscle inflammatory reaction), ocular myopathies congenital ptosis and facial diplegia.\*

**Impairment and Disability Profile:**<sup>2</sup> Fifty-three individuals followed in a regional neuromuscular disease (NMD) clinic from 1982-1992 were reviewed. Thirty-two were males and 21 were female with a mean age of 38±13 years at the time of the first clinic visit. Five (9%) were non-ambulatory with age at loss of ambulation 33±19 years. Only four were known to have died during the 10 year period with age at death 68±9 years. For profile see: [http://nmdinfo.net/report\\_retrieve.php?Report=0016](http://nmdinfo.net/report_retrieve.php?Report=0016)

**Diagnostic Evaluation:** Regardless of the recent advances in molecular genetics, a relevant patient and family history and a focused physical examination is necessary to direct subsequent laboratory tests. Although patients with FSHD may differ, most fit into a clinically typical pattern of presentation.<sup>3</sup>

\* See Glossary on page 19

**Table 1. Clinical Signs: Facioscapulohumeral Muscular Dystrophy**

***Inclusion***

Weakness of facial muscles  
Weakness of scapular stabilizers and ankle dorsiflexors

***Exclusion***

Autosomal-recessive or x-linked inheritance  
Diffuse severe contractures  
Cardiomyopathy  
Extraocular and bulbar weakness  
Sensory loss  
Neurogenic electromyography  
Biopsy suggestive of alternative diagnosis  
Skin rash suggestive of dermatomyositis

***Supportive features***

Prominent asymmetry  
Descending sequence of involvement  
Sparing of deltoids  
Early involvement of abdominal muscles (Beevor's sign)  
Selective involvement of lower trapezius  
Typical shoulder appearance, with straight clavicles and forward sloping of the shoulders  
Relative sparing of neck flexors High-frequency hearing loss or retinal vasculopathy

Laboratory testing shows a serum creatine kinase level that can be normal, but is usually mildly to moderately elevated. Nerve conduction studies are normal, but electromyography usually reveals a myopathic pattern. With the advent of specific FSHD molecular diagnosis, muscle biopsy is no longer a routine procedure and is reserved for patients with suspected FSHD whose DNA testing excludes FSHD.

Current methods for molecular diagnosis of FSHD are highly specific (virtually 100%) and sensitive (greater than 95% accuracy). Molecular diagnosis is performed on DNA extracted from white

blood cells. These undergo several complex biochemical procedures (digestion, gel electrophoresis and hybridization) to determine the structure of the gene that is abnormal in FSHD. In healthy individuals the gene is between 50 and 300 kilobytes (kb) in size, whereas individuals affected with FSHD the gene contains a deletion of variable size resulting in fragments that are from 10 to 38 kb in size.

Molecular diagnosis is indicated to confirm the diagnosis in an individual with typical FSHD or to make the diagnosis in an affected individual with suggestive, but atypical features. Presympto-

matic testing of individuals at risk is possible, but should probably be restricted to consenting adults.

A booklet that reviews genetic testing for FSHD is available online through the RRTC in Neuromuscular Diseases at the website address below. (Facioscapulohumeral Muscular Dystrophy: Making an Informed Choice

about Genetic Testing).<sup>4</sup>

Secondary and associated conditions in FSHD are cardiac conduction abnormalities, hearing loss and retinal telangiectosis\*. Evaluation of these conditions includes periodic EKGs, audiograms, and indirect ophthalmoscopy.

[http://www.nmdinfo.net/resources\\_retrieve.php?Resource=geneticstest](http://www.nmdinfo.net/resources_retrieve.php?Resource=geneticstest)

## ETIOLOGY AND PATHOPHYSIOLOGY

The FSHD mutation is linked to a missing section of DNA on chromosome 4 (chromosomal locus 4q35, at the subtelomeric region of the long arm of chromosome 4). This region normally contains 11 to 150 tandem repeats of a D4Z4 element, but FSHD patients have 10 or fewer because of deletions of repeats. There is evidence for an inverse relationship between the number of the retained repeats and the severity of the disease, the more retained, the milder the disease.

Various models have been proposed to explain the effects of the D4Z4 repeat contraction:<sup>5</sup> (1) upregulation by derepression of genes in the D4Z4 region (including one called FRG1), (2) genes in the region that, if activated instead of suppressed, might cause muscle degeneration, and (3) deletion of genes in the region may change the expression of nearby genes. It has also been proposed that FSHD is a disease of the nuclear envelope. Recent research indicated that the FRG1 gene might be responsible. In a genetically altered mouse model, the higher the FRG1 lev-

els were, the worse the symptoms were in the mouse. In the mouse, the adverse effects were due, indirectly, through at least two other gene proteins; one that regulates muscles ability to contract, and one that can regulate muscle atrophy. The difficulty in determining the etiology of FSHD may be that it is the result of the cumulative effect of decreased levels of many normal protein (forms) and increased levels of many aberrant protein (forms). The coexistence of retinal abnormalities, hearing loss and inflammatory infiltrates in the muscle suggests that a single responsible gene has pleiotropic\* effects. More likely, altered

expression of several genes is responsible for the various manifestations of FSHD.<sup>1</sup>

While the primary molecular events leading to FSHD continue to be investigated, little is known about how they cause the muscle pathology. Initial interest centered on the potential pathogenic role of the inflammatory infiltration found in as many as 30% of FSHD muscle biopsies. However, the pres-



ence of inflammation does not seem to correlate with disease duration or activity, and there is no evidence that patients with inflammation represent a genetically distinct group. Recent research indicates that the pathophysiology of FSHD includes changes in the organization of the muscle sarcolemma (membrane) and its association with nearby contractile structures. This suggests that, as in other muscular dystrophies, the integrity of the sarcolemma may be compromised in FSHD.<sup>6</sup>

Unfortunately, the pathophysiological mechanisms responsible for the progressive muscle weakness and wasting remain unknown. The approach of linkage from gene to protein has not been successful in FSHD as it has been in other hereditary neuromuscular diseases. Despite the elucidation of the genetic lesion in FSHD, neither the causal gene nor the protein products are known, and the nonspecific muscle pathology offers no hints as to underlying mechanisms.<sup>1</sup>

## MANAGEMENT

There is no specific definitive treatment for FSHD. Various drugs that have been tried, without success, include prednisone, creatine, albuterol, and diltiazem. Although currently incurable, FSHD is not untreatable. Management is primarily directed at impairments and the objectives are to inhibit, prevent or treat physical deformity, treat pulmonary conditions and cardiac disorders, when present, and alleviate pain. Overall goals are to maximize functional capacities, prolong or maintain independent functional mobility, and provide access to full integration into the community with good quality of life.

Nutrition:<sup>2,7,8</sup> In comparison to rapidly progressive Duchenne muscular dystrophy, little comprehensive nutritional research has been done in the slowly progressive NMDs, and none was specifically on FSHD as a single group. Using just skin fold thickness, the percent fat of 14 FSHD individuals was similar to that of controls in our RRTC study.<sup>2</sup> In other investigations, using several slowly progressive NMD in a mixed group, there was a reduction in fat-free mass due to muscle atrophy, an increase in fat mass, and energy ex-

penditure was at least 25% lower than in controls. The latter appears to be due to a reduction in physical activity that far exceeds the degree of muscle weakness in most individuals. Increased physical activity and a reduced caloric intake are recommended in these cases. The combination of increased adiposity and sedentary lifestyle in individuals with NMD (as well as in the general population) raises concerns about the development of medical conditions over time. In a recent study, a group of individuals with slowly progressive NMD were found to



have multiple risk factors for cardiovascular disease and diabetes. These risk factors worsened over time, and over 50% satisfied the criteria for metabolic syndrome (a constellation of risk factors that significantly increased the risk for coronary events and type 2 diabetes).<sup>8</sup>

Weakness, Physical Activity and Exercise.<sup>9-14</sup> Weakness due to muscle degeneration is, of course, the primary condition in most NMD. Weakness due to other causes such as decreased-use atrophy is a secondary condition. Reduced physical activity which negatively impacts quality of life and health outcomes is a consequence of all neuromuscular disease. Improvement in physical fitness through increased physical activity is important for health maintenance and disease prevention (coronary artery disease, hypertension, diabetes, osteoporosis, anxiety and depression), and is likely to contribute to improved community integration and the ability to participate in recreational activities. Patterns of physical activity in childhood persist on to adulthood, and obesity is due to a reduction in activity-associated energy expenditure and unchanged caloric intake.

Individuals with NMD represent a very sedentary and deconditioned population with responses to exercise testing that are similar to those found in poorly conditioned (bed rest) able-bodied individuals and aging persons. It is likely, therefore, that the reduction in functional muscle mass in FSHD and other NMDs and the resulting functional impairments are the result of both atrophy of disuse from a sedentary lifestyle and muscle degeneration secondary to the disease.

As previously noted, evidence of low energy expenditure in individuals with NMD has been reported in several stud-

ies. In FSHD, or in other ambulatory, slowly progressive diseases, energy expenditure during physical activity was significantly lower than in control subjects. In addition, patients reported that their exercise was at lower intensity levels.

At least to the extent that reduced physical activity is due to the effects of a sedentary lifestyle resulting in atrophy of disuse, exercise should be helpful to reduce the negative effects of the deconditioned state. Exercise training for individuals with NMD has long been a controversial issue. There are two types of exercise training: resistive strengthening exercise and aerobic exercise training (running, walking, and swimming). In aerobic exercise testing studies (bicycle, treadmill), regardless of the type of neuromuscular disease, cardiopulmonary capacity is decreased (reduction of peak oxygen uptake, work capacity or rate, endurance and cardiac output). These responses are similar to those of deconditioned able-bodied individuals. Several studies of training in individuals with slowly progressive NMD, including FSHD, have reported positive responses. These improvements in cardiopulmonary adaptations are qualitatively similar to adaptations observed in able-bodied persons with no untoward effects due to the disease. In one study of 8 patients with FSHD, 12 weeks of low-intensity aerobic exercise improved maximal oxygen uptake and workload with no signs of muscle damage.<sup>12</sup>

Concern about increased muscle degeneration and further weakness induced by resistive strengthening exercise (overuse weakness) has led many physicians and therapists to avoid recommending it. There is, however, a

significant difference between overuse weakness (found in post polio syndrome) and actual contraction-induced injury. The former appears to be secondary to long-term sustained physical activity of weak muscles, whereas, the latter occurs with a single bout of a high intensity series of muscle contractions, usually eccentric. Resistive exercise training can be either concentric or eccentric. Concentric exercise is when the exercised muscle shortens during the contraction and eccentric exercise is when the muscle lengthens during the contraction. Exercise, either aerobic or resistive, can also be submaximal in intensity or maximal (to the point of fatigue). Regardless, most of the few studies of resistive exercise in slowly progressive NMD, such as FSHD, reported either a moderate increase in strength or a slight reduction in the progression of the weakness. The exception was one study in which high intensity maximal resistive exercise was used to the point of fatigue.

The exercise recommendations made at a recent evidence-based consensus conference were:<sup>14</sup>

1. Adopt an active lifestyle. Physical activities should emphasize recreational and sport activities in combination with an active daily lifestyle and proper nutrition. The goal should be improving functional performance and daily activities.
2. Moderate-intensity resistive strengthening exercise programs can be recommended and will usually result in modest increases in strength. High-intensity resistive exercise and eccentric exercise should be avoided.
3. Moderate aerobic exercise training

can be recommended without concern about any deleterious effect

4. Fatigue can often be reduced by using brief work-rest interval training programs.



**Mobility Assistive Devices:**<sup>1,15</sup> Like individuals with other slowly progressive NMD, people with FSHD usually develop effective adaptive strategies to compensate for their impairments without necessitating the use of assistive devices. Over time, foot dorsiflexion\* weakness often becomes significant in addition to initial and more progressive pelvic girdle weakness. Some patients exhibit the foot drop resulting from weakness of the dorsiflexors very early in the disease course. While amenable to the use of molded ankle-foot orthoses (AFO), if thigh quadriceps weakness is also present, fixed AFOs hinder ambulation, by preventing hyperextension and mechanical locking of the knee. Floor reaction ankle-foot orthoses (FRAFO) are preferable in such instances, as the anterior tibial lock provides extension force to the knees upon floor contact, preventing buckling of the knee. Late in the disease course of early onset FSHD, individuals may also show marked wrist extension weakness in addition to initial and more severe shoulder girdle and arm weakness.

Universal cuffs and other adapted devices may be helpful.

Complete loss of upright ambulation is unusual even late in the disease course. In our RRTC study, only 9% of the 53 patients were non-ambulatory with loss of upright ambulation at  $33 \pm 9$  years of age.<sup>2</sup> Other investigators have, however, reported 20% of patients eventually becoming wheelchair users.<sup>1</sup> When the decision regarding wheelchair use is reached, the goal should be to make the chair the passport to more rather than less activity. Electrically powered chairs may eventually be required for some individuals, although hand operated light high-mobility wheelchairs are usually adequate.

#### **Musculoskeletal Complications:**

Musculoskeletal complications include spine deformity, scapular winging, pain and osteoporosis. Contractures are rare and mild if present. In our RRTC study of 53 patients with FSHD, only three individuals had clinically significant loss of range of motion (ROM) (defined as a reduction in ROM of  $\geq 20$  degrees).<sup>2</sup> When present, management strategies for contractures include stretching, positioning, splinting, orthotics and surgery.<sup>16</sup>

**Scapular Winging:**<sup>1,17-22</sup> Inability to raise the arms to or above shoulder level is one of the major functional impairments in patients with FSHD. This is due to severe weakness of the muscles that fix the scapula to the chest wall. Surgical scapular fixation has been reported to enhance arm mobility significantly in some retrospective non-controlled studies. In general, surgery can be considered in individuals with stable or slowly progressive disease, with reasonable upper arm strength.

However, the benefit of surgery could be short lasting if the patient has rapidly progressive loss of shoulder girdle strength. Moreover, scapular fixation may result in restricted shoulder range of motion and chest wall compliance, especially if done bilaterally. Fixation should preferably be done only on one side. The amount of functional gain that can be expected with surgery can sometimes be assessed by the examiner manually fixing the scapula to the chest wall.

**Spine Deformity:**<sup>2,3</sup> Spine deformity includes scoliosis, lordosis, and kyphosis. Scoliosis is an appreciable lateral curve in the normally straight vertical line of the spine when viewed from the back. Kyphosis is the abnormally increased convexity in the thoracic spine as viewed from the side ("hunchback"). Lordosis is the concavity in the lumbar and cervical spine as viewed from the side. In our RRTC study, only 36% of individuals with FSHD had evidence of spine deformity.<sup>2</sup> Of these 16 patients, 9 (56%) had hyperlordosis. Longitudinal evaluation showed an increase in the hyperlordosis, but no significant progression of the mild scoliosis curve. The lordotic posturing is, at least in part, an attempt to compensate for the hip extensor weakness. There have not been any studies concerning spinal instrumentation in FSHD, and most patients are not interested because of the likelihood that upright ambulation would be lost.

**Pain:**<sup>1,24-28</sup> Pain is a frequent complaint among many individuals with FSHD. In one survey, about 55% of patients with FSHD complained of the presence of pain at least several days a week. Other studies have reported up to 73% of individuals with several slowly pro-

gressive NMD, including FSHD, have pain with it being severe in 27% and interfering with activities of daily living in 39%. Only 36% of the patients, who contacted a health professional, received some kind of pharmacological pain treatment.

Proper treatment is important since pain has an impact on mobility, work, enjoyment of life and recreational activities, and therefore has an important influence on quality of life. There is a broad spectrum of coexisting pain types with a large number of potential causes. However, the characteristics of the pain in FSHD suggest that it is usually musculoskeletal in origin and triggered by changes in posture and laxity of joints, resulting in low back, neck and shoulder pain.

In all reviews, there was a lack of clear efficacy of any one of the many pain treatments used over the others. The lack of efficacy of any single treatment and the under treatment is not surprising, since this also occurs in the general population with musculoskeletal pain. The large spectrum of therapeutic approaches includes physical and



occupational therapy, counseling, hypnosis, massage, chiropractic care, nerve blocks, analgesic drugs (usually nonsteroidal anti-inflammatory agents), muscle relaxants, tricyclic antidepres-

sents, gabapentin, and carbamazepine. Treatments that provided the greatest relief were chiropractic care (manipulation), physical therapy, and nerve blocks, while carbamazepine and tricyclic antidepressants were better among patients with severe pain.

**Osteoporosis and Fractures:** Osteoporosis does not appear to occur with any greater frequency or severity in weight bearing individuals with FSHD than in the general weight bearing population. There have not been any bone density studies in FSHD. Disuse osteoporosis may, of course, develop in individuals who have lost upright ambulation. In these individuals, standard treatment is recommended.

**Anesthesia Risks:**<sup>27,29</sup> Although anesthesia is not a therapy, there are several issues that must be considered when patients with NMD undergo general anesthesia. Anyone having surgery should be aware of the risks associated with the surgical procedure and/or complications that may arise during (usually cardiac) and after (usually respiratory) the surgery. Techniques should be tailored to minimize intra- and post-operative respiratory and cardiovascular depression. In general, several types of complications occur in patients with NMD: rhabdomyolysis (muscle degeneration), cardiac complications, respiratory distress, myotonia or generalized muscle spasms, hyper and hypothermia (abnormally high and low body temperature). Some of these complications appear to be related to the severity of the disease, while other complications, such as respiratory or heart problems, appear to be related to secondary conditions. Inhalation anesthetics, succinylcholine and anticholinesterase drugs should be avoided

since they can provoke malignant hyperthermia, and heart rhythm disturbances. Hypotensive anesthesia is often recommended, since dysfunction of smooth muscle may result in blood loss. Rapid deterioration of cardiac function is usually a contraindication to elective surgery. For patients with declining respiratory function, it is desirable to familiarize the family with the use of non-invasive ventilation ahead of surgery. A discussion of the use of anesthesia in NMD can also be found on the RRTC web site:

<http://www.nmdinfo.net/>

### **Pulmonary Complications:**<sup>1,27,30,31</sup>

Normal breathing depends on the function of the ventilatory pump, which consists of the central respiratory control center in the brain, the rib cage, diaphragm and the intercostal and accessory muscles. Respiratory failure results from: (1) respiratory muscle weakness and fatigue, (2) alterations in respiratory system mechanics and (3) impairment of the central control of respiration. In NMD, progressive muscle weakness and fatigue of the diaphragm and chest muscles lead to what is called restrictive lung disease. Spine deformity also increases the work of breathing as does significant obesity.

Since the muscle weakness in FSHD is usually slowly progressive, significant respiratory involvement is uncommon. In our RRTC study,<sup>2</sup> 13% had severe restrictive lung disease as measured by pulmonary function tests, and 22% had a history of significant pulmonary complications. However, none had acute or chronic respiratory failure that required mechanical ventilation. Using the need for ventilatory support as a criteria for severity (respiratory failure), only 1% of

the Dutch FSHD population required nocturnal ventilatory support. The risk profile for ventilatory dependency was delineated as advanced wheelchair use, moderate to severe kyphoscoliosis, lumbar hyperlordosis and pectus excavatum.

Evidence of respiratory insufficiency should therefore be obtained during routine clinic visits in individuals with severe FSHD and regular monitoring of respiratory function instituted. Symptomatic respiratory insufficiency can be initially managed with night time non-invasive mechanical ventilation. All individuals with NMD should receive routine immunizations, pneumococcal vaccine and annual influenza vaccinations as well as prompt treatment of chest infections.

**Cardiac Complications:**<sup>27,32-35</sup> A comprehensive review of the literature through 1997 concluded that the presence of cardiac abnormalities in FSHD was not well documented. Most studies, including our RRTC investigation,<sup>2</sup> have reported the presence of diverse electrocardiographic abnormalities. Other studies found no abnormalities on electrocardiography, chest radiography, Halter monitoring or echocardiography. The more significant abnormalities found in more recent reports were occasional conduction defects and supraventricular arrhythmia.

It appears that cardiac complications in FSHD are rare. In general, individuals with FSHD have normal longevity. This predisposes them to the usual age-related cardiac conditions, and management of these problems is the same as in non-dystrophic patients. It has also been recommended that the clinical follow-up of patients with FSHD should include periodic EKGs with at-

tentive searching for conduction abnormalities.

**Gastrointestinal Conditions:**<sup>27,36,37</sup>

Symptoms potentially due to malfunction of smooth muscle have been reported in patients with muscular dystrophy for many years. Recently, it has been suggested that some individuals with FSHD and other dystrophies may be prone to nutrient deficiency due to limitations of gastric mobility or oropharyngeal weakness. While unusual, as previously noted, this indicates the importance of nutritional assessment and counseling in patients with NMD.

**Associated Conditions:**<sup>1,38-41</sup> Extramuscular manifestations of FSHD include high-frequency hearing loss and retinal telangiectasis\*, occurring in 75% and 60% of affected individuals, respectively. These conditions are usually asymptomatic or mildly symptomatic, although rare patients with retinal vascular abnormalities can develop retinal exudation leading to retinal detachment (Coat's syndrome). Hearing loss is often more severe in infantile-onset FSHD and if not detected and treated early can interfere with learning and cognitive development. Audiograms should be obtained on all patients diagnosed with infantile FSHD and hearing aids provided when appropriate. While rarely symptomatic, untreated asymptomatic exudates in retinal telangiectasis can eventually lead to blindness, and about 1% of individuals with FSHD will develop visual loss. Periodic examination by indirect ophthalmoscopy of all patients has been recommended since the exudates are treatable.

Epilepsy and mental retardation have been described in severe, infantile FSHD. Therefore, intellectual and neu-

ropsychologic function should probably be evaluated in early onset FSHD. Tongue atrophy has also been reported in a few individuals.

**Cognitive and Psychosocial Issues:**<sup>42-44</sup>

Although current data is limited by small numbers, it does not appear that FSHD individuals are at high risk for significant intellectual defects with the possible exception of those with severe infantile FSHD. In our RRTC study, the mean intelligence (IQ) of 13 adults was not different from published normative data on the WAIS-R, and there were no impairments on the Halstead-Reitan Test Battery.<sup>2</sup>

The results of personality assessment inventories were not significantly different than in individuals with the other five NMDs evaluated in the RRTC study<sup>2</sup>. On the Minnesota Multiphasic Personality Inventory (MMPI), the means for some items (hysteria, depression, hypochondriasis) in all diseases indicated clinical involvement, regardless of the severity of physical impairment. Others have reported that in FSHD, severe disability can be associated with a positive self-image, whereas minimal disability may cause a negative self-image. Abnormal scores, therefore, may reflect problems of applying standard neuropsychologic tests to the physically disabled population. Subjects with physical impairments have somatic problems that can bias subtests of the MMPI. Tests using fewer questions based on physical symptoms such as the California Psychologic Inventory (CPI) showed mean values within normal limits. Regardless, it is well known that individuals with progressively debilitating illnesses, including those with an NMD, are at risk for social, emotional and behavioral

problems. These problems are frequently ignored in our current health care system.

Fortunately, interventions targeted at these problems exist and can be appropriately implemented in programs designed to provide services to the individual. There are three general areas of intervention. First, the need for a supportive therapeutic relationship with professionals providing health care should be emphasized. This includes the physician as a therapeutic agent; family therapy to assist the entire family in coping with the progressive loss involved in NMD, and the supportive relationship of a peer support group. Second, provision of education and information has been shown to diminish the psychological impact of the disease on the individual as well as on the family. Finally, it is necessary to provide specific interventions based on the stage of the disease and the particular physical and psychosocial needs of the individual.

### **Educational and Vocational Concerns:**<sup>43,45-48</sup>

While children and adults with FSHD do not appear to have behavioral or educational problems significantly different from the general population, all children with physical impairments have two special education needs. The first relates to the physical impairments and the second to learning problems, if present. While specific educational interventions for learning disorders are beyond the scope of this review, recommendations to improve educational experiences are essential. Schools must modify the physical environment to be barrier-free. Physical education activities should be modified. Children may need assistance



to participate in the spontaneous social activities that take place in the school environment and some may need assistance with the physical demands of completing assignments. The goal of adaptations should be to allow the child to learn in the best environment available, and should, when possible, remain in a mainstream classroom with peers.

Education is critical since it has a significant effect on employment and the type of occupation suitable for a physically impaired individual. Recommendations for the education of children with NMD have been developed by the RRTC and are available on its website. [http://www.nmdinfo.net/other\\_pubs.html](http://www.nmdinfo.net/other_pubs.html)

In a RRTC study, 40% of 154 adult individuals with slowly progressive NMDs were employed in the competitive labor market at the time of the survey. This was slightly higher than the 31 to 33% of employed work-disabled individuals reported in national surveys at the time. Fifty percent had been employed in the past, 90% had been employed at some time and only 10% had never been employed. Of the total, 22% were employed part time.

There was a disease-employment association and 56% of the individuals with FSHD were employed. This was slightly higher than found in a Dutch study (44%), but considerably lower than reported in a French study (84%).

The RRTC study found significant consumer (self) and provider barriers to employment. Consumer factors associated with employment included type of occupations, education, intelligence, expressed interest in employment, reasons for unemployment, severity of

physical impairments and disability, and psychosocial adjustment. Occupation clearly affected employment with the highest level of unemployment in less skilled and trained workers. Education, related to type of occupation, also had a significant effect on employment. Individuals who had received a college degree were usually in professional/management/technical occupations and were more likely to remain employed. Intelligence, associated with education, was a factor. Unemployed individuals had significantly lower IQs. Reasons for unemployment and interest in employment were related to physical disability. Sixty-four percent of the individuals not employed believed that their physical disability (weakness) was the major or only limitation to employment. Of those not interested in a job, 89% gave the severity of their disability as the reason, but only 50% interested in obtaining employment considered disability as the reason. This is an interesting and important perception, since actual objective measurements of impairment and disability found that there was no significant difference between employed and unemployed individuals. There was also a significant association between psychosocial adjustment and unemployment. This, however, may be both the cause and result of unemployment.

Provider factors associated with employment included consumer awareness of public vocational rehabilitation programs (DR); actual referral to DR (California); and DR (California) counselor and physicians attitudes toward persons with NMD. Results from the RRTC survey indicated that most individuals with NMD were not aware of a state DR, and there was a low DR acceptance level and a low level of refer-

ral to DR by physicians. This was compounded by the lack of information and experience of vocational counselors and physicians with aspects of NMDs. As a result many counselors and physicians believed that individuals with these diseases did not have employment potential.

Because of the negative attitude of many counselors, the RRTC developed and distributed a guide to NMD counselors (also available on the RRTC web site)

[http://www.nmdinfo.net/other\\_pubs.html](http://www.nmdinfo.net/other_pubs.html)

Every state has a vocational rehabilitation department to help disabled individuals obtain jobs.

**Quality of Life Issues:**<sup>49,50</sup> Quality of life is a broad concept that takes into consideration physical (health, physical functioning and independence, etc.), psychological (controlling one's life, life satisfaction and self-acceptance, self-esteem, etc.), social (social support resources, marital and family relations, standard of living, etc.), and financial attributes. From an impairment, function and participation standpoint, educational opportunities, employment opportunities, independent living and community integration, socialization, and family functioning lead to a satisfactory quality of life.

Life satisfaction psychometric assessment studies (very satisfactory, somewhat satisfactory, neither satisfactory nor dissatisfactory, somewhat dissatisfactory) have shown that responses from control, non-disabled subjects ranged between very satisfied and somewhat satisfied with their life in general, whereas, responses from individuals with slowly progressive NMDs such as FSHD, were somewhat satisfied. The latter were least satisfied with

their recreational activities, sexual life, general health and money matters. Other areas with which they were less satisfied than controls were daily living tasks, employment and social life. They were most satisfied with housing and family life, neighborhood and spiritual life. The strongest association with life satisfaction was emotional well-being, perceived control, satisfaction with employment and self-assessed health. Impairment and disability, as measured by degree of mobility, dexterity and activities of daily living, didn't significantly affect life satisfaction.

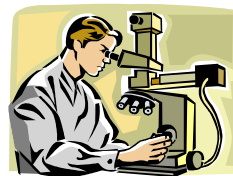
Rather, quality of life depends on whether an individual receives adequate services, and whether or not he has the same choices and opportunities to participate freely in the community and not on the level of physical disability. The greatest problems that individuals with NMD and their parents identified were: lack of information about their disease and available services, poor coordination of services, negative attitudes, and diminished expectations of their potential. Factors related to a good quality of life were related to perceived control and perceived health status. The more that people could do for themselves, either on their own or with personal care assistants, assistive devices and use of technology, the better their quality of life.

There were two other significant observations from these surveys of importance to individuals with NMD and their families. The first was that the quality of life perceived by people with NMD was substantially higher than that presumed by health care professionals. The second problem experienced by many individuals was that they had no

idea what services were available or how to obtain the services that are available. The RRTC website, therefore, includes a directory of national resources for individuals with NMD (<http://www.nmdinfo.net/resources.html>). It should also be noted that most cities in the country have programs for their disabled citizens and many publish a directory of local services and resources.

**Specific Treatment:**<sup>1</sup> No disease-specific therapeutic intervention is possible until the pathophysiology of FSHD is elucidated. However, a number of pharmacological strategies have been evaluated. Clinical trials, for the following compounds have all been negative: corticosteroids, creatine, albuterol (with and without exercise), and diltiazem. Trial of a myostatin inhibitor, MYO-029, has been fully enrolled. In the fall of 2006 safety evaluations should be available.

**Summary:** The emphasis in this review is on the management of the secondary conditions found in FSHD. The comprehensive management of all of the many clinical problems is an arduous task. For this reason, the multidisciplinary approach, found in most MDA supported NMD clinics, is the most effective. Management is best carried out by a team consisting of physicians, social workers, psychologists, and vocational counselors, among others. This review represents current practice parameters for the management of FSHD; evidence-based practice guidelines need to be developed.



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## **Glossary**

*Bulbar muscles* - Muscles of the throat, tongue, jaw and face

*Sensorineural* - involving or relating to sensory nerves.

*Exudative telangiectasia* - the release of a substance with permanent dilation of the capillaries and small blood vessels in the retina.

*Ptosis* - drooping of the upper eyelid, resulting from muscle weakness or inability to move muscles.

*Diplegia* - inability to move corresponding parts on both the right and left sides of the body.

*Pleiotrophic* - Multiple effects from a single gene.

*Dorsiflexion* - Elevation of the foot.

## FOCUS: WEAKNESS AND FATIGUE

Weakness is the primary condition of most neuromuscular diseases. Used in the global sense of the word, weakness is a spectrum ranging from a complaint of fatigue through frank outright paralysis. Like pain, muscle fatigue is a subjective symptom when reported by a patient, while weakness is a measurable observation. From a practical standpoint fatigue can be thought of as short lasting weakness. Weakness occurring with neuromuscular diseases or with disuse (bed rest) is accompanied by muscle fiber degeneration and loss (disease) or atrophy (disuse). In both situations, muscle bulk is reduced. Fatigue, however can occur in diseases without muscle wasting or long lasting loss of strength, such as in myasthenia gravis and the metabolic myopathies. Fatigue occurs following prolonged muscle contractions, with a relatively rapid return of strength following rest.

### WEAKNESS

Weakness may be due to disuse, disease, and some types of exercise, or it may be psychogenic (conversion reaction, depression, malingering).

**Decreased – Use Atrophy.** Disuse or decreased-use weakness is a secondary condition when it occurs in neuromuscular diseases. The word is used to indicate periods of prolonged muscle inactivity in the absence of other injuries to muscle or nerve. It is best typified by prolonged bed rest or immobilization of a body part by a cast. It also occurs during periods of prolonged weightlessness as during space flight. In this condition, there is moderately rapid atrophy of muscle fibers with reduction in muscle weight as great as 25% by six weeks. There is reduction in muscle strength proportionate to the degree of atrophy. The more energy-expensive type fibers (type II-glycolytic) are the ones most susceptible to atrophy and are the same fiber type most severely involved in dystrophy. The adaptations in skeletal muscle disuse or decreased-use atrophy are reviewed in a recent RRTC publication<sup>1</sup> which is available at our RRTC website.

Individuals with neuromuscular dis-

eases represent a very sedentary and deconditioned population. Their responses to exercise testing are similar to those found in poorly conditioned (bed-rest) able-bodied individuals and aging persons. There is evidence that reduction in functional muscle mass in these disorders and the resulting functional impairments are the result of both sedentary imposed atrophy of disuse and muscle degeneration secondary to the disease. In DMD, for example, it is well known that even short periods of bed rest result in significant loss of strength and function that is often not reversible. The relationship between the lack of physical activity, health impairments, and disability is reviewed in a recent RRTC publication<sup>2</sup> and is available at our RRTC website.

**Disease.** Muscle weakness in the various neuromuscular diseases may be rapidly or slowly progressive. Profiles of weakness and other conditions in some of these disorders have been reported in a RRTC journal publication.<sup>3</sup> A comparison in strength and rate of strength loss between ten neuromuscular diseases was also reviewed in a 1996 RRTC newsletter<sup>4</sup> and is available at our RRTC website.

**Exercise Induced Injury and “Overwork Weakness”.**

Concern about increased muscle degeneration and further weakness induced by resistive strengthening exercise has led many physicians and therapists to avoid recommending exercise for patients with neuromuscular diseases.

The term “overwork weakness” was first described in 1875 in the French literature in three patients who had a history of paralytic polio in infancy, and then, many years later as young adults developed significant new weakness and atrophy. All had physically demanding jobs that required strength and repetitive activities. The French neuropathologist Jean Martin Charcot suggested several hypotheses for these new changes including overuse of the involved limbs.<sup>5</sup> In retrospect, this probably what is now called the post-polio syndrome.

The deleterious effect of early physical activity on the acute paralysis of individuals with poliomyelitis was first noted in 1915,<sup>6</sup> and during the polio epidemic of the late 1940s and 1950s, the danger of deterioration of muscle strength following muscular overuse in partially denervated muscle was described in considerable detail.<sup>7,8,9,10</sup> Horstmann, in the most extensive report, reviewed over 400 patients from three epidemics with reference to the amount of physical activity performed around the time on onset of their illness.<sup>11</sup> A significantly higher percentage of non-paralytic than paralytic patients gave a history of bed rest or minimal activity during the early stages of the illness. In all these reports, a secondary decrease in strength was associated with increased muscle activity following recovery of strength after the initial severe loss of strength. This was believed to be due to a direct

degeneration of muscle fibers (myopathy) rather than the fiber atrophy secondary to the initial anterior horn cell infection.<sup>12</sup> Regardless, it was apparent that physical activity such as premature ambulation and vigorous physical therapy had a deleterious effect primarily during the pre-paralytic or paralytic stage of the disease when the anterior horn cells were undergoing active degeneration.

In the 1960s and 1970s, the theory of overuse weakness was extended to other neuromuscular diseases. The possibility was first suggested by a histologic study of the body of a 16-year-old boy with Duchenne muscular dystrophy (DMD).<sup>13</sup> In this individual, the muscles assuming the greatest degree of sustained physical activity, predominately postural antigravity proximal muscles had the most degeneration. This observation was directed towards sustained physical activity over a prolonged period of time and not toward supervised exercise training. As pointed out in the 1980s by Edwards, et al, because of their postural antigravity role, potentially damaging eccentric activity occurs more often in proximal than in distal muscles.<sup>1</sup> He further speculated that as a muscle becomes weaker and unable to meet the functional demands made upon it, the likelihood of accidental stretch becomes greater resulting in a vicious cycle of weakness, stretch, damage, and further weakness.

During this period, muscle derived serum enzymes and other body fluids, and muscle histochemistry became the major procedures in the diagnosis of neuromuscular diseases. Serum enzymes, especially creatine kinase, were felt to be an indirect indication of muscle tissue breakdown and the vulnerability of the muscle membrane. In several studies, serum enzymes were found to be reduced after bed rest and elevated to a much greater

degree after a vigorous strengthening exercise program in several types of dystrophic individuals compared to normal controls, whereas a mild exercise program failed to result in significant enzyme increases.<sup>15,16,17</sup> At this point, investigators and clinicians began to speculate that even supervised exercise training for several weeks might be deleterious and not just sustained physical activity. In retrospect, the enzyme elevations were probably the product of acute contraction-induced muscle injury, and did not necessarily represent a harmful exercise program.

This belief was thought to be supported by a series of animal experimental denervation investigations in the 1970s and 1980s. Denervation was produced by various procedures, and rodents were subjected to either synergistic tenotomy or exercise for several weeks. Muscles were then evaluated for fiber size and type, and muscle weight and protein content. Nerves were examined for myelinated fiber diameter. While the results were mixed, the term overwork-induced was used in the titles of most of these publications.<sup>18-22</sup> In general, nerve fiber diameter decreased and the percent of axonal degenerated fibers increased with overload. In the muscle, weight, tension, and protein content decreased until reinnervation occurred. With synergistic tenotomy alone, weight, tension, and protein content increased. This again was probably contraction-induced injury. In denervated muscle alone, atrophy, especially of the Type IIA fibers was retarded by passive exercise.<sup>23,24</sup>

The pendulum swung back to the sustained physical activity theory of overuse weakness when several members of a family with facioscapulohumeral dystrophy (FSH) were reported to have

hand and arm weakness greater on the dominant or most often used side.<sup>25</sup> This suggested that even usual daily occupations might accelerate the progression of muscle weakness. This possibility was supported by a case history of an individual with scapulothoracic dystrophy employed in an occupation characterized by excessive daily physical activity. His atypical rapid decline in strength was reversed by systematically decreasing his physical activity.<sup>26</sup> However, while the asymmetric weakness in FSH dystrophy has been confirmed in over 50 subjects,<sup>27</sup> it has not been found in any of the other neuromuscular diseases.<sup>28-31</sup>

In the mid 1980s, the poliomyelitis story returned with reports of a post-polio syndrome.<sup>32</sup> This syndrome occurs in persons with good recovery of function following their initial and acute poliomyelitis. More than 30 years later they experience new weakness and fatigue. The weakness has been shown to probably be due to chronically overused motor units and/or muscle overuse since there is no evidence of new acute anterior horn cell degeneration. There apparently is a compensatory overuse of the remaining residual neurons when there was the loss of a large proportion of the motor neuron pool due to the initial poliomyelitis. This is considered to be further support for the long-term sustained physical activity theory.

Studies have shown that post-polio individuals with excessive overuse have almost only Type I fibers (97%) with marked hypertrophy and mostly myosin light chain isoforms in the anterior tibial muscle. Normal subjects had 65% Type I, 25% Type IIA and 10% Type IIB fibers. Post polio individuals who did not use their muscles because of too severe paralysis had a normal fiber type differentiation and fiber atrophy. The change in fi-

ber composition was probably due to transition of Type II to Type I fibers.<sup>33,34,35</sup> There is a marked loss of force in the anterior tibial muscle fibers that is not due to insufficient motor neuron activation or peripheral blocking of the electrical impulse, but is thought to be due to an imbalance between energy resynthesis and energy utilization.<sup>33-36</sup> Chronic muscle overuse may also be involved in post polio individuals. When patients with new weakness are compared to those with no evidence of neurologic compromise, the former had substantially greater serum creatine kinase levels with a high correlation between elevated values and self-reports of strenuous work.<sup>37</sup>

It would appear that overwork/overuse weakness is secondary to long-term sustained physical activity. It is unlikely that it is a danger in short-term strengthening exercise training since most of the human and animal investigations have shown either increases in strength/tension or no change. The re-

lationship between overuse weakness and experimentally produced contraction-induced injury, if any, is unknown. The later is usually a result of single-bout high intensity series of muscle contractions, usually eccentric, while the former seems to be secondary to long-term physical activity. However, injury and repair is likely the normal route of adaptation to increased utilization and stress production in normal skeletal muscle. If the extent of damage in diseased muscle is higher than in normal muscle, the normal balance between injury and repair may shift towards the former by lowering the threshold for regenerative capacity. Regardless, there is a need for further research and consensus regarding the relationship between long-term sustained physical activity, strengthening exercise training, and contraction-induced injury in diseased muscle. Extensive reviews of exercise-induced muscle injury were recently published by the RRTC<sup>38,39</sup> and are available at our RRTC website.

[http://www.nmdinfo.net/other\\_pubs.php](http://www.nmdinfo.net/other_pubs.php)

## FATIGUE

Fatigue is among the most claimed symptoms in patients with neuromuscular diseases despite its diverse etiologies; as high as 80% in some reports.<sup>40-45</sup> However, it appears to be a major complaint only in the metabolic myopathies (a key factor in diagnosis), myasthenia gravis, amyotrophic lateral sclerosis (ALS), myotonic dystrophy (MD), and post-polio syndrome (PPS). There are multiple clinical expressions of fatigue that differ in presentation and consequences, but it is usually described by patients as a disabling exhaustion following "minimal" physical activity.

When reported by a patient, fatigue is a

subjective symptom. As a measurable objective finding it is defined as a decline in force output (or as a percent of the initial force) leading to a reduced performance output during short duration, high intensity exercise or tetanic electrical stimulation. Exhaustion is defined as when the target force can no longer be maintained at the required level. From these force and performance measurements, a "fatigue index" can be calculated. Fatigue can be attributed to several potential mechanisms from brain cortical region to muscle fiber contractile elements. In theory, it is possible to discern central and peripheral fatigue. The for-

mer implies all sites above the neuromuscular junction. Peripheral fatigue mainly involves sarcolemmal propagation, excitation-contraction coupling, substrate availability and contractile structures. Fatigue may be acute or chronic and is a complex psycho-social phenomenon. The relationship between subjective complaint and objective physiological measurement is not clear. However, in ALS, PPS, MD, and the metabolic myopathies, studies have shown

increased muscle contractile fatigability and/or abnormal muscle metabolism.

Be it psychological or physiological, fatigue represents a significant problem in the management of neuromuscular diseases. It clearly has an impact on quality of life.



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## Resources

### ***Facioscapulohumeral Muscular Dystrophy***

The FSH Society is a nonprofit U.S. corporation, organized in 1991, to address issues and needs related to FacioScapuloHumeral muscular Dystrophy (FSHD). It promotes scientific and clinical research; helps information exchange between researchers and clinicians involved in the diagnosis and study of the cause and treatment of FSHD; collects and distributes information about FSHD; fosters communication among national and international interested parties, provides support for those living with FSHD by assisting in the organization of support groups and by serving as a referral source.

FascioScapularHumoral Muscular  
Dystrophy Society (FSH), Inc.  
3 Westwood Road  
Lexington, MA 02420

Tel: Phone: 781-860-0501  
Fax: 781-860-0599  
e-mail: [carol.perez@fshsociety.org](mailto:carol.perez@fshsociety.org)  
Web site: <http://www.fshsociety.org/>

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**MedlinePlus** is a National Library of Medicine and National Institutes of Health web site that contains extensive information about individual diseases and is an excellent resource for a broad array of health and medical information. It contains Internet links to many valuable web sites.

Medline Plus information on facioscapulohumeral dystrophy:  
<http://www.nlm.nih.gov/medlineplus/ency/article/000707.htm>

### ***General Neuromuscular Disease Information***

The **Muscular Dystrophy Association** is a voluntary health agency — a dedicated partnership between scientists and concerned citizens aimed at conquering neuromuscular diseases that affect more than a million Americans. MDA combats neuromuscular diseases through programs of worldwide research, comprehensive medical and community services, and far-reaching professional and public health education.

Muscular Dystrophy Association  
3300 E. Sunrise Drive  
Tucson, AZ 85718  
800-572-1717, Fax: 520-529-5454

[www.mdausa.org](http://www.mdausa.org) (U.S.)  
[www.muscle.ca/](http://www.muscle.ca/) (Canada)  
[www.mda.org.au](http://www.mda.org.au) (Australia)  
[www.muscular-dystrophy.org](http://www.muscular-dystrophy.org) (England)  
[www.mdi.ie](http://www.mdi.ie) (Ireland)

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The mission of the **Muscular Dystrophy Family Foundation** is to fund adaptive equipment. From wheelchairs to van lifts to communication devices and beyond, they can help get the equipment needed to live with No Boundaries®.

Muscular Dystrophy Family Foundation  
2330 North Meridian Street  
Indianapolis, IN 46208  
[mdff@mdff.org](mailto:mdff@mdff.org)

Tel: 317-923-6333 800-544-1213  
Fax: 317-923-6334  
<http://www.mdff.org/>

## Resources (cont.)

**Neuromuscular Disease Center, Washington University, St. Louis, MO** is a good web site with detailed information on genetic, clinical and pathological characteristics of neuromuscular diseases.

Neuromuscular Division  
Box 8111-Neurology  
660 South Euclid Avenue  
Saint Louis, MO 63110

Phone: 314-362-6981  
Fax: 314-362-3752  
[www.neuro.wustl.edu/neuromuscular](http://www.neuro.wustl.edu/neuromuscular)

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**National Organization for Rare Disorders (NORD)**, a 501(c)3 organization, is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and service. Information on more than 1150 rare diseases.

55 Kenosia Avenue  
PO Box 1968  
Danbury, CT 06813-1968

Phone: (203) 744-0100 or-  
[phan@rarediseases.org](mailto:phan@rarediseases.org)  
<http://www.rarediseases.org/>

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**ABLEDATA** is a web site with a database, sponsored by the National Institute on Disability Rehabilitation and Research, that contains information on thousands of assistive technology products. Each product contains a detailed description (including price).

ABLEDATA  
30 Fenton Street, Suite 930  
Silver Spring, MD 20910

1-800-227-0216  
<http://www.abledata.com>

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The **National Institute on Disability and Rehabilitation Research (NIDRR)** provides leadership and support for a comprehensive program of research related to the rehabilitation of individuals with disabilities. All of our programmatic efforts are aimed at improving the lives of individuals with disabilities from birth through adulthood.

National Institute on Disability  
and Rehabilitation Research  
U.S. Department of Education  
400 Maryland Avenue, S.W.  
Washington, DC 20202-2572

Voice/TTY : (202) 245-7640  
<http://www.ed.gov/about/offices/list/osers/nidrr/index.html?src=mr>

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**Gene Tests** A publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons.

University of Washington  
Seattle, WA

<http://genetests.org>