EMERGING CONCEPTS AND TECHNOLOGIES IN NEUROMUSCULAR MEDICINE

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Emerging Concepts and Technologies in Neuromuscular Medicine

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Dr. Griffin received his medical degree from Stanford University, performed an internship in internal medicine and a residency in medicine at Stanford, then held a residency in neurology at Johns Hopkins Hospital. He has been on the faculty at Johns Hopkins since 1976 and has been a professor of neurology and neuroscience since 1986. He was named Director of the Department of Neurology and Neurologist-in-Chief in 1998. Dr. Griffin was an organizer of the North American trial of plasmapheresis for the treatment of Gullian-Barré syndrome (GBS), which was the first demonstration of an effective therapy for GBS. His research interests include immune-mediated nerve diseases, painful nerve diseases, and the basic mechanisms of nerve fiber degeneration and regeneration. Dr. Griffin is a well-known educator and has received several teaching awards.

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Dr. Sanders received his degree in medicine from Harvard Medical School and trained in neurology at the University of Virginia. He is currently a professor of neurology and Director of the EMG Laboratory at Duke University Medical Center. He is the author of many papers on the diagnosis and treatment of neuromuscular diseases, and in 1999, he received the AANEM’s Distinguished Researcher Award. Dr. Sanders is a past-president of the AANEM and has served on the AANEM’s Workshop, Regional Workshop, and Program Committees, among numerous others. He has also been a board member of the American Board of Electrodiagnostic Medicine.

Jerry R. Mendell, MD  
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Dr. Mendell is currently the director of the Center for Gene Therapy at Columbus Children’s Hospital and Ohio State University. He earned his medical degree from the University of Texas Southwestern Medical School in Dallas and performed a residency in neurology at the New York Neurological Institute and the Medical Neurology Branch at the National Institutes of Neurological Disorders and Stroke in Bethesda. He has authored over 260 scientific articles and book chapters, and has published major textbooks and monographs on muscle disease and neuropathies. Dr. Mendell has helped broaden our understanding of spinal muscular atrophy, spinobulbar muscular atrophy, periodic paralysis, inclusion body myositis, and inflammatory neuropathies. He has performed many studies in muscular dystrophy, including authoring, with colleagues from the CIDD study group, the double-blind, randomized controlled study reporting the efficacy of prednisone in Duchenne Muscular Dystrophy. In 1999 he performed the first gene therapy study for muscular dystrophy. In 2004, Dr. Mendell was given Honorary Membership in the AANEM.

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Dr. Bach received his medical degree from the College of Medicine and Dentistry of New Jersey in 1976. He completed residency training in physical medicine and rehabilitation at New York University in 1980. He is a fellow of the Association of Academic Physiatrists, the American College of Chest Physicians, and a fellow of the American Academy of Physical Medicine and Rehabilitation. He was the Medical Director of the Howard Rusk Ventilatory Unit at Goldwater Memorial Hospital from 1980 to 1981 and then developed a noninvasive respiratory management program at the University of Poitiers, France from 1981 to 1983. He is on the faculty of the UMDNJ-New Jersey Medical School as Professor of Physical Medicine and Rehabilitation, Vice Chairman of the Department of Physical Medicine and Rehabilitation, and Professor of Neurosciences. Dr. Bach is also Director of Research and Associate Medical Director of the Department of Physical Medicine and Rehabilitation at University Hospital in Newark. Additionally, he is Co-director of the medical school’s Jerry Lewis Muscular Dystrophy Association Clinic and Medical Director of the Center for Ventilator Management Alternatives.

Course Chair: Kevin R. Nelson, MD

The ideas and opinions expressed in this publication are solely those of the specific authors and do not necessarily represent those of the AANEM.
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Dr. Carter is Clinical Professor of Rehabilitation Medicine at the University of Washington, where he co-directs the Muscular Dystrophy Association (MDA) clinic and attends in the electrodiagnostic lab. He also serves as regional medical director of rehabilitation services for the Providence Health System in Southwest Washington. His clinical research is investigating the relationships between pain, physical disability, and quality of life in neuromuscular disease (NMD). His pre-clinical research involves studying the role of electromyography and muscle magnetic resonance imaging as in vivo measurement tools to follow physiological changes in humans with NMD and transgenic mouse models of muscular dystrophy. He has over 100 peer-reviewed publications in these areas. In 1994 he won the Best Research Paper Published by a Physiatrist Award from the American Academy of Physical Medicine and Rehabilitation. In 1998 he received the Excellence in Research Writing Award from the Association of Academic Physiatrists. In 2002, he received the Excellence in Clinical Care Award from the MDA.

Carlo Martinoli, MD

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University of Genoa
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Dr. Martinoli was born on October 24, 1961 in Genoa, Italy. He received his medical degree in 1986 and became a specialist in radiology in 1989 at the University of Genoa. Starting as a staff radiologist in the Department of Radiology at the University of Genoa, he later became an assistant professor of radiology and then an associate professor of radiology in 2002. His practice has involved ultrasound and magnetic resonance imaging since 1989. He has held 391 lectures in Italy or abroad as an invited speaker at courses or congresses involving radiology. Dr. Martinoli has received the Nycomed Award for his research in radiology, and 23 other awards from scientific societies. He has written or co-authored a total of 491 publications, including 118 articles in peer-reviewed medical journals. Dr. Martinoli is also a councillor of the Executive Committee of the European Society of Skeletal Radiology (ESSR) and the chairman of the Ultrasound Subcommittee of the ESSR.

*Dr. Sanders is a consultant to and is a member of the Speakers Panel for Athena Diagnostics. He receives grant support from Roche Laboratories and is a consultant to Aspreva Pharmaceuticals and Ester Neuroscience. All disclosures received have been noted. Other faculty had nothing to disclose.

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Emerging Concepts and Technologies
in Neuromuscular Medicine

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OBJECTIVES This session will present multidisciplinary emerging concepts and technologies applicable to the spectrum of neuromuscular medicine. After attendance at this session, participants will understand how recent advances in genetics, pathophysiology, as well as how therapeutic and diagnostic techniques are changing our understanding, and may impact the clinical practice of neuromuscular medicine. The discussions will encompass disorders of nerve, neuromuscular junction, muscle, and the musculoskeletal system.

PREREQUISITE This course is designed as an educational opportunity for residents, fellows, and practicing clinical EDX physicians at an early point in their career, or for more senior EDX practitioners who are seeking a pragmatic review of basic clinical and EDX principles. It is open only to persons with an MD, DO, DVM, DDS, or foreign equivalent degree.

ACCREDITATION STATEMENT The AANEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

CME CREDIT The AANEM designates attendance at this course for a maximum of 5.5 hours in category 1 credit towards the AMA Physician’s Recognition Award. This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he/she actually spent in the activity. The American Medical Association has determined that non-US licensed physicians who participate in this CME activity are eligible for AMA PRA category 1 credit. CME for this course is available 9/05 - 9/08.
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MUSCLE SPECIFIC TYROSINE KINASE POSITIVE MYASTHENIA GRAVIS

Up to 20% of patients with generalized myasthenia gravis (MG) do not have detectable antibodies to the acetylcholine receptor (AChR). Although clinical characteristics of these seronegative patients (SNMG) are similar to those of seropositive MG (SPMG), subsets of SNMG patients have been identified with predominant oculobulbar weakness and poor response to therapy.

Muscle specific tyrosine kinase (MuSK) is expressed exclusively at the neuromuscular junction in mature muscle (Figure 1). In the developing muscle, MuSK, which is activated by motor nerve-derived agrin, is essential in aggregation of the AChR. The role of MuSK in adult muscle is still uncertain. Antibodies to MuSK have been reported in 40-50% of patients with generalized SNMG, and have recently been reported also in ocular myasthenia. Anti-MuSK antibodies interfere with AChR clustering in vitro, suggesting that they interfere with maintenance of normal AChR density at the end-plate.

Recognition of this immunologically distinct condition has led to efforts to define the clinical features of MuSK+ MG. Several clinical patterns have been reported in these patients. Among 37 MuSK+ patients from Italy, most had weakness of cranial and bulbar muscles, with frequent respiratory crises. Many MuSK+ patients from this author’s clinic had prominent neck, shoulder, and respiratory weakness and variable responses to cholinesterase inhibitors, leading to the suggestion that there may be several distinct clinical presentations of MuSK+ MG: patients with severe facial and pharyngeal muscle weakness; those with predominately neck, shoulder, and respiratory weakness (“restricted”); and a third group, in which the clinical pattern is indistinguishable from the majority of patients with SPMG.

In a prospective study, anti-MuSK antibodies were found in 12 of 32 patients with generalized SNMG (38%), and all patients were women. Subsequently, 10 additional MuSK+ patients have been identified, including 1 man (Table 1). Of these 22 patients, 10 had clinical and EMG findings typical for MG: they had fluctuating ocular and bulbar weakness, usually improved with cholinesterase inhibitors, and usually had decremental responses to repetitive nerve stimulation (RNS) and increased jitter in patterns seen in SPMG. Eight patients had weakness predominantly or exclusively in neck, shoulder, or respiratory muscles, and frequently had increased jitter or decremental responses only in shoulder or neck muscles. In these patients, ocular muscles were usually spared or became involved only late, and EMG findings in many of them showed findings suggesting myopathy. Four patients, including the only man with MuSK+ MG in this series, had progressive facial and pharyngeal weakness and atrophy, with ocular symptoms usually developing late in the disease. Eleven patients were African-American, which represents a significantly higher proportion than in almost 900 patients with acquired MG in the Duke MG Data Repository, which includes 200 SNMG patients.

In most seronegative and seropositive MG patients who have limb or bulbar muscle weakness, jitter is increased in the extensor digitorum communis (EDC) muscle. In a previous study, increased jitter in this muscle was found in only 6 of 12 MuSK+ patients. Studies in four additional MuSK+...
patients from Japan demonstrated abnormal jitter in the EDC in two. This relatively low frequency of abnormal jitter in the EDC was further confirmed in a cohort comparison study from this author’s clinic: only 59% had abnormal jitter in the EDC, compared to 80% of contemporaneous SN/MuSK- patients and 91% of SPMG patients (Stickler, Massey, and Sanders, in press). Two MuSK+ patients had normal jitter in both the EDC and frontalis muscles, but markedly increased jitter and blocking in neck extensor muscles. In several of this author’s MuSK+ patients, the suspicion of MG first arose when motor unit action potentials in neck muscles were noted to have excessive “jiggle.”

Responses to treatment of these MuSK+ patients were frequently not typical of MG. Ten MuSK+ patients improved on pyridostigmine, but 11 did not and 2 became worse. Several patients developed profuse fasciculations after edrophonium or pyridostigmine. All 16 patients treated with plasma exchange had dramatic and rapid improvement. Ten became asymptomatic after immunosuppression with combinations of prednisone, cyclosporine, and mycophenolate. Thymectomy was performed in 11; 1 of these patients is in stable clinical remission on no medications, and several others are asymptomatic on immunosuppression. However, it is not possible to determine if thymectomy contributed to the clinical improvement in these patients.

CONCLUSIONS

Up to 50% of patients with generalized SNMG have serum antibodies to MuSK. Because many patients with anti-MuSK antibodies have clinical features, electrodiagnostic findings, and responses to cholinesterase inhibitors that differ from typical MG, it can be difficult to make the diagnosis. Electrodiagnostic abnormalities may not be found as diffusely as in other forms of MG, thus it may be necessary to examine different muscles when the diagnosis of MuSK+ MG is being considered. This would include testing muscles that are predominantly involved clinically, such as neck extensor muscles.

Studies of intercostal and biceps muscles from MuSK+ patients have not demonstrated significant end-plate receptor loss or morphological changes. However, the potentially more limited distribution of physiologic abnormalities may

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**Figure 1** The post-synaptic muscle membrane. In most myasthenia gravis patients, antibodies are directed against the main immunogenic region (MIR) of the acetylcholine receptor (AChR). Closely associated with the AChR is muscle specific kinase (MuSK), which is activated by nerve-derived agrin. (Copyright D.B. Sanders, 2004)
limit the interpretation of such studies in MuSK+ MG, as abnormalities might not be seen in the muscles that are usually biopsied. Biopsy studies in muscles that have been shown to have increased jitter or decrement to RNS will help clarify the role of anti-MuSK antibodies in producing electrophysiologic abnormalities.

Responses to therapy are variable in MuSK+ MG patients, although plasmapheresis produces consistently marked benefit. Many patients achieve an excellent response to various forms of immunosuppression, but others have persistent weakness and atrophy despite aggressive immunotherapy. Benefit from thymectomy has not been demonstrated, and the best treatment for MuSK+ MG patients has not yet been determined.

**NEW TREATMENTS FOR MYASTHENIA GRAVIS**

**Mycophenolate Mofetil**

Mycophenolate mofetil (MMF) is a new generation immunosuppressive agent approved in the United States in 1995 for prophylaxis of organ rejection. It is a potent inhibitor of inosine monophosphate dehydrogenase, the key enzyme in the *de novo* purine nucleotide synthesis pathway. Because lymphocytes depend primarily on *de novo* pathways, MMF selectively impairs proliferation of activated B and T lymphocytes. It suppresses humoral immune response by B lymphocytes, but has no effect on IL-1 or IL-2.

In 1998, Hauser and colleagues reported successful treatment of a refractory MG patient with MMF. A subsequent 6-month, open label pilot study showed that MMF appears to be effective as adjunctive therapy in 67% of refractory and steroid-dependent MG patients. Several other retrospective series and case reports have suggested a possible role for MMF in the treatment of MG. A retrospective analysis of the use of MMF in 85 patients with MG demonstrated improvement in 76%. Initial objective improvement was seen within 11 weeks, on average, and in less than 16 weeks in 88% of cases. Side-effects to MMF were observed in 27% of patients, but required discontinuation in only 6%.

There are currently two ongoing clinical trials designed to demonstrate the efficacy and safety of MMF in MG. The first, an investigator-initiated study jointly supported by the Orphan Products Development Program of the United States Food and Drug Administration and Roche Laboratories, is designed to demonstrate that MMF with low-dose prednisone as initial immunosuppression improves MG better than low-dose prednisone alone after 3 months. The author is the Principal Investigator of this study, in which 80 immunosuppressant-naive patients with seropositive MG will receive 20 mg prednisone/day plus 2.5 g MMF or placebo for three months. Efficacy is determined by change in strength, assessed by a quantitative MG score. Patients then have the option of receiving open-label MMF for an additional 6 months, as the dose of prednisone is tapered. This study is being carried out at 16 United States sites and is scheduled to complete enrollment in the fall of 2005.

A parallel study, supported by Aspreva Pharmaceuticals, in collaboration with Roche Laboratories, is designed to demonstrate the steroid-sparing effect of MMF in 136

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**Table 1** Demographics, electrodiagnostic findings, and response to treatments among 22 patients with muscle specific kinase and myasthenia gravis.

<table>
<thead>
<tr>
<th>Clinical Pattern</th>
<th>“Typical MG”</th>
<th>“Restricted”</th>
<th>Facial/Pharyngeal</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>10</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>F:M</td>
<td>10:0</td>
<td>8:0</td>
<td>3:1</td>
</tr>
<tr>
<td>Age Onset (Range)</td>
<td>31.2 (14-59)</td>
<td>38 (21-54)</td>
<td>27.8 (8-45)</td>
</tr>
<tr>
<td>Race (W:B:A)</td>
<td>5:4:1</td>
<td>3:5:0</td>
<td>2:2:0</td>
</tr>
</tbody>
</table>

**Electrodiagnostic Findings:**

<table>
<thead>
<tr>
<th>RNS (Abnormal/tested)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hand</td>
<td>3/5</td>
</tr>
<tr>
<td>Shoulder</td>
<td>1/3</td>
</tr>
<tr>
<td>Face</td>
<td>1/1</td>
</tr>
<tr>
<td>Any muscle</td>
<td>2/4</td>
</tr>
</tbody>
</table>

**SFEMG (Abnormal/tested):**

<table>
<thead>
<tr>
<th>EDC</th>
<th>5/8</th>
<th>3/8</th>
<th>2/4</th>
<th>10/18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>5/5</td>
<td>5/7</td>
<td>4/4</td>
<td>14/16</td>
</tr>
<tr>
<td>Other</td>
<td>1/1</td>
<td>3/3</td>
<td>-</td>
<td>5/5</td>
</tr>
<tr>
<td>Any muscle</td>
<td>8/8</td>
<td>8/8</td>
<td>3/3</td>
<td>19/19</td>
</tr>
</tbody>
</table>

**Response to:** (Improved/treated)

| Pyridostigmine | 7/10* | 3/7 | 0/4* | 10/21* |
| Prednisone     | 7/7   | 3/5 | 2/2  | 12/14  |
| Azathioprine   | 1/5** | 0/2 | 1/7** | 6/7    |
| Cyclosporine   | 4/4   | 2/3 | 1/1  | 9/10   |
| Mycophenolate  | 4/4   | 4/5 | 6/6  | 16/16  |
| Plasma exchange| 9/9   | 6/6 | 1/1  | 16/16  |
| IVIg            | 2/2   | 2/2 | 2/2  |       |

*Two were worse
**Two other patients had allergic reaction or toxicity

A = Asian; B = black; EDC = extensor digitorum communis; F = female; IVIg = intravenous immunoglobulin; M = male; RNS = repetitive nerve stimulation; SFEMG = single-fiber EMG; W = white.
patients with seropositive MG. This study is a randomized, double-blind, placebo-controlled, 36-week multicenter trial of MMF in patients receiving prednisone, to determine the ability of MMF to maintain or improve symptom control as prednisone is reduced. It is being carried out at 19 countries in North America, Europe, Latin America, and Asia, and is scheduled to be completed in late 2006.

**EN101**

Antisense oligodeoxynucleotides are short segments of chemically-modified deoxyribose nucleic acid or ribonucleic acid (RNA) that interact with mRNA transcripts by base-pairing, thus interfering with biosynthesis of specific proteins. EN101 is an orally administered antisense oligodeoxynucleotide targeted against the mRNA that encodes production of acetylcholinesterase (AChE).\(^\text{32}\) It reduces the endogenous production of AChE, thus reducing the concentration of AChE at the end-plate, while avoiding the upregulation of this enzyme that follows administration of exogenous AChE inhibitors. Preliminary trials have demonstrated clinical benefit from single doses or short courses of EN101 in patients with MG. More extensive studies of long-term benefit and safety are currently underway.

**Tacrolimus**

Tacrolimus is a macrolide antibiotic that inhibits lymphokine production, with a mechanism of action (and toxicity) similar to cyclosporine. It suppresses AChR-Ab production and T-cell responses in experimental autoimmune MG. There have been a number of reports of benefit from tacrolimus in MG, mostly from Japan.\(^\text{9,13-15,22,34,36}\) but it is not clear that this agent has any advantage over cyclosporine, with which it also shares toxicity.

**Rituximab**

Rituximab is a human-mouse monoclonal antibody against the B-cell antigen CD20, and is used as an effective therapy for CD-20+ B-cell non-Hodgkin’s lymphoma. There have been several reports of improvement in isolated cases of MG after administration of rituximab.\(^\text{11,35,37}\) It is administered intravenously in weekly or bi-weekly courses, with a relatively benign side-effect profile. Studies are currently underway to assess its potential in autoimmune diseases, including MG.

**Etanercept**

Etanercept is a component of the ligand-binding portion of the human tumor necrosis factor (TNF) receptor linked to the Fc portion of human IgG1, produced in tissue culture of hamster ovary cells.\(^\text{23}\) It binds TNF-α and TNF-β, blocking their binding to cell surface TNF receptors, thereby inactivating these receptors. TNF-α has been implicated in the development of MG\(^\text{3}\) and experimental autoimmune MG,\(^\text{16}\) as well as other autoimmune diseases. TNF-α blocking agents have been shown to be beneficial in rheumatoid arthritis and ankylosing spondylitis, and a recent pilot study of etanercept in 11 steroid-dependent MG patients showed clinical improvement and reduced steroid requirements in 6 of 8 patients completing a 6-month trial. Further studies of efficacy and safety are needed to assess its potential role in MG.

*Dr. Sanders is a consultant to Athena Diagnostics and Aspreva Pharmaceuticals, and receives grant support from Roche Laboratories.*

Acknowledgements. Drs. Janice Massey, Vern Juel, and Robert Kurtzke provided information on MuSK+ MG patients. MuSK antibodies were measured by Dr. Angela Vincent (Neurosciences Group, Weatherall Institute of Molecular Medicine, Oxford, UK)\(^\text{17}\) or Athena Diagnostics (Worcester, MA).

**REFERENCES**


INTRODUCTION

Gene therapy for muscular dystrophy (MD) represents a promising avenue of pursuit for a disease with a limited repertoire of treatment. Successes in recent research have paved the way for advancing gene therapy for muscle disorders. Nevertheless, significant challenges remain before gene therapy can deliver on the promises avowed by early pioneers of the field. This manuscript will examine the progress and the hurdles remaining to achieve meaningful gene therapy for MD.

Gene therapy for MD embraces several concepts including replacing or repairing a defective gene, or modifying or enhancing cellular performance employing genes that are not directly related to the underlying defect (e.g., improving strength with IFG-1, and preventing muscle breakdown through calpain inhibition). The general principles apply to all forms of MD, although emphasis in this review will be on Duchenne muscular dystrophy (DMD).

THE MOLECULAR DEFECT IN DUCHENNE AND RELATED DYSTROPHIES

Understanding the gene defects in the MDs has expanded at an exponential rate since the identification of the dystrophin gene for DMD in 1987. In fact, it is most incredible that Edward Meryon, an English physician described the disease in 1851, yet its cause remained enigmatic for more than 125 years. Gene therapy represents an important theoretical tool by which to correct the underlying mutant gene.

A compelling need for treatment places DMD at center stage for gene therapy. Duchenne muscular dystrophy is the most common life-threatening childhood form of MD. In addition, there are convenient large and small animal models of dystrophin deficiency that provide an accessible prototype for proof of principle studies. The x-linked MD (mdx) mouse has a relatively mild phenotype except for the diaphragm muscle, which more closely simulates the human disease. In addition, a mouse model null for both dystrophin and...
utrophin is useful because it demonstrates significant weakness, an attenuated lifespan, and dystrophic limb muscle.

The dystrophin gene is the largest in the human genome, encompassing 2.6 million base pairs of DNA and containing 79 exons. Approximately 60% of dystrophin mutations are large deletions that lead to frameshift errors downstream, 6% represent duplications, and the remainder are small mutations below the resolution of multiplex polymerase chain reaction that must be identified by gene sequencing. Approximately 13% are point mutations causing stop codons. Super hot spots for deletions can be identified within the coding sequence of the gene at CpG dinucleotides and intronic mutations may be found in as many as 7% of cases.

A major function of dystrophin is to promote membrane stability against contraction-induced injury by providing a mechanical link between the contractile apparatus and the sarcolemma. Dystrophin, however, is not an isolated player in the muscle membrane. It is part of a multimeric transmembrane complex, the dystrophin-glycoprotein complex (DGC) that contributes to the structural stability of the muscle cell membrane.23 At the sarcolemma, β-dystroglycan binds intracellularly to dystrophin, which binds the actin cytoskeleton, and extracellularly to α-dystroglycan. α-dystroglycan provides the link to the basal lamina with high affinity binding to the extracellular matrix protein laminin, and other extracellular matrix proteins. In addition to dystroglycan and dystrophin, the DGC in muscle cells contains the sarcoglycan complex composed of four sarcoglycan proteins (α, β, γ, δ) and sarcospan. Intracellularly, dystrophin is required for anchorage of the syntrophin-dystrobrevin subcomplex 9 (consisting of a pair of syntrophins [α1 and β1] and α-dystrobrevin). In DMD, α1-syntrophin and β-dystrobrevin are absent or markedly reduced at the sarcolemmal membrane and β1-syntrophin undergoes upregulation. α-Syntrophin and a-dystrobrevin interact with neuronal nitric oxide synthase (nNOS) and localize it to the sarcolemma. Figure 1 shows predicted positions for these membrane-related proteins.

**ADENO-ASSOCIATED VIRUS**

The development of safe and efficient gene transfer vehicles is critical for the success of gene therapy. One of the most promising viral vectors is based on adeno-associated virus (AAV), a member of the family Parvoviridae, subfamily Parvovirinae, and genus Dependovirus. Adeno-associated virus was discovered as a co-infecting agent during an adenovirus outbreak, without any apparent pathogenicity. No human disease caused by AAV has been detected. One of the most dramatic developments in AAV biology has been the recognition of the broad diversity of AAV serotypes and genomic variants. Well over 100 AAV variants have been isolated from various species including nonhuman primates. Current candidates for gene therapy include nine AAV serotypes (AAV1-9). Advantages of each are under intense investigation to establish specific tropism relevant to the target tissue. AAV1, AAV6, and AAV8 are emerging as promising viral vehicles for transducing skeletal muscle.

All members of the AAV family are single-stranded deoxyribonucleic acids (DNA) viruses with a genome comprising approximately 4.7 kb encoding the two large open reading frames (ORF) rep and cap. The 5′ open reading frame rep encodes four overlapping, multifunctional proteins (Rep78, Rep68, Rep52, and Rep40) controlled by two different promoters. The large Rep proteins (Rep78 and its splice variant Rep68) are controlled by the p5 promoter and are necessary for viral DNA replication, transcriptional control, and site-specific integration. Rep52 and its splice variant Rep40 are known as small Rep proteins. They are transcribed from the p19 promoter and play an essential role in the accumulation of single-stranded progeny genomes used for packaging. The 3′ ORF cap accommodates the three capsid proteins VP1, VP2, and VP3 at a ratio of 1:1:18. They are controlled by the p40 promoter, share the same stop codon, but differ because of alternative splicing and different initiation codons resulting in progressively shorter proteins from VP1 to VP3. Inverted terminal repeats (ITRs) ranging between 143-167 nucleotides (variation in serotypes) flank the viral genome. The ITRs are required for replication and encapsidation of the viral genome and seem to have weak promoter activity. For use in gene therapy, the transgene of interest is inserted between the ITRs, which remain after removal of the viral genome. The insert capacity of AAV at less than 5 kb is one of its limitations as a delivery vehicle for gene therapy.

**IMPACT OF SERIOUS ADVERSE EVENTS**

Serious adverse events have changed the landscape for gene therapy. In September 1999, a death occurred during a gene therapy clinical trial that involved the transfer of an adenoviral (Ad) vector containing the ornithine transcarbamylase gene. Although the vector was primarily delivered to the liver, postmortem analysis found it in a variety of tissues and death was attributed to systemic Ad vector-induced shock syndrome, acute respiratory distress, and multi-organ system failure. This event had ramifications throughout the gene therapy world. Anxiety intensified in the autumn of 2002 because of a report of T-cell leukemia in a patient with X-linked severe combined immunodeficiency disease (X-SCID) treated by ex vivo, retroviral-mediated gene transfer of the
IL2rg gene. The risks for cancer are presumed to be related to insertional mutagenesis, supported by evidence for retroviral vector integration in proximity to LMO2, a known human T-cell oncogene. The issue, however, further intensified when two additional X-SCID patients developed leukemia, and one of the three died of a cancer-related complication. The United States Food and Drug Administration (FDA) reacted by halting all gene therapy trials for SCID. Subsequently, an advisory board met in March 2005 and permitted continuation of gene transfer for adenosine deaminase deficiency (ADA)-SCID, in contrast to the X-linked variant. These events have clearly changed the environment for clinical gene transfer studies. For one thing, transgene expression of vector from an episomal location, as exhibited by AAV, may no longer be considered a disadvantage for gene therapy. In fact, more research is likely to be directed toward preventing transcriptional silencing from episomal gene expression using strategies that include regulatory sequences, introns, and native promoter elements. From a regulatory perspective, informed consent documents will clearly need to state the risks of neoplasia and death following gene therapy clinical trials. Protocols employing viruses dependent on genome integration for gene expression, such as retroviruses and lentiviruses will undergo closer scrutiny by regulatory agencies. Even presumably safe vectors such as AAV will require long-term experience in human trials to unequivocally establish safety.

ADAPTING THE DYSTROPHIN GENE TO ADENO-ASSOCIATED VIRUS

The tremendous size of the dystrophin gene (2.4 megabases; mb) and messenger ribonucelar acid (mRNA) (14 kb) are formidable obstacles for DMD gene therapy. The muscle isoform of dystrophin comprises four domains: the N-terminal, a central rod domain with 24 spectrin-like repeats and 4 hinge regions, and cysteine-rich and C-terminal domains. The application of many emerging gene-delivery systems to DMD therapy depends on the required minimum size of a functional dystrophin expression cassette. Dystrophin can retain significant function even when missing large portions of its sequence. Large, in-frame deletions in the central-rod domain often lead to the milder Becker MD. The Becker patient reported by England and colleagues, with a deletion from exon 17 to 48, had 46% of the coding region from the dystrophin gene removed and the patient remained ambulatory after age 61. This deletion resulted in a protein containing approximately 8.5 of the 24 spectrin-like repeats normally found in the rod domain. A mini-dystrophin modeled after the exon 17-48 deletion in the mdx mouse model for DMD was highly, but not fully, effective in preventing dystrophy.

A careful series of studies from the Chamberlain Laboratory have generated small dystrophins that maintain functional capabilities approaching that of the full protein. Studies in transgenic mice and AAV-mediated gene transfer demonstrate that specific rod-domain deletions can be combined with additional deletions of the C-terminal domain to engineer mechanically functional micro-dystrophins that can reverse morphological features of MD. The most efficient modification of the dystrophin protein requires a rod domain with retention of pairs of spectrin-like repeats for optimal function (deletion of all spectrin repeats has no therapeutic value). Eight spectrin-like repeats optimize the construct, but fewer repeats, even those with five repeats benefit the mdx mouse. Hinges found in the rod domain also influence outcome. Retaining the normal flanking spectrin repeats in proper relation to the hinge provides optimal results for correcting the dystrophic phenotype.

The ability to construct small dystrophins that fit the size limitations of AAV and demonstrate the ability to reverse the...
phenotype is a major step toward adapting gene transfer as a tool for treatment for this lethal disease. Nevertheless, the limitations of small dystrophins should be emphasized since these altered dystrophin constructs, can at best, rescue a severe dystrophy and transform it to a milder type. The full-length dystrophin is needed for complete restoration of both morphology and strength.

**DYSTROPHIN REQUIREMENT FOR GENE REPLACEMENT**

An important issue is the range of dystrophin needed for clinical gene transfer. On the one hand, it has been illustrated that dystrophin levels reaching 50 times normal are without pathological consequences, emphasizing a convincing margin of safety. An equally encouraging observation for skeletal muscle gene transfer is indicated by significant correction of muscle pathology by a meager level of dystrophin replacement equivalent to approximately 20% of wild-type levels. Of interest are two exceptions. The diaphragm muscle appears to be equally content with even lower levels of dystrophin replacement than limb muscles. On the other hand, the requirements for replacement of cardiac dystrophin appear greater and must reach the 50% level to treat the cardiomyopathy.

**REACHING REMOTE SITES IN GENE TRANSFER**

A prerequisite for successful gene therapy for MD is the ability to transduce limb muscles, diaphragm, and heart by gene delivery via a vascular route. However, the vascular endothelium has imposed itself as a surprisingly impenetrable barrier. Nevertheless, several recent reports provide a glimpse at the future of gene therapy for MD. Gregorevic and colleagues used a protein that makes vessels transiently permeable—vascular endothelial growth factor (VEGF). A transgene cassette composed of microdystrophin under control of muscle specific promoter in rAAV6 achieved widespread transduction of skeletal muscle when injected into the bloodstream (tail vein) of mice with VEGF. Injection of $10^{12}$ vector genomes of rAAV6 reduced serum creatine kinase (CK) levels by approximately 50% and resulted in a mosaic pattern of expression with reduced susceptibility to eccentric contractions compared to mdx mice. While this phenotypic correction was incomplete, a dose-response effect was demonstrated since higher doses (e.g., $10^{13}$ vector genomes) resulted in a far more widespread expression pattern of expression within the muscle and more complete reversal of the dystrophic phenotype.

Overall these studies are encouraging. However, one shortcoming of delivery with VEGF is that vector genomes are detected not only in skeletal muscle, but brain and testes as well. The authors were aware that this broad tropism of VEGF-mediated gene delivery is an undesirable consequence, compensated in part by the guided tissue specific expression of the muscle specific promoter. Still to be overcome, however, is the poor expression of the current version of the CK6 promoter in cardiac muscle. The CK6 promoter also leads to poor expression in the diaphragm of the mdx mouse. In contrast, the constitutive cytomegalovirus (CMV) promoter clearly results in high levels of dystrophin expression in both heart and diaphragm.

Additional recent experiments have demonstrated that rAAV8 is highly efficient for crossing the blood vessel barrier and will express in the heart and skeletal muscles of mice and hamsters. Cardiac expression is a potential advantage of this vector but studies using this serotype have not been done with small dystrophins. In fact, the studies by Wang and colleagues used a double-stranded rAAV8 with a reduced insert capacity, below the threshold for dystrophin. Green fluorescent protein was used as a marker for tissue expression. Further studies are needed with rAAV8 to determine if standard single-stranded AAV8 vectors will be useful as a delivery tool for small dystrophins.

**STAGING GENE THERAPY STUDIES TO ACHIEVE MEANINGFUL RESULTS**

An important question frequently asked by regulatory agencies (i.e., FDA and Recombinant Advisory DNA Committee [RAC]) relates to the staging of gene therapy studies to achieve clinically meaningful results for MD. Phase I projects use a single muscle paradigm to demonstrate safety. In such clinical experiments one could only expect localized muscle expression close to the site of injection with no functional advantage for the patient.

Clinical gene therapy studies for MD are in their infancy. Only a single preliminary clinical study of gene transfer has been performed, involving two patients with a-sarcoglycan deficient MD (LGMD2A). rAAV2 was used to transfer the gene under control of the CMV promoter. In 1999, small dystrophins were not yet available for clinical studies. The extensor digitorum brevis muscle was chosen as the target for gene transfer for safety considerations. This is a small intrinsic foot muscle with only vestigial function. The study was approved by FDA as a dose-escalation study, but only two patients were completed because gene therapy studies were stopped as a direct result of the unrelated Gelsinger tragedy. Nevertheless, this study of a-sarcoglycan gene transfer was valuable in several ways despite its abrupt and early termination: (1) one of the two patients had limited transgene expression without evidence of toxicity or rejection; (2) the gene delivery and monitoring protocol provided a valuable experience for planning other trials such as the upcoming
DMD gene transfer trial approved by the RAC on December 18, 2004.

An important question at hand is what follows single muscle injections for gene transfer. One might envision a multiple muscle injection paradigm that could improve strength to a group of limb muscles. For example, facilitating arm function following a high-dose, multiple-injection paradigm, could benefit eating, writing, using a computer, etc. Improving leg function through multiple muscle injections to the quadriceps could also help standing or even prolong ambulation. The inefficiency of this approach is obvious and the need for a large number of injections is at the very least impractical.

It is more likely that following the single muscle transfer stage, meaningful gene therapy for MD will advance through a stage of regional vascular delivery prior to systemic vector delivery. A study in the hemophilia dog model used regional delivery with impressive success and could be adapted to a delivery. A study in the hemophilia dog model used regional vascular delivery prior to systemic vector delivery. The stages of regional vascular delivery prior to systemic vector delivery. The definitive stage of clinical gene therapy will most likely be systemic delivery with ease of administration by injection of vector through a venous route similar to tail vein infusion in the mdx mouse. In patients, additional vector modifications may be required to increase surface binding to the blood vessels or muscle to achieve this ultimate step in gene therapy.

STAGES OF ADENO-ASSOCIATED VIRUS TRANSDUCTION

The stages of rAAV transduction are schematically shown in Figure 2. These have been described in an excellent review article by Ding and colleagues. A full understanding of gene transduction has important implications for achieving success in clinical trials: insight to the rate-limiting steps in transduction will permit scientists to focus on strategies to overcome the barriers to success. A practical consideration is potentially reducing the requirement for high titers of vector. The challenge can be appreciated in the context of the need for as much as a thousand-fold increase in vector titer needed to take benchside successes in the mdx mouse to bedside. Reducing these prerequisites enhances the safety of gene transfer as well as being more compatible with potential limitations in vector production technology for treating a significant number of patients.

MODIFYING ADENO-ASSOCIATED VIRUS ATTACHMENT RECEPTORS

Binding to the surface of the target cell through receptors and coreceptors is the initial event in transduction. Table 1 summarizes the current knowledge of AAV attachment receptors and coreceptors. The ability to infect different cell types and tissues is based on capsid protein recognition by cell surface receptors. For skeletal muscle, AAV2 depends on heparan sulfate proteoglycan (HSPG) as its receptor. Evidence also demonstrates the use of HSPGs by AAV3 as an initial attachment receptor. In contrast, sialic acid has been identified as a primary attachment receptor for AAV4 and AAV5. N-linked sialic acid is used by AAV5, whereas AAV4 preferentially uses O-linked sialic acid for attachment. The attachment receptors for AAV1 and AAV6-9 have not been identified.

Two coreceptors for AAV2 have been identified. These include αVβ5 integrin and fibroblast growth factor receptor type 1. Levels of αVβ5 integrin expression appear to influence the efficiency of rAAV2 transduction in certain cell types and inhibition of αVβ5 integrin with blocking antibodies can prevent internalization of bound rAAV2 on the surface of HeLa cells. Platelet-derived growth factor receptor...
is considered to be the co-receptor for AAV5. More work is needed to more fully understand receptor binding of other serotypes.

A complete understanding of AAV receptors would enable expanded use of technologies that mix and match serotypes for enhanced binding and transduction. For example, if one knows that AAV1 yields the most efficient, long-term transduction in skeletal muscle, and AAV6 or AAV8 cross the vascular barrier more efficiently, hybrid or mosaic serotypes may be manufactured for transgene packaging. Such techniques are referred to as cross-packaging, or pseudo-packaging.5,26,35

This application represents a valuable tool for targeting and enhancing transduction for gene therapy for muscle diseases.

**RECEPTOR-MEDIATED ENDOCYTOSIS AND ENDOSONAL TRAFFICKING**

Binding is followed by rapid uptake of AAV into cells, estimated to occur within 100 ms in cell culture.28 Once this takes place, a cascade of events is initiated which is best studied with AAV2 where HSPG-bound rAAV2 enters cells through clathrin-coated pits in a dynamin-dependent process.4 rAAV5 also utilizes clathrin-coated pits, despite a different primary attachment receptor (sialic acid).3

More studies of endosomal processing and AAV trafficking need to be performed in skeletal muscle to identify rate limiting steps relevant to future clinical gene therapy studies. Most of the available information has been generated in HeLa, 293 and NIH 3T3 cell lines. Evidence favors that clathrin-coated vesicles mature into early endosomes of relatively low density and neutral pH. Through processes not completely understood, the virions then traffic to late endosomes of relatively high density and low pH. Support for this acidified corridor is based on biochemical studies demonstrating reduced AAV2 transduction following modifications of the environment that raise intracellular pH (e.g., bafilomycin A1, a proton inhibitor and ammonium chloride).20

In the late endosomal compartment, modifications of the virion take place that are critical for uncoating and nuclear transport. For example, when directly injected into the cytoplasm, labeled rAAV2 fails to accumulate in the nucleus.13 Conflicting data also needs resolution on the distal pathway to nuclear delivery. Trafficking through the perinuclear recycling endosome (PNRE) has been proposed based on Cy3-labeled AAV2 and inferences from the transferrin pathway.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Attachment Receptor</th>
<th>Co-Receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAV1, 6, 7, 8, 9</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>AAV2</td>
<td>HSPG</td>
<td>a5bV, FGFR1</td>
</tr>
<tr>
<td>AAV3</td>
<td>HSPG</td>
<td>Unknown</td>
</tr>
<tr>
<td>AAV4</td>
<td>O-linked sialic acid</td>
<td>Unknown</td>
</tr>
<tr>
<td>AAV5</td>
<td>N-linked sialic acid</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

AAV = adeno-associated virus; HSPG = heparan sulfate proteoglycan.
Others favor that both AAV2 and AAV5 bypass the PNRE and travel directly to the trans-Golgi network prior to nuclear entry. The pathways need not be mutually exclusive, in that saturation of one trafficking pathway may allow use of the second alternative pathway.

ENDOSOMAL ESCAPE AND NUCLEAR TRANSLOCATION

It is generally believed that AAV particles are transported to the nucleus prior to uncoating. Little is known about the processes that control nuclear translocation across the nuclear pores. In most cell lines studied, nuclear transport of AAV appears to be a slow and inefficient process. Only a small portion of internalized AAV can be found in the nucleus. Several agents appear to promote nuclear accumulation of AAV and rAAV transduction. These include proteosome inhibitors, hydroxyurea, and adenovirus. It is believed that these agents enhance endosomal and cytoplasmic processing rather than by facilitating nuclear transport, although the exact site of augmentation of transduction is not known. It remains undefined if nuclear transport of AAV particles requires capsid modifications and/or association with transport receptors. Nucleolin (a protein that shuttles from the cytoplasm to the nucleus) has been implicated, although the process may not be the same for all paroviruses.

NUCLEAR GENE CONVERSION

Unlike other DNA-based viral vectors such as adenovirus, when AAV sheds its capsid, a single-stranded DNA (ssDNA) genome is delivered to the nucleus. This must be converted to double-stranded DNA (dsDNA) to become transcriptionally active. The ssDNA to dsDNA conversion is a well-documented rate-limiting step. This process contributes to the slow onset of transgene expression where a few weeks are often required to achieve levels that could be clinically meaningful. For laboratory studies, a more rapid onset of gene expression would permit more opportunities for observation at a reduced cost that ultimately impact planning of gene transfer clinical trials.

Presently many investigators are pursuing the potential advantages of self-complementary (SC) rAAV vectors to increase the rate and in vivo expression levels. These unique vectors encapsulate a single-stranded hairpin that upon nuclear entry, rapidly anneal to form a double-stranded DNA transcriptional template. Skill in producing these vectors has rapidly spread through the molecular community based on ground-breaking studies of McCarty and colleagues. The principle of vector production is based on deletion of the terminal resolution site within the 5' ITR resulting in nearly exclusively packaging of the single-stranded dimeric replicative form. Self-complementary vectors are efficient for muscle and other tissues including brain and liver. The trade-off for clinical studies is the reduced capacity for transgene insertion compared to standard single-strand rAAV vectors (2.2 kb vs 4.4 kb). For example, small dystrophins are not applicable to SC rAAV vector technology, but small therapeutic genes or small RNA-based therapeutics would be appropriate.

SUMMARY

Gene therapy as a potential treatment tool for MD is poised for clinical trials. There is an overwhelming consensus that AAV is the vector of choice for MD gene therapy. By all indications it is safe, relatively free of immunogenicity, although the degree of immunosuppression that must accompany clinical trials remains to be established. The biggest single factor permitting advances in gene therapy is the spectrum of AAV serotypes currently available for gene transfer. This includes the ability to manipulate these serotypes, even to the degree of creating hybrid vectors. Knowledge is sorely needed on AAV trafficking and delivery to the nucleus, especially in skeletal muscle. The future looks bright with a steady, consistent assault on this means of treatment. Success will most likely be achieved in a stepwise manner with regional delivery clearly in sight and systemic vascular delivery, a potentially attainable goal.

REFERENCES

Respiratory Management of Patients With Neuromuscular Disease

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“Throughout the ALS process, I have learned many things. I have learned that having ALS does not necessarily mean a death sentence, that I am not living with a life-threatening disease, but rather with a life-enhancing condition.”
The Honorable Justice Sam Filer, Superior Court Judge and ALS ventilator user with tracheostomy tube since 1989, “spoken” via voice synthesizer at Beyond the ICU III, Perspectives on Ventilation, Committee for Independence in Living and Breathing, Toronto, Canada.

INTRODUCTION

All patients with respiratory impairment have either primarily oxygenation impairment from lung or airways disease, or ventilatory impairment due to central hypoventilation or respiratory muscle dysfunction. Patients with neuromuscular disease have primarily the latter but are usually evaluated and treated as though they have primarily oxygenation impairment with bronchodilators and supplemental oxygen instead of respiratory muscle aids. Failure to aid the respiratory muscles leads to hypercapnic respiratory failure or, more frequently, to acute respiratory failure due to an impaired cough during otherwise benign upper respiratory tract infections.

There are numerous publications concerning the use of nocturnal low span bi-level positive airway pressure (PAP) that have resulted in a statistically significant, but clinically insignificant, prolongation of life. Whether symptomatic or not, patients with neuromuscular diseases (NMD) are routinely evaluated by polysomnography. Polysomnography is designed to evaluate for central and obstructive apneas and hypopneas but not for hypoventilation secondary to respiratory muscle weakness. Thus, the interpretation of the study is usually inappropriate and results in the patient being treated with bi-level PAP at spans too low to adequately rest the inspiratory muscles, assist cough, or prevent respiratory failure. Pressure-cycled ventilators, like bi-level devices, cannot be used for air stacking nor can they provide the occasional deep volumes of air that are required for coughing, increasing voice volume, or maintaining pulmonary compliance. Therefore, with the exception of advanced bulbar-onset amyotrophic lateral sclerosis (ALS) patients and other patients unable to air stack, volume-cycled ventilators need to be used for noninvasive mechanical ventilation.

Since respiratory muscle aids are rarely used properly—making respiratory failure inevitable—Duchenne muscular dystrophy (DMD) patients usually die in their early twenties, 90% of spinal muscle atrophy (SMA) type 1 children die by 12 months of age, and patients with ALS die a mean of 15-18 months from the time of diagnosis. Even those who undergo elective tracheotomy usually die from complications of the tube. The typical patient uses nocturnal low span bi-level PAP until developing a respiratory tract infection that evolves into pneumonia because he/she cannot cough effectively. Next, the patient receives supplemental oxygen,
arrests, is intubated, and when unable to ventilator wean or when extubation is deemed unsafe, undergoes tracheostomy. In a recent report, however, 55 DMD patients using inspiratory and expiratory muscle aids in an oximetry feedback protocol had survival prolonged thus far by 5.8 ± 4.6 years (range 26-44 years). The aid protocol included using noninvasive intermittent positive pressure ventilation (IPPV) 16 to 24 hours per day. Five of the patients had become dependent on continuous noninvasive IPPV for over 2 years without ever being hospitalized. Four had been extubated or decanu- lated and switched to continuous noninvasive IPPV. One- half (eight) of the patients previously managed with tracheostomy tubes died because of tube-related complications. Only three protocol users died, in each case from congestive heart failure.11,15 Likewise, 26 ALS patients have become continuous ventilator users without tubes or hospitalizations and others with no ability to breathe have been decanu- lated for up to 10 years before bulbar dysfunction necessitated recanulation.10 Of 45 severe SMA type 1 children, 39 have survived age 2, 16 age 6, and 4 age 10 without tracheostomy tubes, because of the use of respiratory muscle aids to facilitate extubations despite failure to ventilator wean.15 Likewise, few if any high level spinal cord injured patients who are continuously ventilator dependent need to keep their tracheostomy tubes.7

In Great Britain, 82% of ALS patients die receiving morphine and 64% receive benzodiazepines while few (if any) are provided with the means to prevent respiratory death.18 This “palliative” approach hastens death by carbon dioxide (CO2) narcosis and renders oximetry useless.19,20,21 Over a recent 5- year period, there were 12 New England Journal of Medicine articles published on assisted suicide for ALS, but not one on preventing respiratory failure. This lack of using noninvasive ventilation on assisted suicide is likely because clinicians typically judge quality of life to be unacceptable and the disease terminal. They also are unfamiliar with life-sparing interventions and there is family bias against ventilator use—which in the physician’s mind is associated with tracheostomy. Non- intervention in fatal illness becomes a self-fulfilling prophecy.5

In 1909 Freud said, “People who want to make a living from the treatment of nervous patients must clearly be able to do something to help them.” In today’s economic environment in which it is fiscally prohibitive for committees of physicians to address the multisystem complications of neurologic disease, the NMD physician needs to understand the cardiopulmonary, orthopedic, gastrointestinal, nutritional, and other prophylactic interventions to maximize duration and quality of life.

Surveys of Jerry Lewis Muscular Dystrophy Association clinic directors in 1992 and 2000 indicated that scoliosis surgery and other vital interventions were not being offered to the majority of DMD patients in large part because of the perception that their life expectancies were too short.5,12 This no longer needs to be the case.

RESPIRATORY MUSCLE EVALUATION AND AIDS

Although respiratory muscles are many and their strength can be easily, objectively, and precisely evaluated by comparison with manual muscle testing, few NMD physicians are equipped to evaluate them. Pulmonary function laboratories are prepared to assess for lung/airway diseases but not for neuromuscular weakness. Respiratory evaluation requires a spirometer for measurement of vital capacity (VC) in both sitting and supine positions and maximum insufflation (air stacking) capacity (MIC), peak flow meter to measure unassisted and assisted cough flows, end-tidal CO2 analysis, and oximetry.3

The three respiratory muscle groups are inspiratory, expiratory, and bulbar. Decreased inspiratory and expiratory muscle function results in decreased VC and alveolar hypoventilation but rarely in CO2 narcosis and death unless the patient is receiving supplemental oxygen.14 Expiratory muscle dysfunction coupled with inspiratory dysfunction result in an ineffective cough. Ninety percent of episodes of respiratory failure in muscular dystrophy patients (almost all of which are preventable) are caused by cough impairment during otherwise benign respiratory tract infections.14 Once cough peak flows (CPF) decrease below 160 L/m they are no longer effective and pneumonia and acute respiratory failure become certain during bronchial infections.15 Fortunately, both inspiratory and expiratory muscle weakness can be easily compensated for by physical medicine aids. Numerous patients with no muscle function below the neck and no measurable VC for over 50 years have never been intubated or had tracheostomy tubes.3

The three goals of management are: (1) to provide insufflations to optimally expand the lungs and chest walls to maintain compliance and promote lung growth in children; (2) to maintain normal alveolar ventilation around-the-clock; and (3) to maximize CPF. These goals are attained by using inspiratory and expiratory muscle aids.

What are Physical Medicine Respiratory Muscle Aids?

Inspiratory and expiratory muscle aids are devices and techniques that involve the application of forces to the body or pressure changes to the airway to assist inspiratory or expiratory muscle function. Body ventilators act on the body to assist inspiration just as an abdominal thrust can assist coughing. Negative pressure applied to the airway during expiration
also assists the expiratory muscles for coughing, just as positive pressure applied to the airway during inhalation, or non-invasive intermittent positive pressure ventilation (IPPV), assists the inspiratory muscles. Note that continuous positive airway pressure (CPAP) neither assists inspiratory nor expiratory muscles and should rarely if ever be used for these patients.

**Goal One: Maintenance of Lung and Chest Wall Mobility**

As the VC decreases, the largest breath can only expand a small fraction of the lungs. Like limb articulations, the lungs and chest wall require regular mobilization. Use of incentive spirometry or deep breathing can expand the lungs no greater than the VC and is, therefore, useless. Lung mobilization can be achieved by air stacking, by providing deep insufflations, or by nocturnal high span bi-level PAP for infants.9

A patient’s MIC is the largest volume of air that can be held with a closed glottis.16 The patient uses a mouthpiece to “air stack” consecutively delivered volumes from a volume-cycled ventilator or a manual resuscitator to maximum lung inflation. This is performed multiple times, three times daily. If the lips or cheeks are too weak to permit air stacking via a mouthpiece, it is performed via a nasal interface or Bennett Lipseal™. Most patients can learn to use glossopharyngeal breathing (GPB) for lung expansion to or beyond the MIC.8 The MIC VC difference is a function of bulbar muscle integrity.16 If the bulbar muscles are too weak for deep air stacking, single deep insufflations are provided via a Cough-Assist™ at 40-70 cm water (H2O) three times daily.

Regular lung expansion can increase MIC, maximize CPF, improve pulmonary compliance, prevent atelectasis, and provide mastery of noninvasive ventilation. Lung mobilization is also needed to promote lung growth and chest wall development in children. While infants cannot air stack, nocturnal use of high span (inspiratory positive air pressure—expiratory air pressure greater than 10 [IPAP-EPAP>10]) bi-level positive airway pressure (BiPAP) has been demonstrated to prevent pectus excavatum and promote lung and chest wall growth for infants with SMA and paradoxical breathing.10 Any patient capable of air stacking who loses breathing tolerance during chest colds, can use noninvasive ventilation continuously or be extubated directly to it. This is extremely important for avoiding tracheostomy because such patients are extubated without being ventilator weaned.

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**Goal Two: Maintain Normal Alveolar Ventilation**

**Inspiratory Muscle Aids**

Intermittent positive pressure ventilation delivered via volume-cycled machines can be noninvasively delivered via Lipseals™, Oracles, nasal, and oral-nasal interfaces for ventilatory support during sleep, with the patients trained and equipped in the out-patient setting. Lipseals™ and Oracles can provide essentially closed systems of ventilatory support.3

Patients requiring around-the-clock support use simple 15 or 22 mm angled mouthpieces held between the teeth for IPPV during the day. To use mouthpiece IPPV effectively and conveniently, adequate neck rotation and oral motor function are necessary to grab the mouthpiece and receive IPPV without air leakage.

When the lips are too weak to grab a mouthpiece, the patient can use an intermittent abdominal pressure ventilator6 or continue nocturnal nasal IPPV through daytime hours, alternating nasal interfaces to vary skin pressure. A popular interface for daytime use a nasal interface, because this permits the use of glasses and does not obstruct vision.

This author has never found the use of oronasal interfaces to be necessary. One can provide an essentially closed system of ventilatory support by using a Lipseal™ and placing cotton pledgets in the nostrils, sealing the nostrils with an adhesive bandage. It is crucial to avoid the depression of ventilatory drive by the use of sedative medications, oxygen, or daytime hypercapnia that results in oxyhemoglobin desaturation to below 95%. As long as ventilatory drive is not depressed, even patients with little or no measurable VC can be safely ventilated day and night by nasal or oral ventilation.

Other than continuous dependence on noninvasive ventilation, benefits from part-time use include respiratory muscle rest, increased tidal volumes, alveolar ventilation and blood gases, improved lung compliance and chemotaxic sensitivity, and possibly improved ventilation/perfusion matching by reducing atelectasis and small airway closure. To accomplish optimal rest, high volumes or pressure spans should be used, that is, assist-control mode at volumes of 800-1500 ml for adults and inspiratory to expiratory PAP (IPAP to EPAP) spans of 13-17 for bi-level PAP users. Patients adjust the volume of air taken to vary tidal volume, speech volume, and
cough flows, as well as to air stack. There are no significant complications of noninvasive IPPV and continuous users who learn GPB need not worry about accidental disconnection or ventilator failure and can use GPB instead of daytime ventilatory support.

Goal Three: Facilitate Airway Clearance

Chest percussion and vibration are not substitutes for coughing. Bulbar, inspiratory, and expiratory muscles or respiratory aids are needed for coughing.

Manually Assisted Coughing

If the VC is under 1.5 L, air stacking or insufflating the patient is followed by an abdominal thrust timed to glottic opening to increase cough flows. When this is inadequate due to difficulty air stacking, the most effective alternative is mechanically assisted coughing (MAC).

Mechanically assisted coughing is the combination of mechanical insufflation-exsufflation (pressures usually +40 to -40 cm H₂O delivered via oronasal interface or invasive tube) coupled with an exsufflation-timed abdominal thrust. Lungs are insufflated until fully expanded and then exsufflated until fully emptied. Normal cough and exsufflation volumes exceed 2 liters in adults.

Whether via the upper airway or via indwelling airway tubes, routine airway suctioning misses the left main stem bronchus approximately 95% of the time. Mechanically assisted coughing, on the other hand, provides similar flows in both left and right airways without the discomfort, fatigue, or trauma and it can be effective when suctioning is not. It takes the place of inspiratory and expiratory but not bulbar muscles. Thus, even its optimal use can not avert tracheostomy for long if bulbar function is inadequate to prevent continuous aspiration of saliva (as in advanced bulbar ALS) to the extent that the oxygen saturation via pulse oximetry (SpO₂) decreases below 95%, the only indication for tracheotomy in these patients. In a recent study, over 90% of ALS patients whose SpO₂ baseline decreased below 95% and could not be normalized by respiratory aids underwent tracheostomy or were dead within 2 months. On the other hand, adults with very functional bulbar muscles (SpO₂>94%) such as those with non-bulbar ALS, myopathies, or SMA types 2 or 3 often have assisted CPF that exceed 6 L/s, and therefore, do not need to use MAC or tracheostomy tubes despite continuous ventilator dependence. Thus, the patients who need MAC the most are those whose bulbar muscle function can maintain adequate airway patency but is insufficient to permit optimal air stacking for assisted CPF over 250-300 L/m. This is typical of most patients with NMDs except for those with no measurable CPF due to advanced bulbar ALS.

The Oximetry Feedback Respiratory Aid Protocol consists of using an oximeter for feedback to maintain SpO₂ greater than 94% by maintaining effective alveolar ventilation and airway secretion elimination by using inspiratory and/or expiratory aids. This is most important during respiratory tract infections and when extubating patients with little or no breathing tolerance.

Noninvasive IPPV is overwhelmingly preferred over tracheostomy for speech, sleep, swallowing, comfort, appearance, security, use of GPB, and overall usage. Another study demonstrated a 200% cost savings by using noninvasive ventilatory support methods for patients with no ventilator-free breathing by facilitating community living. On the other hand, infants with SMA type 1 who undergo tracheotomy lose all ability to breathe unaided and do not develop the ability to speak whereas infants with the same disease severity who are maintained by noninvasive methods usually require only nocturnal high-span BiPAP and usually develop the ability to verbalize.

SUMMARY

Both inspiratory and, indirectly, expiratory muscle activity can be assisted by GPB. This technique involves the glottis projecting air into the lungs. One breath usually consists of 6-9 gulps of 60-100 ml each. Glossopharyngeal breathing can provide an individual who has little or no measurable VC with normal lung ventilation throughout daytime hours and perfect safety in the event of ventilator failure day or night. The safety and versatility afforded by GPB are key reasons to eliminate tracheostomy in favor of noninvasive aids. This author’s center has managed approximately 1000 patients who have used continuous long-term noninvasive ventilatory support for up to 57 years. Hundreds of hospitalizations have been avoided by using continuous ventilatory support along with MAC. This cannot be done by using nocturnal low-span bi-level PAP and it will not be done without using mouthpiece IPPV. To accomplish these outcomes, one must use these methods.
REFERENCES

Maximizing Quality of Life With Rehabilitation Interventions for Patients With Neuromuscular Disorders

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INTRODUCTION

The World Health Organization (WHO) defines quality of life (QoL) as “an individual’s perception of their position in life in the context of the culture and value systems in which they live, in relation to their goals, expectations, standards, and concerns.” Health-related QoL is a broad concept affected in a complex way by an individual’s physical health, psychological state, personal beliefs, social relationships, and their relationship to salient features of their environment. Although it is widely acknowledged that this is an area of concern for people with neuromuscular disorders (NMDs), there have been remarkably few studies that have systematically assessed QoL in individuals with NMDs. This may be due in part to the fact that QoL is perceived as a somewhat vague entity that many people are concerned about, but something that nobody clearly knows what to do about.

This manuscript will discuss the value of assessing health-related QoL and then describe, in detail, rehabilitation modalities that can maximize QoL for patients with NMD.

QUALITY OF LIFE

What is Health-related Quality of Life and Why Do We Measure It?

Why should a clinician measure health-related QoL? Perhaps the most compelling reason is that QoL is of primary importance to our patients with NMDs that we serve. Although as physicians we tend to focus on biochemical and physiological information, such information is only of interest to our patients to the extent that biomedical factors influence their functional status and emotional well-being. For example, although two patients with the same hereditary peripheral neuropathy may have similar ratings of pain and mobility, they may report markedly different role functions. One might be working, while another may quit his or her job and may report significant depression. These differences are of huge importance in a time of ever-increasing burden on social welfare systems, including Social Security disability income.

Several studies have shown that health care professionals frequently underestimate the QoL of their patients and it is well-known that physicians consider their patients more impaired than the patients themselves. This is important because this misconception may affects the physician’s expectations, treatment choices, and final treatment. In the most glaring cases, a physician’s subjective, but incorrect, assessment of a disabled individual’s quality of life may prevent life-sustaining interventions. Since judgment of the patient’s QoL is often used to determine appropriate medical procedures, it is critical that an accurate assessment of a patient’s QoL is conducted.

An additional reason to assess patient QoL is to give the clinician valuable information that can help in making the best choices in patient care. Understanding how a disease affects
the quality of life of a patient can improve the interaction between the doctor and patient. Information about how a disease affects the functional and emotional status of the patient gives the doctor a better insight into the patient’s needs. It can provide longitudinal data regarding changes in the patient’s quality of life. It may also indicate the functional and emotional tradeoffs of a particular treatment that may prolong a person’s life, but at considerable costs to their QoL. Reliable measurements of quality of life can be important tools in the appraisal of health care services and health care policy. Research that utilizes quality of life as an outcome measurement will ensure that factors affecting the whole person over a range of areas will be taken into consideration.

It should be noted that misconceptions regarding the quality of life of individuals with disabilities are not limited to physicians. The same phenomenon has been shown in close relatives. The way the individual views his or her own quality of life is frequently different than that reported by close relatives or caregivers.

Methods to Assess Quality of Life

To study the effect of disability on QoL, investigators have traditionally focused on objective indicators such as the individual’s functional ability in terms of his or her capacity to carry out activities of daily living, ability to work, employment status, income, and number of times the individual engages in social activities per week. QoL is inferred from these findings. The effectiveness of rehabilitation treatments is evaluated by the improvement in these domains. Table 1 shows the dimensions that are most important in determining quality of life. This method uses the sum total of a person’s scores on components that can objectively be measured to define QoL. These objective components are valued by most people as having easily established “best” and “worst” extremes. For example, being more educated is valued higher than being less educated.

Since these objective approaches do not take into account other dimensions affecting QoL, such as expectations, assessment instruments have also been developed to ascertain the patient’s subjective feelings about various aspects of their life.

Some of the more widely used instruments to measure HRQOL are the Medical Outcomes Study Short Form 36, the Nottingham health Profile, the Sickness Impact Profile, and the World Health Organization Quality of Life instrument. Potential uses of QoL tools for patients with NMD include: (1) monitoring the health and social status of a given population, (2) evaluating health care policy, (3) conducting clinical trials, (4) assessing the effectiveness of rehabilitation services and (5) justifying the allocation of limited social and healthcare resources, and (6) tailoring management to the needs of the patient. The purpose of these instruments is to determine the congruence of aspiration and accomplishments in a variety of different areas. The benefit of using subjective scales is that they permit individuals to ascribe meaning to their situation. They also permit comparison between the objective and subjective measurements. Many researchers and clinicians now agree that assessment of QoL requires a multifaceted approach in order to obtain a comprehensive assessment of the impact of an illness, a treatment, or rehabilitative services on quality of life.

Health-related QoL in Patients with Neuromuscular Disorders

There is incredible diversity in the individuals who have NMDs. This may be a reason why very few QoL studies have been conducted to determine the effect of a NMD on QoL. Studies that have been performed have been criticized because many differing NMDs were lumped together in a poorly defined study group and the studies predominately used generic instruments to define QoL. Thus they rarely used clinically meaningful data on physical and emotional functioning, and focused instead on the extreme manifestations such as severe pain rather than looking at how patients experience and deal with their NMD. Recently, some disease specific QoL assessment tools, most notably the NeuroQoL, the Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSQ-40), among others, have been developed for specifically for NMD patients. These disease-specific measures are especially useful in differentiating QoL and psychosocial functioning of patients as their NMD progresses. Beyond ALS, there is a dearth of studies that have used QoL measurements to study other NMDs. We have previously published a study that used the SF-36 to assess QoL in subjects with slowly progressive NMD. Our data revealed that NMD patients have significant bodily pain, which significantly impairs their QoL. This was confirmed in a follow-up study we did using different pain assessment tools. Our current study indicates that pain is a common and significant secondary problem for many persons with NMD. While pain appears to have a significant impact on QoL in persons with NMD, it appears to be particularly severe in persons with ALS, who appear to be particularly sensitive to the effects of pain on their lives. Our findings also suggest that the pain of persons with NMD is under-treated.

In a previous study we noted a very high incidence of neuropathic pain in Charcot-Marie-Tooth (CMT) disease. Their pain was a much larger problem than is reported in the literature and it significantly affects their physical role and vitality. The reason why the pain has not been considered to be a serious problem may be due to the fact that physicians focused on the extensive mobility impairments in CMT patients and did not fully appreciate the pain involved.
The remainder of this paper will now focus on specific clinical problems in NMD and medical and rehabilitative interventions that help to maximize QoL in this patient population.

CLINICAL PROBLEMS AND TREATMENT PARADIGMS

Rehabilitation

Exercise Paradigms to Improve Strength

Skeletal muscle weakness is the ultimate cause of most clinical problems in NMDs. There have been a number of well-controlled studies documenting the effect of exercise as a means to gain strength in NMDs, although much remains to be learned in this area. In slowly progressive NMDs, a 12-week moderate resistance (30% of maximum isometric force) exercise program resulted in strength gains ranging from 4-20% without any notable deleterious effects. However, in the same population, a 12-week high-resistance (training at the maximum weight a subject could lift 12 times) exercise program showed no further added beneficial effect compared with the moderate resistance program, and there was evidence of overwork weakness in some of the subjects.

In a study comparing patients with CMT and to patients with myotonic muscular dystrophy (MMD), only the CMT patients appeared to benefit significantly from a strengthening program. This clearly points out that the most effective exercise regimens for neuropathies and myopathies are most likely going to be different, although further investigation is needed. In rapidly progressive disorders like DMD and ALS, there is active ongoing muscle degeneration and the risk for overwork weakness and exercise induced muscle injury is much greater. In this population exercise should be prescribed with caution and a common sense approach.

Studies have been done comparing mdx mice to normal control mice. The mdx mice lack dystrophin and are a genetically homologous murine model of DMD. In voluntary running protocols, it is clear that dystrophin-deficient muscle is very susceptible to exercise-induced muscle injury, particularly eccentric (lengthening) muscle contractions. Interestingly, mdx mice show considerable avoidance behavior for exercise compared to normal mice. This may be an intuitive survival strategy. Following ad libitum exercise on a flywheel, the extensor digitorum longus (EDL) and soleus muscles of adult mdx mice weakened significantly. There was also histochemical evidence of considerably more damage compared to control, non-exercised, mdx muscles. Taking animal studies and the available human studies into consideration, it is advisable that all patients with NMDs be advised not to exercise to exhaustion, due to the risk of exercise-induced muscle damage. NMD patients in an exercise program should be monitored for signs of overwork weakness. This includes excessive delayed onset muscle soreness (DOMS). This usually occurs 24-48 hours following exercise. Other warning signs include severe muscle cramping, heaviness in the extremities, and prolonged dyspnea.

Submaximal, low-impact aerobic exercise (walking, swimming, stationary bicycling) will improve symptoms of fatigue via enhancement of cardiovascular performance and increase muscle oxygen and substrate utilization. This is important because fatigue is a significant limiting factor in physical performance in patients with NMDs. Fatigue in this setting is likely multifactorial, due to deconditioning and impaired muscular activation. Improving cardiopulmonary performance through aerobic exercise will improve not only physical functioning but also improve mood state and help fight depression and osteoporosis, which in turn reduces fracture risk. Patients with NMD have been noted to have higher depressions on the Minnesota Multiphasic Personality Inventory (MMPI). Aerobic exercise will also help achieve and maintain ideal body weight, and improve pain tolerance. In terms of monitoring progress in an exercise program, there are a number of reliable, functional assessment tools that have made it much easier to assess the effectiveness of exercise interventions, including the Timed Motor Performance assessment, which is a good simple measurement scale that can be used at routine clinic visits.
terms of testing static muscle strength, manual muscle testing has been shown to be unreliable in NMD patients.\textsuperscript{6,92,117} A hand-held myometer or MicroFET type of strength measuring device is far more reproducible and just as easy to use in a clinical setting.\textsuperscript{93,96} Although very reliable, quantitative isokinetic strength testing requires too much sophisticated equipment to be useful in clinic.\textsuperscript{129,134} While this is a good choice for research, none of these clinical measurements approach the accuracy of in vitro contractility measurements.\textsuperscript{24,102,106}

Despite all the benefits, exercise does create clinical problems.\textsuperscript{76,116,154} Muscle cramping is common in patients with NMD and is often exacerbated by exercise. True muscle spasms, related to upper motor neuron spasticity, are also seen in ALS.\textsuperscript{61} There are a number of pharmaceutical interventions that may help. Baclofen is a good initial choice as it acts via motor neuron inhibition at the spinal cord level.\textsuperscript{23,45,76} Tizanidine and gabapentin may also be helpful in this setting, particularly if neuropathic pain is also present. Benzodiazepines (or other centrally acting muscle relaxants) may contribute to respiratory suppression. Dantrolene is contraindicated because it impairs excitation-contraction coupling, which produces too much muscle weakness to be used in NMD patients. Mexilitine is particularly useful in myotonia congenita (Thomsen’s disease) but cardiac conduction must be monitored. Non-ballistic, sustained muscle stretching is also helpful and should be routinely done after exercise.

Managing Neuromuscular Contractures and Scoliosis: Stretching, Bracing, and Surgery

Joint contractures and scoliosis are a major clinical problem in NMD, particularly DMD and SMA II patients.\textsuperscript{26} Routine examination of the spine and major joints in NMD patients should be done at each clinic visit. Contractures appear to be related to prolonged static limb positioning and frequently develop shortly after the patient becomes wheelchair dependent.\textsuperscript{23} In ambulatory patients, upper extremity contractures may occur, and be complicated by joint subluxation, particularly in the shoulder girdle. Slings may provide support but will not prevent contracture formation. Again, stretching and positional splinting may slow the progression of contractures, although the actual efficacy of this has not been well studied or documented in the literature. Surgical release of contractures in the lower extremities may allow a patient to be functionally braced. This may prolong ambulation although a number of studies have shown that weakness, not contractures, contribute most to the loss of functional ambulation.

Scoliosis does not appear to be related to the loss of ambulation.\textsuperscript{10,11,113,120} Several studies have shown no direct relationship between scoliosis and wheelchair dependence. One large study by Lord and colleagues reported an almost a 4 year difference between wheelchair dependency and the onset of significant scoliosis in DMD patients.\textsuperscript{113} Indeed, many DMD and SMA II patients will develop scoliosis before they become wheelchair dependent. Disease progression with increasing weakness of trunk musculature is more likely the major underlying cause of neuromuscular scoliosis.\textsuperscript{78,123} However, trunk flexor or extensor strength is very difficult to measure.\textsuperscript{92,94,97} In NMD patients, scoliosis did not correlate with trunk strength tested by MMT, although this method is not capable of measuring asymmetric strength and is not a reliable method of strength testing in this population.\textsuperscript{125}

Near the time of the adolescent growth spurt Duchenne muscular dystrophy patients typically develop scoliosis. In contrast, SMA II patients develop scoliosis much earlier.\textsuperscript{85,87} In both DMD and SMA, studies have shown that thoracolumbar curves are much more common than lumbar curves. Patients with DMD and SMA should be followed closely with serial radiographs as the curve may progress suddenly. Importantly, spinal bracing has not been shown to be effective in preventing progression of neuromuscular scoliosis, although most of the studies were done in patients with SMA. Thus spinal instrumentation and fusion is the only known, effective treatment option.\textsuperscript{131} This should be done before the primary curve is 25 degrees and the forced vital capacity (FVC) is greater than 50% of predicted. Complications increase substantially if the patient already has compromised breathing, yet correction of the scoliosis with fusion has not been shown to improve pulmonary function. Nonetheless, it does improve quality of life by making positioning, seating, and transfers much easier. If the curve has progressed beyond 40 degrees, successful correction via fusion is much less likely.\textsuperscript{127}

For the extremities, bracing should be done with the goal of improving function and joint stability. Long-leg bracing to prolong ambulation time in DMD has been one of the best-studied uses in NMD. A number of studies have shown that ambulatory ability may be prolonged up to two years with long-leg braces and appropriate contracture release. However it is not clear if this represents a subset of patients with a slower disease progression and relatively less weakness.\textsuperscript{136} Further, there does not appear to be any clear association between prolonging ambulation with long-leg bracing and delaying or decreasing scoliosis in DMD. If bracing is used, a “long-leg brace” or knee-ankle-foot orthosis (KAFO) is generally needed due to the amount of weakness in hip and knee extension as well as ankle plantar flexion and dorsiflexion.\textsuperscript{126}

Most CMT patients require “short-leg braces” or ankle-foot orthoses (AFOs). It is best if these are custom-made with a lightweight polymer (polypropylene or carbon fiber). They
should fit intimately to avoid skin problems and provide good stability. If a pressure sore occurs, the patient should be taken out of the brace until it heals. Double metal upright AFOs may be built into the shoe but are usually too heavy and may limit ambulation for those patients with proximal muscle weakness. If there is significant ankle instability noted, then the braces should be high profile (come around in front of the malleoli). Pes cavus and hammertoe deformities can be accommodated with built-up arches and metatarsal bars. Charcot-Marie-Tooth and other sensory neuropathy patients are at very high risk for skin ulcers and neuropathic arthritis (Charcot joint). Thus skin integrity and joint stability should be checked at every clinic visit.

Patients with NMD weakness may benefit from bracing, depending on the distribution of weakness, gait problems, and joint instability. The decision to brace should include the risk of added weight of the brace and the willingness of the patient to use the brace. Neuromuscular disease patients should be referred for a course of physical therapy after being fitted with braces to help them learn to use the devices effectively.

Vocational and Psychosocial Issues

Reactive clinical depression may occur in any NMD patient and is particularly common in advanced ALS and DMD patients. As noted previously, studies on NMD patients have shown elevated scores for depression on MMPI testing. In one investigation, depression was more closely associated with level of independent functioning than limb strength, suggesting good family, social, and religious support systems are critical. Depression in other family members and caregivers should not be overlooked. Group and family counseling may be beneficial. Patients with NMDs should be referred to a support group, which is an excellent resource for psychological support and problem solving. If necessary, referral to a mental health professional should be done. Antidepressant medicine may help with mood elevation and improve appetite and sleep. In ALS patients the tricyclic antidepressants with significant anticholinergic activity will dry oral secretions and reduce drooling.

Cognitive involvement is common in MMD and some mitochondrial myopathies. Learning disabilities are also seen in about one-third of boys with DMD. Beyond that, most people with NMD show normal intelligence. Unfortunately, employment rates for people with NMDs are significantly less than for the able-bodied population. In the NMD population, a higher level of education correlated more closely with employment rate than did functional level or physical performance. Level of self-esteem noted on personality testing also correlated positively with education and employment. This implies that altered personality profiles in NMD patients may be a factor in the ability to integrate in to mainstream society and hold steady employment. In this regard, education appears as important as physical abilities with respect to employability and self-esteem in people with NMDs.

Equipment

Proper equipment can significantly improve quality of life for an NMD patient. Common examples include hospital beds, commode chairs, wheelchairs and wheelchair ramps, handheld showers, bathtub benches, grab bars, and raised toilet seats. An occupational therapist is best qualified to determine if any of these devices would be useful for the NMD patient.

Wheelchairs are a critical component of mobility in those with severe NMD. Wheelchairs need to be fitted appropriately with the right frame size, type of seat, lumbar support and cushioning to avoid pressure ulcers. Other mechanical devices, such as the Tilt-N-Space (Postural Seating Materials, Inc, Lawrence, KS) allow the patient to independently propel the wheelchair seat, providing improved comfort and better pressure relief for the skin. These devices can often be retrofitted on to existing chairs. The patient should be evaluated by a physical or occupational therapist to ensure proper wheelchair prescription. Simply giving the patient a prescription for a wheelchair frequently results in a chair that does not fit properly or has improper components. Power wheelchairs are indicated in most NMD patients who can no longer ambulate and do not have enough upper extremity strength to independently propel a manual chair. Although expensive, power wheelchairs can be justified to third party payers on the basis that they help prolong independent mobility, thus decreasing medical and psychological comorbidity.

In patients who can still ambulate, walkers or quad (4-point) canes help reduce fall risk. Pressure-relieving mattresses, with foam wedges for proper positioning, help prevent pressure skin ulcers. In some NMD patients, particularly ALS, severe weakness in neck musculature causes may produce neck pain and muscle spasms. A cervical collar, particularly the Freeman or Headmaster type, which is a wire-frame collar with padding over the pressure points, may be very helpful. In patients with dysarthria, typically ALS patients, augmentative communicative aids, including an alphabet board, word board, or computer based speech synthesizer, can maintain
functional communication. A speech language pathologist is best qualified to determine which, if any, of these devices would work best.

**MANAGING MEDICAL CO-MORBIDITY**

**Restrictive Lung Disease**

It is important to realize that this is a very significant problem for many patients with NMD. Despite the frequent reference of having restrictive lung disease (RLD), the lung in NMD is often normal. The problem is with a “weak bellows”, i.e., weakened diaphragm, chest wall, and abdominal muscles. This causes patients with NMD may have problems getting air in to and out of the lungs, including coughing.

The most severe respiratory complications are usually seen in ALS, DMD, SMA, and MMD. Although respiratory failure in FSHD is unusual, a recent study identified 10 FSHD patients on nocturnal ventilatory support at home, representing approximately 1% of the Dutch FSHD population. Severe muscle disease, wheelchair dependency, and kyphoscoliosis appeared to be risk factors for respiratory failure in FSHD.

There have also been numerous case reports on respiratory failure in people with CMT, the etiology of which has remained elusive. Electrodiagnostic and pathologic studies on the phrenic nerve in CMT confirm that it is involved in the disease. In one study, phrenic nerve latency was abnormally prolonged in 96% of CMT subjects, but significant PFT abnormalities and clinical symptoms were uncommon and did not correlate with the phrenic nerve latencies. Periodic assessment of respiratory function is indicated in all patients with NMD.

**Cardiac Complications**

Cardiac involvement may occur in many of the hereditary muscular dystrophies, including DMD, BMD, MMD, and some cases of LGMD. Cardiac involvement is not seen in the peripheral neuropathies or motor neuron diseases. A very high (60-80%) occurrence of cardiac involvement is present in DMD and BMD subjects of all ages. Dystrophin has been localized to the membrane surface of cardiac Purkinje fibers, perhaps contributing to the very high incidence of electrocardiogram (ECG) and echocardiographic abnormalities in DMD and BMD in the preadolescent years. In spite of this, only about 30% of DMD patients have clinically significant cardiac complications. The myocardial impairment may remain clinically silent until the late stages of the disease. This may be due to lack of physical activity. Pulmonary hypertension also has been implicated in the cardiorespiratory insufficiency of DMD. Death has been attributed to congestive heart failure (CHF) in as many as 40% of patients with DMD by some investigators. Importantly, severe cardiac involvement in BMD may occasionally precede the clinical presentation of skeletal myopathy. Moreover, cardiac compromise can be disproportionately severe relative to respiratory compromise in some patients with BMD. Thus ECG and echocardiography screening of all BMD patients at regular intervals is indicated. Patients with myocardial involvement need close follow-up and management by a cardiologist with expertise in this area. Successful cardiac transplantation has been reported in BMD patients with cardiac failure who remained ambulatory.

There is also a high incidence of ECG abnormalities in MMD. Studies have shown that about one-third of MMD patients have first-degree AV block, while about one-fifth have left axis deviation. Only 5% have left bundle branch block. Bundle of His conduction delays have also been rarely reported. Complete heart block, requiring pacemaker placement, is very rare but can occur. Patients with MMD should receive routine cardiac evaluations.

**Pain**

Pain is a significant problem for most patients with NMD, although it is not typically a direct consequence of the disease. Most commonly the pain is caused by immobility. This may lead to adhesive capsulitis, low back pain, pressure areas on the skin, and generalized myofascial pain. Neuropathic pain is a significant problem for patients with CMT and likely is a direct consequence of the neuropathy. Pharmacological management of pain in NMD includes initial acetaminophen (1000 mg every 6 hours), which may be used along with a nonsteroidal anti-inflammatory drug (NSAID). If there is evidence of any active inflammatory process such as joint effusion or tenosynovitis, NSAIDs may be particularly helpful. Tricyclic antidepressants (TCAs) and antiepileptic drugs (AEDs) are often helpful, particularly for neuropathic pain. The AED gabapentin also has the added benefit of reducing spasticity via glutamate and gamma-aminobutyric acid pathways. Opioids may be necessary for refractory pain. If required, opioids are best administered on a regular dosing schedule and titrated to the point of comfort. Cannabinoids, the active ingredients in marijuana (cannabis), have a number of pharmacological properties that may be applicable to the management of ALS and other NMDs. These include analgesia, muscle relaxation, bronchodilatation, saliva reduction, appetite stimulation, and sleep induction. In addition, cannabinoids have strong anti-oxidative and neuroprotective effects,
Nutritional Management

Nutrition may be a significant problem in the more severe NMDs, where there is a tendency towards obesity shortly after the loss of functional ambulation. Recent evidence has shown that the NMD patient population is at a higher risk for developing metabolic syndrome. Obesity is common in NMDs, particularly DMD where a prevalence of 54% has been reported. Weight control has its primary rationale in ease of care, particularly transfers and skin care, decreasing post-operative complication risk, and decreasing risk of developing metabolic syndrome.

Conversely, the advanced stages of DMD, ALS, and SMA may be marked by malnutrition. As previously noted, if there is severe respiratory compromise, the increased work of breathing may drastically increase caloric needs. The situation is complicated by the fact that this is often a time when the patient loses the ability to self-feed. Caloric requirements should be assessed by a nutritionist and proper dietary requirements constructed for the patient. This should be routinely done for all NMD patients with a forced vital capacity of less than 50% predicted. Percutaneous endoscopic gastrostomy (PEG) tube placement may facilitate nutrition because it eases intake of large amounts of calories and fluids. Patients should be reassured that they may still eat food orally for enjoyment, provided they have intact swallowing function. Another complicating factor in DMD patients is gastroparesis, which may make feeding more difficult.

Dysphagia and dysarthria may occur in ALS and some rare forms of SMA, due to involvement of the bulbar musculature. Early signs of dysphagia include a hoarse voice and persistent cough, particularly after swallowing liquids. This may indicate micro aspiration. It is best to consult a speech language pathologist at the first sign of dysphagia. They will perform clinical swallowing evaluations and make recommendations on dietary modification and safe swallowing strategies. Such strategies include thickening liquids, double swallow, chin tucks, head turn, and eating only food textures that easily form. A modified barium swallow (MBS) study, whereby the patient swallows various textures of solid food and liquid laced with barium, is helpful for accurately determining aspiration, as well as characterizing which food textures the patient can safely swallow. However, this does involve exposure to radiation.

Flexible endoscopic evaluation of swallowing (FEES) is a new, alternative test to the MBS employing an endoscope designed specifically to assess the swallowing mechanism. FEES directly assess both motor and sensory components of swallowing by direct visualization of the reaction of the larynx to a stimulus delivered by the endoscopic camera, which is then photographed. This test clearly shows places where sensory reactions are impaired, and this can guide the consultation of what foods patients can safely swallow. The main advantage of FEES is the direct observation through a real-time endoscopic camera, of food transversing the patient’s oropharynx and esophagus. The test allows a speech-language pathologist to instruct the patient on making physical maneuvers that find the least restrictive method of food travel through the throat and into the stomach. The patient can also provide feedback to the clinician during the test so volume and thickness of the food can be altered to avoid any choking sensation during the exam.

Despite all of these interventions, a PEG tube may become necessary for nutrition. In rapidly progressive diseases such as ALS, malnutrition, and the attendant wasting or cachexia, may occur rapidly. This is a grave clinical situation, and may also arise in an infant or young child with SMA who cannot take enough oral nutrition. In SMA, caloric needs are often increased by respiratory compromise and increased work of breathing. A PEG can readily address this need and provide access for supplemental nutrition. Again, it is critical to educate the patient and family early in the disease process so they can make informed decisions.

If aspiration of oral secretions becomes intractable and better airway access becomes absolutely necessary, the informed patient may choose to have a laryngeal diversion (laryngotra-}

[...]

...ceostomy) procedure. This completely eliminates the possibility of aspiration and requires much less deep suctioning than a tracheostomy. The tracheostoma does not require any hardware, such as a tracheostomy tube, and the patient still may take food for pleasure without risk of aspirating. The primary disadvantage is complete loss of phonation, since air no longer flows through the vocal cords. Consequently, this procedure is recommended only when severe dysarthria accompanies dysphagia. While preserving the ability to phonate, a tracheostomy actually increases aspiration risk, requires significantly more care, and may not improve airway access. In either case, it is critical that the patient understand that tracheostomy or laryngeal diversion, while making it easier to use mechanical ventilation, may not necessarily improve their quality of life. Fortunately, with the advancements in noninvasive ventilation, these options now used only infrequently.
Pharmaceuticals That May Improve Function or Prolong Life

Major pharmacologic advances have occurred over the past decade. Although a comprehensive discussion of clinical trials is beyond the scope of this paper, some of the major advances will be noted. Given the severity of the disease and the rapid progression, ALS has received the most attention in terms of pharmaceuticals aimed at prolonging life. Riluzole is a neuroprotective agent that appears to inhibit glutaminergic neurotransmission in the spinal cord. Riluzole is the first agent approved by the Food and Drug Administration (FDA) for use in ALS patients. Although it has only a modest beneficial effect at improving life expectancy in patients with ALS, Riluzole is nonetheless an advancement. Various neurotrophic growth factors also appear quite promising, particularly insulin derived growth factor, commercially known as myotrophin. Recent data suggests that the naturally occurring, nonpsychotropic cannabinoid, cannabidiol, may have a potential role as a therapeutic agent for the neurodegenerative disorders produced by excessive cellular oxidation, such as ALS. This compound is chemically classified as a terpene, similar to tamoxifen, which has been shown to prolong cell survival in a mouse model of ALS. This suggests a similar mechanism of action although this remains to be delineated.

Duchenne muscular dystrophy, also a severe disease, has received intensive study. Although not FDA-approved for this indication, prednisone, at 1 mg/kg/day, given to boys with DMD aged 4-8 years, has been shown to prolong the time of ambulation and at least should be considered for use in this disease. The positive effect of glucocorticoids on muscle function in muscular dystrophy have been known for some time and have similar, if not more profound, effects in animal models. Major side effects of prednisone include weight gain, osteoporosis, and mood lability. Deflazacort has similar beneficial effects and may have slightly less side effects than prednisone however it is not currently available in the United States. Oxandrolone may also have a modest beneficial effect in DMD. There have also been several recent randomized, crossover, placebo-controlled pilot studies of extended release albuterol in patients with dystrophinopathies (DMD and BMD) and FSHD. Outcomes were isometric knee extensor and flexor strength and manual muscle testing (MMT). There was some small evidence of benefit in the dystrophinopathies but not FSHD. However, larger, double blind, randomized studies are necessary to confirm these results.

There is evidence showing a modest positive benefit of the protein creatine monohydrate in DMD and ALS for transient improvement of strength. Initial studies of creatine in humans with ALS and hereditary neuropathies showed little beneficial effect. This was disappointing since creatine had a tremendous beneficial effect in the mouse model of ALS. Human trials of a timed release form of creatine are on-going in ALS. Modafinil (Provigil) is approved by the Food and Drug Administration (FDA) to treat the symptoms of fatigue and excessive daytime sleepiness (EDS) in narcolepsy. However, fatigue and subsequent EDS secondary to fatigue, are also common symptoms in many neurological disorders. Patients with myotonic muscular dystrophy (MMD) have fatigue and EDS, which can be a significant cause of disability. Patients with MMD have shown efficacy with modafinil at dosing of 200 to 400 mg/day. The most commonly reported side effects of modafinil include nausea, nervousness, anxiety and insomnia. A recent study showed some improvement in fatigue in ALS with 200 to 400 mg of modafinil taken daily. However, further study is warranted before conclusive recommendations can be made.

Palliative and End of Life Care Issues

Although DMD and ALS are both ultimately fatal conditions, it may take many years before the patient succumbs to its effects. In the process, the disease contributes to more and more debility for the patient and leads to important ethical and humanitarian issues. Patients may have a great deal of time to think of their impending death and also the various decisions they will need to make at different stages of their disease. It is imperative that a social worker is involved early following the diagnosis to aid in the various decisions facing the patient. One such important choice is the decision regarding durable power of attorney. A living will may also be drafted in regards to the patient’s wishes for the extent of medical intervention, not only near end of life but in the event of an unforeseen medical complication as well. As a patient enters hospice level care these issues take on a greater importance. Even though a patient may have accepted the eventual death resulting from the NMD, it is often difficult for a patient to accept hospice care, as this implies that the disease has entered its terminal stage. Therefore, it is especially important at these times to not only be sensitive to a patient’s needs, but to also assist the patient in making practical decisions. It is also important for patients to be referred to a support group early. The Muscular Dystrophy Association (MDA) usually will have local branches that can identify the most convenient support group. The importance of support groups should not be underestimated as they can provide not only psychological support, but also further education and serve as a resource for problem solving and recycling of equipment such as modified beds, lift devices and communication equipment. Modern medicine is continually
advancing and has numerous interventions that can prolong life. Although there are a great deal of potential medical interventions, the physician should be sensitive to the possibility that a patient with an advanced NMD may reject such interventions. It is the patient, and not the physician, who determines whether to initiate life-sustaining therapy, artificial devices, or interventions that compensate for the failing organ or system to prevent death. Mechanical ventilation, artificial hydration, and nutritional supports being the most obvious examples. Both legally and ethically, a competent patient or their legal guardians, have the right to refuse any prescribed intervention or treatment. The physician and nurse’s role is to thoroughly explain the consequences of the patient’s decision, as well as to foster and respect the patient’s autonomy. It is important, however, to note that this does not extend to the practice of physician-assisted suicide. It is an illegal act raising severe ethical concerns, which in itself deserves volumes, and cannot be adequately dealt with in this review. It is interesting to note, however, that according to a recent study, approximately 56% of ALS patients surveyed in Washington and Oregon would consider this alternative. The stunning number of patients who would consider physician-assisted suicide is perhaps an indication that the quality of care in the final stages of ALS may be inadequately addressed. Studies indicate that ineffective communication between physician and patient, as well as poor quality of life for the patient as perceived by the physician, may have a negative impact on the patient’s quality of life. It takes a great deal of time to explain all of the end of life issues, including available treatment options and choices. Without this investment of time by the physician, a patient may be unaware of the available services and choices. An appropriate level of care for ALS or end-stage DMD patients may change frequently and thus necessitates a close follow up. Even in the advanced stages of the disease, optimizing in-home care with hospice can maximize the quality of life for the remaining time in these patients. In general, in-home care is underutilized or initiated too late. Effective hospice care provides an interdisciplinary team of professionals whose goal is to support the patient and the family through their remaining days together. It can provide invaluable psychological, emotional, and spiritual support for both the patient and the family in a familiar and comforting setting.

**FUTURE AREAS OF RESEARCH**

Understanding of the molecular basis of many myopathies has greatly enhanced diagnostic accuracy and may provide the basis for therapeutic intervention. There has been significant improvement in the functional imaging of muscle, particularly in the field of magnetic resonance imaging (MRI). This may someday help facilitate earlier and more physiologically accurate diagnosis of NMD, as well as help delineate functional anatomy and pathophysiology in unusual cases of NMD. There has also been vast improvements in electrophysiological and electrodiagnostic techniques that allow for improved accuracy in detecting pathophysiology in the peripheral nervous system.

Stem cell therapy holds some promise for replacing diseased muscle. However, it is important for the clinician and patient to realize that these diseases would not be cured by stem cell treatment, as this would not correct the underlying genetic defect. Despite this it may be possible to significantly improve function by growing new muscle tissue through stem cell therapy. Further, it may be possible to treat these diseases with genetically modified (corrected) stem cells, which would not only improve function but partially correct the genetic abnormality. There are various myotrophic growth factors currently in development that may enhance nerve and muscle repair and growth.

Increased understanding of the molecular basis of many muscle diseases has greatly enhanced diagnostic accuracy and the ability to do prenatal diagnostic screening. This has also provided the groundwork for therapeutic intervention. Techniques are being developed for gene insertion and DNA repair using a number of vectors, including gutted viruses. This may ultimately lead to a true cure.

Important advances in the use of reliable functional assessment tools have made it easier to judge the effectiveness of experimental interventions. The Timed Motor Performance assessment is a good example of a simple measurement scale that can be used at routine clinic visits.

**SUMMARY**

Major advances in the fields of biomedical engineering and computer science have provided our NMD patients with more functional equipment, allowing better strategies for improvement of quality of life. As progress continues to change our management, it also changes patients’ expectations. For example, now many patients with DMD are living well in to adulthood, going to college and starting careers. Many patients with severe NMD may live through child bearing years, possibly bearing children, and expecting to enjoy a high quality of life. A comprehensive medical and rehabilitative approach to management of the NMD patient can often fulfill these expectations and help them enjoy an enhanced quality of life.


INTRODUCTION

With progressive refinement of broadband high-frequency transducers, improved capabilities of near-field focusing, and the introduction of compound imaging, diagnostic sonography is becoming a well-accepted and widespread modality for the evaluation of the musculoskeletal system. The improved performance of recent transducers has enabled this technique to be used in recognizing subtle anatomic details at least equal to or even smaller than those depicted with surface-coiled magnetic resonance imaging (MRI). It has also made it possible to depict a wide range of pathologic conditions affecting nerves and muscles. In addition to the need for high-end technology, nerve sonography also requires knowledge of the anatomy of the limbs and extremities and the close correlation of imaging findings with the patient’s clinical history and the results of electrophysiology studies. Sonography performed by a skilled operator provides low-cost, noninvasive imaging with a high speed of performance, and several important advantages over MRI, including higher spatial resolution, the ability to explore long segments of nerve trunks in a single study, and the ability to examine tissues in both static and dynamic states with real-time scanning. Besides assessing nerves, the status of muscles can be evaluated with sonography as well.

This manuscript will review the sonographic appearance of normal nerves and muscles and describe the main sonographic findings in the most common nerve disorders, with a special focus on entrapment syndromes and nerve traumas. Considerations on neurogenic atrophy of muscles will also be reviewed.

NORMAL NERVE AND MUSCLE

Sonography directly images nerves and demonstrates their echotexture made of multiple hypoechoic structures (fascicles) embedded in hyperechoic background (epineurium) (Figures 1A and 1B). Using high-resolution broadband probes, an accurate one-to-one comparison between sonographic findings and histology can readily be obtained. Nerves appear as flexible structures and may change in shape from round to oval depending on the width of their anatomic passageways and the nature of the perineural structures. Across the joints, they traverse osteofibrous tunnels that redirect their course. At these sites, normal nerves may assume a more homogeneous hypoechoic appearance due to a tight package of fascicles. Nerves are poorly anisotropic structures and therefore do not require a perpendicular orientation of the probe to be correctly imaged. As a rule, transverse...
planes are the best to follow contiguously throughout the limbs. Although all main nerve trunks can be readily displayed in the extremities due to their superficial position and absence of intervening bone, depiction of peripheral nerves is not possible everywhere with sonography. In fact, most cranial nerves, the nerve roots exiting the dorsal, lumbar, and sacral spine, the sympathetic chains, and the splanchnic nerves in the abdomen cannot be visualized due to a deep course or interposition of bony structures. Because of their peculiar appearance, some anatomic variants and congenital anomalies of nerves can be recognized with sonography as well. Among these, the proximal bifurcation of the median nerve, the fusiform enlargement of the median nerve at wrist by fibrofatty tissue (fibrolipomatous hamartoma), and the striking hypertrophy of nerves in Charcot-Marie-Tooth syndrome are reported in the literature.

Normal skeletal muscles exhibit a striated appearance composed of straight hyperechoic lines reflecting the fibroadipose septa which have parallel arrangement and cross a homogeneous hypoechoic background (Figures 1C and 1D). The ratio between hyperechoic and hypoechoic components of muscles reflects the proportion between stromal tissue and muscle fascicles and differs among muscles. The internal arrangement of fibroadipose septa may change with age. Depending on the orientation of fibroadipose septa, sonography can detect the internal architecture of muscles (unipennate, bipennate, circumpennate). Intramuscular aponeuroses forming tendons appear as hyperechoic bands and are usually better delineated on short-axis planes (Figures 1C and 1D). Muscles differ from nerves in that they are anisotropic structures: therefore, even subtle tilting of the probe may result in their hyperechoic or hypoechoic appearance. Sonographic examination of muscles performed during contraction can show changes in size and relationship between muscle fascicles and fibroadipose septa. Contracted muscles appear thicker and more hypoechoic than at rest. Shortening of muscles can be observed in real-time during concentric contractions. Regarding anatomic variants, partial (involving one head) or complete muscle aplasia can be readily assessed with sonography. In these cases, sonography is helpful in differentiating true aplasia from marked hypoplasia of a given muscle. The occurrence of accessory or supernumerary muscles can be assessed with sonography as well.

**ENTRAPMENT NEUROPATHIES**

In nerve entrapment syndromes, sonography can demonstrate changes in both nerve shape and echotexture, the most common being sudden flattening (notch sign) with focal reduction in the nerve cross-sectional area at the compression point and nerve swelling that occurs proximal to the level of compression (Figures 2A – 2D). The nerve swelling is typically fusiform, extending 2-4 cm in length, and appears maximal in close proximity to the compression level, where the nerve abruptly flattens. Based on these findings, sonography is an accurate means to identify the level of compression as located just ahead of the swollen nerve portion. Although nerve flattening should be regarded as the main sign of nerve compression, quantitative analysis of nerve thickening by means of the ellipse formula \[\text{Area} = \pi \times (\text{AP diameter}) \times (\text{LL diameter})\] has proven to be the most consistent diagnostic criterion at various entrapment sites. In entrapment neuropathies, the nerve echotexture may become uniformly hypoechoic with a loss of the fascicular pattern at the level of the compression site and proximal to it. In general, the hypoechoic changes in the epineurium occur gradually and become more severe as the nerve progresses toward the site of compression. Depiction of such changes may increase the diagnostic confidence and may be helpful to determine the exact level of entrapment. An enhanced depiction of intraneural blood flow can also be appreciated with color and power Doppler techniques as a sign of local disturbances in the nerve microvasculature that occur in a compressive setting. The hypervascular pattern is more often seen in swollen hypoechoic nerves of patients with chronic disease. One should be aware that not all the stages of nerve entrapment pathology are recognized with sonography: at early stages, clinical examination and electrophysiology findings are often the only positive findings.

The most common sites of nerve compression that are amenable to sonographic examination are: the spinoglenoid-supraspinous notch area in the posterior shoulder for the suprascapular nerve; the quadrilateral space for the axillary nerve; the spiral groove of the humerus for the radial nerve; the supinator area at the elbow for the posterior interosseous nerve; the wrist for the superficial branch of the radial nerve; the cubital and Guyon tunnels for the ulnar nerve; the carpal tunnel for the median nerve; the posterior hip or proximal thigh for the sciatic nerve and the fibular tunnel for the common peroneal nerve; and the tarsal tunnel for the tibial nerve.

At the posterior shoulder, the suprascapular nerve may be compressed against the floor of the suprascapular and spinoglenoid fossae of the scapula by ganglion cysts expanding on the posterior aspect of the shoulder as a result of extrusion of joint fluid through a tear of the posterior glenoid labrum. The suprascapular nerve may be visualized with sonography in the spinoglenoid notch adjacent to the suprascapular artery. Percutaneous aspiration of the cyst can be successfully attempted with sonography. Another critical area for nerve entrapment in the shoulder is the quadrilateral space for the axillary nerve. Stretching injuries or fibrous bands can lead to nerve entrapment at this site. The axillary nerve is small to be examined with sonography, but the selective atrophy of
the innervated muscles in absence of a tendon tear strongly supports the hypothesis of a nerve lesion.24

At the middle arm, the radial nerve winds closely around the humeral shaft in the spiral groove passing between the heads of the triceps. At this site, the radial nerve may be compressed by a displaced humeral fracture, a hypertrophied callus, or osteosynthesis. Sonography is able to depict a stretched and displaced radial nerve which appears swollen and hypoechoic.2,30 At the lateral elbow, the radial nerve divides into a superficial cutaneous sensory branch and a deep motor branch (posterior interosseous nerve). Sonography can visualize the divisional branches of the radial nerve and can follow the posterior interosseous nerve as it pierces the supinator muscle, passing between the superficial and deep parts of this muscle. At this site, the posterior interosseous nerve may be compressed by space-occupying lesions or fibrous bands. The superficial branch of the radial nerve typically undergoes entrapment at the wrist (Wartenberg syndrome), possibly mimicking de Quervain’s disease. Sonography can help the diagnosis in compression neuropathies involving the divisional branches of the radial nerve.4,8

At the medial elbow, the ulnar nerve passes through the cubital tunnel. Sonography can identify the compressed nerve at either the condylar groove or the edge of the aponeurosis of
the flexor carpi ulnaris by a variety of extrinsic causes, including bony spurs, anomalous muscle, ganglia, or elbow deformities from previous fractures. In early studies, a nerve cross-sectional area larger than 7.5 mm$^2$ at the epicondyle was established as the threshold value for cubital tunnel syndrome. More recently, the mean cross-sectional area of this nerve was found to be 7.9 mm$^2$ in the normal population. At the wrist, the ulnar nerve passes alongside the pisiform and superficial to the flexor retinaculum, through the Guyon tunnel. Ganglion cysts, accessory muscles, and pseudoaneurysms of the ulnar artery can be depicted with sonography at this site. In the arm, the median nerve runs adjacent to the brachial artery. This relationship makes it susceptible to compression from hematoma or pseudoaneurysm following percutaneous brachial artery catheterization for carotid and vertebral angiography. In this setting, sonography can diagnose nerve compression and guide fine needle aspiration of the hematoma to achieve relief of symptoms.

In the forearm, the anterior interosseous nerve may be compressed by fibrous bands arising in the pronator area or by anomalous muscle bellies. Sonographic signs of such rare entrapment, which is also referred to as the Kiloh-Nevin syndrome, mainly refer to the atrophy of the innervated muscles. Compression of the median nerve at the carpal tunnel level is the most common entrapment neuropathy. A median nerve cross-sectional area of greater than or equal to 9 mm$^2$ or greater than or equal to 10 mm$^2$ calculated at the proximal carpal tunnel (scaphoid-pisiform level) or at the proximal edge of the retinaculum is reported as the best diagnostic criterion for the diagnosis of carpal tunnel syndrome (CTS). Dynamic scanning may also reveal a restricted motion of the

Figure 2 Carpal tunnel syndrome. (A) Longitudinal 12-5 MHz sonogram of the wrist shows flattening (white arrow) of the median nerve in the carpal tunnel and swelling (open arrow) of the nerve portion proximal to the compression point (arrowheads). (B,C) Transverse 12-5 MHz sonograms obtained (B) at the proximal edge of the retinaculum and (C) within the carpal tunnel, demonstrate a sudden change in the cross-sectional area of the median nerve (arrows) at the point where the nerve gets deep to the transverse carpal ligament. (D) Correlative postcontrast fat-suppressed transverse magnetic resonance imaging of the wrist demonstrates a hyperintense median nerve (arrow) within the carpal tunnel. ft = flexor tendons.
compressed nerve beneath the retinaculum during flexion and extension of the fingers. Extrinsic causes for median nerve entrapment can be identified with sonography, including tenosynovitis of flexor tendons, ganglia, amyloidosis, anomalous muscles, and displaced bone.

The sciatic nerve is more often compressed behind the hip joint and along the proximal thigh by deep space-occupying lesions, such as hematomas and lipomas. In the popliteal fossa, the sciatic nerve divides into the tibial and the common peroneal nerves. Peroneal nerve entrapment usually occurs where the nerve winds around the fibular neck (fibular tunnel) and divides into its two major branches, superficial and deep. Peroneal nerve entrapment may result from space-occupying lesions (e.g., ganglion cysts arising from the proximal tibiofibular joint) or may be secondary to a fibular fracture, dislocation, application of skeletal traction, and casts in the knee area. Peroneal intraneural ganglia are hypoechoic cysts with posterior acoustic enhancement located within the peroneal nerve. Proximal tibial nerve lesions are less common than lesions here affecting the common peroneal nerve.

At the medial ankle, the tibial nerve passes in the tarsal tunnel between the flexor hallucis longus and the flexor digitorum longus tendons. The main trunk of the tibial nerve is entrapped in the retromalleolar region, whereas the divisional branches of the nerve are usually involved at the distal tunnel. Space-occupying lesions at the medial ankle, such as flexor or tenosynovitis, ganglia related to the tarsalcalcaneal joint, fascial septa, anomalous tendon or muscle, and fracture residuals may cause tarsal tunnel syndrome. Sonography is able to image the entire course of the tibial nerve and its branches throughout the tunnel and can provide information on the nature and extent of space-occupying lesions. A hypoechoic swollen nerve or a different size between its medial and lateral branches may be found.

NERVE TRAUMAS

Traumatic nerve lesions derive from traction, contusion, and penetrating traumas. Nerve stretching injuries typically occur in association with repetitive strain or strain lesions, as well as with overuse. A characteristic traction injury is one involving the brachial plexus nerves based on an avulsion mechanism. In complete nerve lacerations, sonography demonstrates disruption of the roots with retraction and wavy course of the distal nerve ends. When traction causes a partial nerve tear, a spindle neuroma can develop as an irregular swelling of hypoechoic tissue along the course of the severed nerve. Contusion traumas occur more often in sites where nerves run close to bony surfaces and are, therefore, more susceptible to external injuries. In most cases, this trauma is self-resolving and has no sonographic findings. Repetitive minor contusion traumas usually cause abnormalities within the nerve substance that can be detected with sonography. A typical contusion trauma of nerves involves the ulnar nerve at the cubital tunnel in patients with absence of the retinaculum. In predisposed subjects, the repeated friction of the nerve against the tip of the medial epicondyle during elbow flexion may cause chronic damage and functional deficit. In these cases, the nerve appears swollen and hypoechoic as a result of fibrous changes. Dynamic scanning during elbow flexion and extension movements allows an easy depiction of the intermittent dislocation of the ulnar nerve over the epicondyle. Repeated nerve contusion of the interdigital nerves in the forefoot leads to the development of a fusiform hypoechoic mass elongated along the major axis of the metatarsals, which is commonly referred to as Morton’s neuroma. Sonography has a reported 95-100% sensitivity, 83% specificity, and 95% accuracy in the diagnosis of Morton’s neuromas. The coexistence of an enlarged intermetatarsal bursa can explain the mixed or anechoic appearance of some lesions and their extension dorsal to the plantar aspect of metatarsals. In penetrating wounds, there may be partial or complete transection of nerve fascicles. In complete tears, stump neuromas (terminal neuromas) appear as small hypoechoic masses in continuity with the opposite edges of the severed nerve (Figure 3). Usually, the size of neuromas is slightly larger than the axial diameter of the nerve. Most have well-defined margins; however, when they are attached to the surrounding tissues by adhesions and scarring tissue, their borders may be irregular or poorly defined. In a preoperative setting, sonographic depiction of neuromas may map the location of the nerve ends that may be displaced and retracted from the site of injury. Sonographic findings of incidental iatrogenic injuries to peripheral nerves have been described at various sites.

NEUROGENIC MUSCULAR ATROPHY

In neuromuscular disorders, such as Duchenne muscular dystrophy, spinal muscle atrophy, and congenital myopathies, the histological architecture of muscles is disrupted by muscle cell replacement with connective tissue and fat. Similarly, neuropathies are often associated with selective atrophy of the innervated muscles. Sonography is able to evaluate the size and echotexture of the affected muscles comparing both extremities. A definite loss in bulk of the affected muscle would suggest atrophy. This can be appreciated by simple pattern-recognition analysis (concave or straight muscle boundaries instead of the normal convex surface). Because side-to-side differences in muscle thickness rarely exceed 20%, measuring the muscle diameters or cross-sectional area with the electronic calipers of the equipment seems to be a more reliable means to assess volume changes in a given group of muscles. The ratio of muscle thickness to subcutaneous fat thickness
was found helpful for specific neuromuscular disorders (decreased ratio in spinal muscle atrophy). In neuromuscular disorders, however, sonography has shown some limitations compared with MRI. The complex distribution of muscle involvement in some dystrophies seems more reliably mapped with MRI for its better anatomical rendering and panoramic view. Based on echotextural pattern analysis, sonography is not as accurate as MRI to distinguish early neurogenic atrophy (in which changes are mainly related to extracellular edema) from late atrophy (in which muscle tissue is gradually replaced by fat). Different from MRI in which early denervation is appreciated with a homogeneous hyperintense pattern on T2 and short tau inversion recovery (STIR) sequences (increase in free-water content) and late denervation with a hyperintense pattern on T1-weighted images (fatty replacement), both processes have a similar hyperechoic pattern and can be differentiated with difficulty on sonography (Figures 4A – 4D).20 Quantification of muscle echotexture to estimate the severity of atrophy would reduce the observer variability but is strongly influenced by the scanner and the equipment settings.1,32,36 Apart from the above limitations, sonography can be considered a useful complementary tool to electrophysiology studies to provide information on muscle morphology beyond the scope of electrodagnosis.

SONOGRAPHICALLY GUIDED NERVE INTERVENTIONAL PROCEDURES

In recent years, sonography has been increasingly used to guide regional anesthesia of the limbs. In this setting, sonographic guidance has the advantage of checking the advancement of the needle in real-time while avoiding inadvertent harm to the nerve and adjacent structures, such as organs and vessels. Different techniques have already been described to perform sonographically assisted blocks of brachial and lumbar plexus nerves, psoas compartment, and inguinal and pudendal nerves.19,25 In addition, promising approaches to treat painful neuromas, such as stump and Morton's neuromas, by means of injecting a steroid, phenol, and alcohol inside the mass can be performed under sonographic guidance with high success rate and prompt relief of symptoms.13,35

Figure 3 Nerve trauma. Longitudinal 12-5 MHz sonogram of the popliteal fossa in a diabetic patient with amputated lower leg shows the sciatic nerve (arrows) ending in a terminal neuroma (asterisk). The neuroma develops from the resected fascicles as a hypoechogenic irregular mass contained within the nerve sheath.
SUMMARY

Peripheral nerves probably represent one of the best applications of musculoskeletal sonography due to the high lesion detection rate and diagnostic accuracy of this technique combined with its low cost, wide availability, and ease of use. The refinement of high-frequency linear-array transducers has improved the ability of sonography to detect fine textural abnormalities as well as to identify a variety of pathologic conditions. With these transducers, characteristic echotextural patterns, closely resembling the histologic ones, are typically depicted in these structures. Sonography can support clinical and electrophysiological testing for detection of compressing lesions caused by nerve entrapment in a variety of osteofibrous tunnels of the limbs and extremities. Congenital anomalies, nerve tears and neurogenic tumors can also be diagnosed. In most cases, a focused sonographic examination can be performed more rapidly and efficiently than MRI.

REFERENCES


Figure 4  Neurogenic atrophy of muscles in two different patients with recent onset (A,B) and long-standing (C,D) peroneal neuropathy. (A) Transverse 12-5 MHz sonogram over the tibialis anterior muscle with (B) fat-suppressed T2-weighted magnetic resonance imaging (MRI) correlation demonstrates normal volume and diffusely hyperechoic appearance of the muscle (arrowheads). The abnormal echotexture is related to intramuscular edema (curved arrow). (C) Transverse 12-5 MHz sonogram over the tibialis anterior muscle with (D) T1-weighted MRI correlation reveals decreased volume and hyperechoic appearance of the muscle (arrowheads). Although similar to that seen in (A), the abnormal echotexture reflects fatty atrophy (curved arrow).