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NM Update Course II: Inflammatory Myopathies/Myotonic Disorders

Table of Contents

Course Committees & Course Objectives 4

Faculty 5

Therapy for Inflammatory Myopathies
Richard J. Barohn, MD 7

Inflammatory Myopathies
Steven A. Greenberg, MD 15

Myotonic Dystrophies
Bassam A. Bassam, MD 21

Nondystrophic Myotonic Disorders
Bakri Elsheikh, MBBS 27

Neuromuscular Vignettes
Annabel K. Wang, MD 33
Gregory T Carter, MD, MS
Andrew W. Tarulli, MD

No one involved in the planning of this CME activity had any relevant financial relationships to disclose. Dr. Barohn is involved in Speaker’s Bureaus with Genzyme and Grifols and is on Advisory Boards for both MedImmune and Novartis. Any conflict of interest has been resolved according to ACCME standards. Dr. Greenberg is on the advisory boards for MedImmune and Novartis and has sponsored research from MedImmune. Any conflict of interest has been resolved according to ACCME standards.

Chair: Dianna Quan, 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.
Objectives

Objectives - Participants will acquire skills to (1) utilize a pattern recognition approach elucidated through clinical vignettes in the diagnosis and management of patients with inflammatory myopathies and myotonic disorders, and (2) practice the vignette-based format used for many questions on the NM medicine board examination.

Target Audience:
• Neurologists, physical medicine and rehabilitation and other physicians interested in neuromuscular and electrodiagnostic medicine
• Health care professionals involved in the management of patients with neuromuscular diseases
• Researchers who are actively involved in the neuromuscular and/or electrodiagnostic research

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 this live activity for a maximum of 3.25 AMA PRA Category 1 Credits™. If purchased, the AANEM designates this enduring material for a maximum of 5.75 AMA PRA Category 1 Credits™. 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. Physicians should claim only the credit commensurate with the extent of their participation in the activity. CME for this course is available 10/2012 - 10/2015.

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NM Update Course II: Inflammatory Myopathies/Myotonic Disorders

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Therapy for Inflammatory Myopathies

Richard J. Barohn, MD
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Immunosuppressive therapy is the mainstay of treatment in patients with active disease related to dermatomyositis (DM), polymyositis (PM), and necrotizing myopathy (NM)\(^1\) (Table). Autoimmune NM is often more resistant to immunosuppressive therapy than DM and PM, particularly if there is an underlying malignancy or a statin trigger. The overwhelming majority (23/25) of statin-associated necrotizing autoimmune myopathy (SANAM) cases required more than one immunosuppressive agent with relapse in 12 cases following immunosuppressive therapy tapering.\(^2\) However as in DM and PM, immunosuppressants such as prednisone in combination with methotrexate (MTX) or azathioprine (AZA) are the mainstay of treatment in autoimmune NM. For resistant or severe cases, adding intravenous immunoglobulin (IVIg) may be helpful. Third-line drugs include mycophenolate mofetil, cyclosporine, tacrolimus, rituximab, etanercept, and cyclophosphamide.

The few published randomized controlled trials of immunosuppression in DM or PM compared placebo to AZA,\(^3\) plasma exchange,\(^4\) or IVIg.\(^5\) In addition, randomized controlled trials compared MTX with AZA,\(^6\) cyclosporine with MTX,\(^7\) and IV MTX with oral MTX plus AZA.\(^3,6,8\) The only positive-controlled trials are a small cross-over study of IVIg in DM\(^5\) and a randomized, double-blind, placebo-controlled trial of etanercept (50 mg subcutaneously weekly) for 52 weeks in 16 DM subjects.\(^9\)

**Corticosteroids**

While no controlled trial has been performed using corticosteroids (CS), there is general agreement that these are effective in DM, PM, and NM. Corticosteroids can be used in a wide range of regimens and routes of administration. Prednisone 1 mg/kg/d (60-100 mg) can be administered for 4 weeks followed by an abrupt or tapered conversion to an every other day schedule. This taper is slower in patients with severe disease. A daily CS schedule is necessary in well-controlled hypertensive or non-brittle diabetic patients. While most patients feel immediately better after taking CS, strength improvement is delayed by 2-3 months after the onset of treatment. An immediate response may suggest an alternate diagnosis such as polymyalgia rheumatica. For the first 3 months, the typical adult patient remains on prednisone 60-100 mg every other day or its equivalent. If no improvement is noted after 3-6 months, or if weakness reoccurs during the taper, a second-line immunosuppressive agent such as AZA, MTX or IVIg can be started. These treatments are initiated early on with CS therapy in patients with uncontrolled hypertension, diabetes, osteoporosis, or obesity and in those with baseline severe weakness. For good responders, a taper by 20 mg/month until 40 mg every other day, then by 10 mg/month, will reduce the prednisone dose to 20 mg every other day after 6-8 months from the initiation of therapy. After that, the taper is by 5 mg, and the interval is every 3 months to reach the minimal effective dose. In severe cases, the author prefers starting with a 5-day IV pulse methyprednisolone therapy followed by high-dose oral prednisone in combination with a second-line drug.

Recently, a randomized multicenter double-blind clinical trial compared oral dexamethasone pulse therapy to daily prednisolone in 62 patients with subacute onset myositis.\(^10\) The pulsed regimen consisted of dexamethasone given as six cycles of 40 mg/day for 4 consecutive days at 28-day intervals. While pulsed high-dose oral dexamethasone was not found to be superior to daily prednisolone as
first-line treatment of idiopathic inflammatory myopathies, it caused substantially fewer side effects. Ten patients (33%) treated with prednisolone and one patient (4%) treated with pulsed dexamethasone developed diabetes mellitus. Mood changes occurred in 20 patients (67%) and eight (29%), respectively. Treatment adjustments for comorbid conditions (hypertension, diabetes mellitus) were needed in one patient in the dexamethasone group, compared with 15 patients in the prednisolone group. However, there was a large number of early discontinuations in both groups (21 and 17, respectively) for a variety of reasons.

Because the risks of longterm CS therapy are numerous, discussing those with the patient as well as establishing a monitoring plan in collaboration with the primary care physician is integral to the management plan. Before CS initiation, a purified protein derivative skin test can identify the need for isoniazid in previously exposed cases. As CS is started, a baseline bone dual-energy X-ray absorptiometry scan is obtained and the patient is requested to seek an ophthalmologic examination, with yearly followup for both. Patients are maintained on oral calcium 500-600 mg two to three times daily with vitamin D 400 IU daily. In juvenile DM (JDM), the incidence of vertebral fracture 12 months following steroid initiation was 6% and these were mostly asymptomatic. The risk of fracture increased with higher steroid dose, and in the first 6 months with greater increases in body mass index or greater declines in spine Z scores. Patients and their families are asked to be alert about personality changes and psychiatric side effects. Patients are also directed to reduce the salt and carbohydrate in their diet and visit regularly with the primary care physician for blood pressure, serum glucose and potassium. The author advocates the pneumococcal vaccine and yearly flu shots. Given the immunosuppressed state, evidence indicates that seroprotection of the influenza A/H1N1 vaccine is significantly reduced DM patients compared to control subjects. In a retrospective study of 279 PM/DM cases over 15 years, 37% were admitted for a severe pyogenic infection (n = 71) mostly due to aspiration pneumonia or for an opportunistic infection (n = 33). There are currently no consensus criteria to identify patients who are at high risk for Pneumocystis carinii pneumonia (PCP) infection and would therefore benefit from prophylaxis. Patients with total lymphocyte counts < 800/μL and/or CD4 lymphocyte counts < 200-400/μL are likely to benefit from PCP prophylaxis prior to initiation of and in the course of immunosuppressive therapy.

**METHOTREXATE**

Methotrexate, an antifolate that inhibits lymphocyte proliferation, is an effective more rapidly acting second-line steroid-sparing immunosuppressant. Oral MTX can be started at 7.5 mg/week, and in 2 weeks increased to 15 mg/week in two divided doses. The dose is then increased by 2.5 mg/week at 3 months, depending on response

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Route</th>
<th>Dose</th>
<th>Side effects</th>
<th>Monitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>By mouth</td>
<td>2-3 mg/kg/day; single a.m.dose</td>
<td>Flulike illness, hepatotoxicity, pancreatitis, leucopenia, macroglossy, neoplasia, infection, teratogenicity</td>
<td>Monthly blood count, liver enzymes</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>By mouth</td>
<td>4-6 mg/day; single a.m. dose</td>
<td>Bone marrow suppression, hepatotoxicity, infection, neoplasia, teratogenicity, infection</td>
<td>Monthly blood count, liver enzymes</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>By mouth</td>
<td>1.5-2 mg/kg/day; single a.m. dose</td>
<td>Bone marrow suppression, infertility, hemorrhagic cystitis, alopecia, infections, neoplasia, teratogenicity</td>
<td>Monthly blood count, urinalysis</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>IV</td>
<td>1 g/m²</td>
<td>Same as by mouth (although more severe), and nausea/vomiting, alopecia</td>
<td>Daily to weekly blood count, urinalysis</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>IV</td>
<td>2 gm/kg over 2-5 days; then every 4-5 days as needed</td>
<td>Hypotension, arthralgia, diarrhea, flushing, nephrotoxicity, headache, nausea, aseptic meningitis, anaphylaxis, stroke</td>
<td>Heart rate, blood pressure, creatinine/BUN</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>By mouth</td>
<td>7.5-20 mg weekly, single or divided doses; 1 day a week dosing</td>
<td>Hepatotoxicity, pulmonary fibrosis, infection, neoplasia, infertility, leucopenia, alopecia, gastric irritation, stomatitis, teratogenicity</td>
<td>Monthly liver enzymes, blood count; consider liver biopsy at 2 gm accumulative dose</td>
</tr>
<tr>
<td>Methylprednisone</td>
<td>IV/M</td>
<td>20-50 mg weekly; 1 day a week dosing</td>
<td>Same as by mouth</td>
<td>Same as by mouth</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>By mouth</td>
<td>1-1.5 gm twice a day</td>
<td>Myelosuppression, GI (diarrhea, nausea, abdominal pain), peripheral edema, fever, infection, opportunistic infection, malignancy, teratogenicity</td>
<td>Monthly blood count</td>
</tr>
<tr>
<td>Prednisone</td>
<td>By mouth</td>
<td>60-100 mg/day for 2-4 weeks, then 100 mg every other day; single a.m. dose</td>
<td>Hypertension, fluid and weight gain, hyperglycemia, hypokalemia, infection, aseptic femoral necrosis</td>
<td>Weight, blood pressure, serum glucose/potassium, cataract formation</td>
</tr>
<tr>
<td>Rituximab</td>
<td>IV</td>
<td>Two doses of 750 mg/m² administered 2 weeks apart</td>
<td>Mild infusion-related adverse events (headache, nausea, chills, hypotension), anaphylaxis, infection</td>
<td>CD19 counts (&lt; 5%), IgG level (keep above 30% of the lower normal limit)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>By mouth</td>
<td>0.1-0.2 mg/kg/day split into two daily doses</td>
<td>Nephrotoxicity, GI (diarrhea, abdominal pain), hypertension, electrolyte imbalance, tremor, infection, hepatotoxicity, teratogenicity</td>
<td>Blood pressure, creatinine/BUN, and electrolytes, monthly trough level (aim 5-15 ng/ml)</td>
</tr>
</tbody>
</table>

BUN = blood urea nitrogen, GI = gastrointestinal, IgG = immunoglobulin G, IM = intramuscular, IV = intravenous
to reach the maximum weekly dose of 25 mg. Daily folic acid 0.8-1.0 mg orally is also administered to prevent stomatitis. Some advocate skipping folic acid on the day of MTX administration.

Besides stomatitis, potential adverse events include alopecia, pneumonitis, teratogenicity, induction of malignancy, susceptibility to infections, and renal insufficiency. For bone marrow suppression and liver toxicity, complete blood count, differential count, and liver function tests are monitored weekly in the first 4 weeks, then monthly for 6 months, and every 3 months thereafter while on a stable dose. Methotrexate-induced pneumonitis can be difficult to distinguish from myositis-associated interstitial lung disease (ILD). It is not used in patients with known ILD or in those with the Jo-1 antibodies.

Therapeutic effects of oral MTX are often noticeable after 4-8 weeks. If no improvement is observed by that time, the dose is escalated. In nonresponders and in more severe cases, the author recommends MTX IV or intramuscular treatment at a dose of 0.4-0.8 mg/kg weekly injections, increasing it by 5 mg every week to reach up to 60 mg weekly. Leucovorin rescue on the day after parenteral MTX administration is needed for doses as high as 50 mg.

**Azathioprine**

Azathioprine, an anti-metabolite that blocks T-lymphocyte proliferation, is a very effective second-line steroid-sparing immunosuppressant with delayed onset of response. It is administered in divided doses of 2-3 mg/kg/day, ranging 100-250 mg/day. Start with 50 mg/day for a week before gradually increasing the dose over 1-2 weeks to 100-150 mg/day. In 3-6 months, the author may increase it to the maximum range of 200-250 mg/day. Onset of response is delayed to at least 4-8 months and peaks at 1-2 years. It is therefore not surprising that the 3-month placebo controlled trial of AZA did not show any efficacy. However, hand grip strength improvement after 1 year was no different when comparing the AZA to MTX recipients. Prior to AZA initiation, it has recently been suggested to test for thiopurine methyltransferase activity. Its deficiency predicts an increased risk of hematologic toxicity. In homozygous cases AZA is contraindicated in while in heterozygous patients lower doses may be carefully tried. A meta-analysis of 54 observational studies and one randomized controlled trial did not demonstrate sufficient evidence to address the effectiveness of thiopurine methyltransferase activity pretesting. In clinical practice, the author monitor patients’ blood cell counts weekly at the initiation of AZA, then monthly. A flu-like reversible acute hypersensitivity reaction affects 12% of users in the first 2 weeks of therapy. It is associated with a rash, elevation in liver enzymes, and pancreatitis. Some may tolerate a re-challenge. Delayed adverse events include myelosuppression, hepatotoxicity, susceptibility to infection, malignancy, teratogenicity, rash, alopecia, fever, and arthralgias.

As long as the patient remains on stable AZA doses, CBC and liver enzymes should be monitored every week for 4 weeks, then monthly for 6 months, and then, for the risk for delayed toxicity, every 3 months. When liver enzymes are markedly elevated (above two times the normal limit), AZA should be stopped for several months until enzymes normalize before the patient may be re-challenged, at times successfully. It is important to obtain levels of liver-specific gamma-glutamyl transferase since transaminases may be released from necrotic muscle fibers.

The dose is adjusted to treatment response and to maintain the white cell count above 3,500 and the absolute lymphocyte count below 1,000. If the white cell count falls below 2,500 or the absolute neutrophil count is below 1,000, AZA administration must be interrupted. Patients taking allopurinol, an inhibitor of the main detoxification pathway, require AZA dose reduction to 25-33% of the above. Angiotensin converting enzyme inhibitors must be avoided due to the serious risk of severe leukopenia.

**Intravenous Immunoglobulin**

Intravenous immunoglobulin, a pooled gammaglobulin product from several thousand blood donors, has a complex immunomodulatory mechanism of action. Potential mechanisms include modulation and inhibition of pathogenic autoantibodies; suppression of proinflammatory cytokines; blockade of Fc receptor, macrophage colony stimulating factor, and monocyte chemotactant protein-1 increase; alteration of T cell function; suppression of circulating CD54 lymphocytes; and inhibition of cell transmigration into the muscle. A randomized-controlled trial with optional cross-over showed that IV Ig 2 gm/kg administered monthly for 3 months was very effective (9/12) in treatment-resistant DM. Though prospective controlled trials are lacking, IV Ig is also believed to be effective in PM17,18 and NM. The American Academy of Neurology 2012 guidelines recommend IV Ig as possibly effective and to be considered for treating nonresponsive DM cases. There was insufficient evidence to support or refute the use of IV Ig in PM or inclusion body myositis. In a recent retrospective inception cohort, all 78 JDM cases were treated steroids but 30 were treated additionally with IV Ig. The IV Ig group maintained similar or lower disease activity than control subjects. To achieve a more rapid improvement in severely affected patients IV Ig in instituted in addition to IV solumedrol as initial therapy. Occasionally, the author will administer IV Ig as maintenance therapy in otherwise refractory patients, or more commonly to reduce long-term CS dose. Dosing is 2 g/kg total initially, given divided over 2-5 days, and then infusions are repeated every 2-4 weeks, with a total monthly dosage of 0.4-2.0 g/kg.

Patients are closely monitored with the first infusion, starting at a very slow rate of 25-50 cc/hr for 30 min, which is increased progressively by 50 cc/hr every 15-20 min up to 150-200 cc/hr. Mild reactions (headache, nausea, chills, myalgia, chest discomfort, and back pain) occur in 10% and are improved with slowing the infusion rate and are preventable with premedication with acetaminophen, benadryl, and if need be IV methylprednisolone. Moderate rare reactions include chemical meningitis and delayed red, macular skin reaction of the palms, soles, and trunk with desquamation. Acute renal failure is uncommon and related to patient dehydration and the sucrose or maltose diluent. Other severe and rare reactions are anaphylaxis, stroke, myocardial infarction, or pulmonary emboli due to hyperviscosity syndrome. The latter is more likely to occur in old age, immobility, diabetes, thrombocytemia, hypercholesterolemia, hyper gammaglobulinemia, and cryoglobulinemia. Avoid using IV Ig in patients with several of these risk factors and place IV Ig recipients on low-dose aspirin prophylactically. The extremely rare patients with total IgA deficiency should not be receiving IV Ig. In an uncontrolled preliminary report, seven Caucasian women (four with DM and three with PM) with median disease duration of 72 months were treated with subcutaneous IG. Over a median followup period of 14 months, all patients showed a favorable clinical response leading
to reduction of the daily maintenance prednisone dose by a mean of 23 mg and three patients were able to discontinue prednisone altogether.21 These encouraging findings have not been validated in a controlled study.

**Refractory Patients**

In refractory patients, mycophenolate mofetil22 is started as a third-line agent and, in severe cases, rituximab23-24 or cyclophosphamide as well. Other third-line drugs include etanercept, cyclosporine, tacrolimus,25 and chlorambucil26 (Table). A large multicenter clinical trial to clarify the role of CD20 depletion using rituximab in refractory PM and DM adults and children was conducted. The results were presented at the 2010 American College of Rheumatology Annual meeting and the article is currently in press.27 Two-hundred patients with DM, JDM, or PM were randomized to receive rituximab early (Group A) or late (8 weeks later, Group B) in the course of this 44-week trial. The primary endpoint measure compared the time to achieve the definition of improvement (DOI) on two consecutive visits between both groups. The secondary endpoint measure was the difference in time to achieve 20% improvement on manual muscle testing on two consecutive visits between both groups. Another secondary endpoint measure was to compare between groups the proportion of patients achieving the DOI at week 8. There were no significant differences between Group A and B in the primary (20.2 and 20.0 weeks, respectively) and in the secondary endpoints since the proportion of early and late rituximab patients achieving DOI at week 8 was 21% and 15%, respectively (p = 0.32). It is likely that the study-delayed treatment design hampered the detection of a significant benefit of rituximab as 83% of refractory cases met the DOI following rituximab treatment. In a small uncontrolled study, rituximab improved six of eight refractory signal recognition particle-positive patients on manual muscle strength and/or resulted in creatine kinase (CK) decline as early as 2 months after treatment.28 Quantitative levels of serum anti-SRP antibodies also decreased after rituximab treatment. Furthermore, anti-SRP-positive myositis appears to be one of the few autoimmune diseases in which specific autoantibody levels are correlated with surrogate disease activity markers.29

In a controlled trial of etanercept, five of 11 subjects in the etanercept arm were successfully weaned off prednisone whereas none of the five placebo-recipients could be weaned off.9 The median of the average prednisone dosage after week 24 was lower in the etanercept group (1.2 mg/day) than in the placebo group (29.2 mg/day). Five etanercept-treated subjects and one placebo-treated case developed symptomatic ILD. The secondary endpoint measure was the proportion of patients achieving the DOI at week 20. There were no significant differences between Group A and B in the primary (20.2 and 20.0 weeks, respectively) and in the secondary endpoints since the proportion of early and late etanercept patients achieving DOI at week 20 was 21% and 15%, respectively (p = 0.32). It is likely that the study-delayed treatment design hampered the detection of a significant benefit of etanercept as 83% of refractory cases met the DOI following etanercept treatment. In a small uncontrolled study, etanercept improved six of eight refractory signal recognition particle-positive patients on manual muscle strength and/or resulted in creatine kinase (CK) decline as early as 2 months after treatment.28 Quantitative levels of serum anti-SRP antibodies also decreased after etanercept treatment. Furthermore, anti-SRP-positive myositis appears to be one of the few autoimmune diseases in which specific autoantibody levels are correlated with surrogate disease activity markers.29

**IDIOPATHIC INFLAMMATORY MYOSITIS ASSOCIATED WITH INTERSTITIAL LUNG DISEASE**

Corticosteroids are the first-line drug for idiopathic inflammatory myositis (IIM) associated with ILD, but most patients require an adjuvant immunomodulating drug.32 In cases of ILD refractory to steroids, mycophenolate mofetil,33 cyclosporine, and tacrolimus have been shown to be effective second-line agents.25 Early intervention with prednisolone and cyclosporin A (CsA) combination therapy and tight control of the daily CsA dose (by monitoring the blood level 2 hours post-dosing) improved pulmonary function test and chest imaging findings in DM cases with acute-to-subacute ILD.34 Rituximab and cyclophosphamide are third-line options to arrest progression in cases of refractory ILD. A third of treated cases experience resolution of pulmonary involvement, whereas 16% deteriorated.35 Factors predictive of poor ILD prognosis include older age, symptomatic ILD, lower values of vital capacity and diffusing capacity for carbon monoxide, a pattern of interstitial pneumonia on high resolution computed tomography scan and lung biopsy, and steroid-refractory ILD. There is increased mortality rate in patients with deteriorating ILD as compared to those without ILD deterioration (47.1% versus 3.3%).

**PROMISING THERAPIES**

Tocilizumab, a humanized anti-IL-6 receptor antibody, is Food and Drug Administration (FDA)-approved for the treatment of moderate-to-severe rheumatoid arthritis.36 Ogata and Tanaka recently reported the first two cases of refractory PM who responded to tocilizumab with reduction in CK as well as in one of the cases resolution of myalgia and stabilization of disease activity and in the other disappearance of the high-intensity zones in the thigh muscles on magnetic resonance imaging.37 Abatacept, a fusion protein between Ig and the extracellular domain of cytotoxic T-lymphocyte antigen 4, exerts its anti-inflammatory effect by down-regulating T-cell activation and is FDA-approved for moderate-to-severe rheumatoid arthritis. A refractory JDM case responded to abatacept IV and topical sodium thiosulfate (which promotes vasodilation and vascularization) with significant reductions in muscle and skin inflammation, decreased corticosteroid dependence, and an arrest of calcinosis progression.38 A bedridden PM patient had a very good clinical response to abatacept.39 Therefore, abatacept may hold promise as steroid-sparing agent for the treatment of refractory DM.

There are anecdotal reports of immune ablation similar to that achieved following myeloablative autologous hematopoietic stem cell transplantation through the intensive administration of alemtuzumab, an anti-CD52 antibody. A patient with refractory PM responded rapidly to a single course of treatment with alemtuzumab.39 Another case of refractory juvenile PM treated with alemtuzumab had stable clinical improvement for more than 6 years.40 However, a refractory adult PM case developed Epstein-Barr virus-driven lymphoproliferative disorder 9 weeks after alemtuzumab therapy.41 In a preliminary report, 10 patients with refractory or severe DM/PM underwent allogeneic mesenchymal stem cell transplantation and all initially improved in their serum CK, patient global assessment by visual analogue scale, and muscle strength by manual muscle test.42 However, three had recurrence of disease activity 6-8 months after the transplant of whom two underwent a second transplant with good
clinical response in one case. The efficacy of allogeneic mesenchymal stem cell transplantation in DM or PM has yet to be confirmed in controlled trials.

Recently an old therapy, intramuscular ACTH, has been reported to be effective for inflammatory myopathy. This drug is surprisingly FDA-approved for the treatment of dermatomyositis and polymyositis.

**PHYSICAL THERAPY**

In addition to pharmacotherapy, it is generally agreed upon that physical therapy, orthotic devices, occupational therapy, and exercise are beneficial in DM, PM, and NM as early as 2-3 weeks from the acute phase. While other studies have reported the safety and benefits of resistive exercise in active patients 1-3 months into their treatment, most of the studies have been in chronic PM or DM. All studies demonstrated the efficacy and safety of exercise as measured by the Functional Index, SF-36, muscle histology, muscle magnetic resonance imaging scanning, or creatine phosphokinase levels. Besides improved muscle strength and increased maximal oxygen uptake, resistance exercise training of eight myositis patients resulted in marked reductions in gene expression, reflecting reductions in proinflammatory and profibrotic gene networks, together with a reduction in tissue fibrosis. In severe cases, the author will start with passive range of motion exercises initially and will usually wait for the first month to 3 months for strength and CK to start responding to pharmacotherapy before subjecting severely weakened muscles to a rigorous strengthening exercise program. In patients with mild-to-moderate weakness, the author will initiate a strengthening program after 2-4 weeks of steroid initiation. Since pain from arthralgia and possibly arthritis is relieved by joint flexion, early mobilization is important to prevent flexion contractures of the large and small joints, especially in JDM. There may also be a role for creatine monohydrate supplementation as it improves functional performance without significant adverse effects.

**PROGNOSIS**

The prognosis of DM, PM, and NM is in general favorable with some exceptions. An associated malignancy portends a poor prognosis for recovery and increases mortality. SANAM is resistant to treatment. Concomitant ILD or Jo-1 or signal recognition particle autoantibodies predict a poorer prognosis. Overall, drug-free remissions are rare except in JDM. Recent series underline that only 20-40% of treated patients will achieve PM/DM remission, whereas 60-80% will experience a polycyclic or chronic continuous course of the disease. On medium- and longterm followup, up to 80% of treated PM/DM patients are still disabled based on Health Assessment Questionnaire scores. The overall mortality ratio in PM/DM patients also remains two- to threefold higher compared with the general population, with cancer, lung, and cardiac complications and infections being the most common causes of death. Poor prognostic factors in PM/DM patients include older age, male gender, non-Caucasian ethnicity, longer symptoms duration, ILD, cardiac involvement, dysphagia, cancer, and serum myositis-specific antibodies (including coexistence of anti-Ro52 and anti-Jo1 antibodies, presence of anti-signal recognition particle antibody, anti-155/140, and anti-CADM-140 antibodies). Complete remission of PM/DM was less frequent (13.6% versus 41.1%) and the mortality rate (47.8% versus 7.3%) was higher in elderly patients than in younger patients. In a recent series, the coexistence of Ro52 and Jo1 antibodies was associated with more severe myositis/joint impairment, symptomatic ILD, increased risk of cancer, and higher mortality. Anti-SRP antibody is associated with acute onset of refractory necrotizing myositis and antibody titers correlate with CK levels and disease activity. Anti-155/140 antibody is associated with malignancy, whereas the presence of anti–CADM-140 antibody is associated with amyopathic DM and rapidly progressive ILD.
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Inflammatory Myopathies

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CASE PRESENTATION

Case One
A 35-year-old woman developed difficulty arising from a chair, climbing stairs, washing her hair, and removing items from shelves in her closet. Symptoms progressed in intensity for 3 months and she then developed a fine pruritic rash along her upper anterior chest and dry, cracking hands with discoloration on the back of her fingers. Physical examination showed an erythematous rash around the eyes and on the anterior chest, purplish discoloration of papules on the back of the hands, particularly over the joints, and moderate weakness of neck flexion, shoulder abduction, arm flexion, hip flexion, and knee flexion. She was unable to arise from a chair without using her hands to push off. Laboratory studies showed a normal serum creatine kinase (CK) (63 IU/ml). Complete blood count, electrolytes, antinuclear antibodies (ANA), and aspartate aminotransferase/alanine aminotransferase were normal. The muscle biopsy is shown in Figure 1.

Figure 1. Hematoxylin and eosin stained sections from muscle biopsy Case One. Used with permission from the author.

Case Two
A 67-year-old man developed slowly progressive difficulty walking with a tendency for his knees to buckle, difficulty climbing stairs, and difficulty holding eating utensils and turning keys. Serum CK was 845 IU/L. He underwent muscle biopsy, was diagnosed with polymyositis (PM), and treated with prednisone 60 mg orally daily. Three months later followup CK was 252 IU/L but there was no improvement in strength. He continued to weaken, while remaining on high-dose prednisone, which was eventually tapered 1 year later. He underwent another consultation, which showed generalized weakness with a marked preference for wrist and finger flexors (Figure 2), and quadriceps, with relatively spared arm abductors. He underwent repeat muscle biopsy (Figure 3).

Figure 2. Preferential involvement of finger flexors over finger extensors in Case Two. Used with permission from the author.
Muscle pathology of second biopsy, hematoxylin and eosin staining, Case Two. Inset shows enlargement of the central myofiber. Used with permission from the author.

CASE DISCUSSIONS

Case One

This patient developed proximal weakness along with a skin rash, immediately raising the possibility of dermatomyositis (DM). The description of the rash including purplish papules over the dorsal finger joints suggests the presence of Gottron’s papules. The normal serum CK makes unlikely certain inherited muscle diseases but does not diminish the possibility of DM, as CKs are often normal in DM. The muscle biopsy demonstrates perivascular and perimysial location of inflammatory cells (Figure 1A) and the presence of perifascicular atrophy (Figures 1A and 1B) that is evident as basophilic atrophic fibers around the periphery of fascicles. Perifascicular atrophy is virtually diagnostic of DM.

Case Two

This patient developed slowly progressive weakness of the hands and quadriceps by history and by physical examination had marked weakness of finger flexors in contrast to finger extensors. This pattern immediately suggests sporadic inclusion body myositis (sIBM). The muscle biopsy (Figure 3) shows endomysial inflammation with invasion of non-necrotic muscle fibers (arrow) and rimmed vacuoles (arrowheads). The lack of clinical response to prednisone, despite reduction in serum CK values, is characteristic, as is the initial diagnosis as PM.

GENERAL DISCUSSION

The inflammatory myopathies are diseases in which muscle appears to be injured by the immune system. The clinical features and pathogenesis have been recently reviewed and much of the material that follows is adapted from such recent reviews.1,5

The principal subtypes are DM, inclusion body myositis (IBM), and PM, though many patients have syndromes that are not easily classified and may best be labeled as nonspecific (or unspecified) myositis. Other subtypes include necrotizing myopathy, overlap syndromes (inflammatory myopathy occurring in a patient with a connective tissue disorder such as mixed connective tissue disease), granulomatous myositis, and eosinophilic myositis. The mechanisms initiating and maintaining these diseases are not well understood.6

Dermatomyositis

Dermatomyositis affects children and adults. Adult DM generally presents as subacute progressive painless proximal weakness, a skin rash, or both. Juvenile DM (JDM) may present similarly or as an acute or subacute febrile illness followed by skin, muscle, or sometimes multisystem involvement. The mechanism of disease is associated with induction of the type I interferon pathway.4

The skin involvement in DM may have diverse manifestations, including a heliotrope rash (purplish discoloration) on the eyelids; an erythematous rash on the face, neck, and anterior chest (“V-sign”), upper back (“shawl sign”), elbows, or knees; a purplish scaly papular rash on the extensor surface of the hands (Gottron’s papules); thickened and cracked skin on the dorsal and ventral surfaces of the hands (“mechanic’s hands”); and other changes. Subcutaneous calcinosis is a significant problem in JDM and uncommon in adult DM. Cutaneous symptoms in DM have a high impact on lowering quality of life in patients and include prominent pruritus.7,8

The pattern of proximal limb weakness in DM is not distinctive and does not distinguish DM from many other myopathies. Significant muscle asymmetries or prominent distal (forearm or lower leg) weakness together with skin rash should prompt consideration for sarcoidosis, for which clinical involvement similar to DM has been recognized.9 Normal serum CK may be present in patients with progressing disease and does not exclude the diagnosis. When elevated serum CK is present in DM, reductions generally occur with treatment, and elevation with relapse.

Additional evaluation of adult patients with DM should be performed because of its association with two other important clinical syndromes: interstitial lung disease and malignancy. Pulmonary function tests, chest computed tomography (CT), and laboratory testing for the presence of antihistidyl transfer RNA antibodies (anti-Jo-1 antibodies) should be considered in all patients with DM. Malignancy has been estimated to be associated with 6-45% of adult patients with DM, with age-associated increased risk particularly in women over 40 years old. A malignancy evaluation—including physical examination (skin examination, breast and pelvic examinations in women, and testicular and prostate examination in men), blood studies (complete blood count, liver function tests, lactate dehydrogenase, and prostate specific antigen), stool studies for occult blood, CT (chest, abdomen, and pelvis), and colonoscopy—should be considered in every adult patient with a new diagnosis of DM.

Muscle biopsy is an important diagnostic procedure in DM. The clinical syndrome in patients with typical skin and muscle features is quite specific for DM though some patients with sarcoidosis have been reported with similar clinical but distinct pathological features.10-12 The most supportive diagnostic feature of muscle pathology for DM evident in routine clinical studies is the presence of perifascicular atrophy, small myofibers that are
slightly darker and bluish in color in hematoxylin and eosin sections, typically located at the edges of fascicles.

**Inclusion Body Myositis**

Inclusion body myositis affects adults during middle age and later life. The name was first applied to a patient with symptom onset at age 18 and findings at age 26 consisting of lordotic posture, leg limb-girdle weakness, and no atrophy or weakness of the quadriceps. This patient would not meet current criteria for the diagnosis of IBM. Although onset over age 50 has been emphasized, symptom onset prior to age 50 is common (18-20% of patients). Diagnosis has historically been frequently delayed by a mean of 5-8 years from symptom onset. The mechanism of disease may be linked to nuclear degeneration and the redistribution of the normally nuclear protein TDP-43 to the sarcoplasm.

The clinical presentation of IBM is quite distinct from that of other inflammatory myopathies. Atrophy and weakness of wrist and finger flexors and quadriceps are distinctive and physical examination should focus on careful testing of these muscle groups. Comparison of wrist and finger extendors with corresponding flexors may demonstrate the greater involvement of the flexors and asymmetries. Relative preservation of deltoids, in comparison to the forearm flexors, can be impressive, in marked contrast to the pattern of weakness seen in DM and PM. Contrasts between severe biceps weakness, but better preserved brachioradialis, and severe deep flexor weakness, but uncommonly involved adductor pollicis, have been emphasized as well. Involvement of tibialis anterior may also be distinctive in IBM. Dysphagia can be a significant problem, with a prevalence estimated as high as 66%. Serum CK is only modestly elevated; research criteria have proposed diagnostic criteria of an upper limit of 12 times the upper limit of normal, though patients with higher values, up to 16 times the upper limit of normal, have been reported. Serum electrophoresis and the more sensitive immunofixation should be considered because some patients have a detectable serum monoclonal immunoglobulin population.

The presence of multiple myofibers surrounded by inflammatory cells and many myofibers with rimmed vacuoles is highly supportive of a pathological diagnosis of IBM. Both IBM and PM (see below) may have similar patterns with respect to the location of inflammatory cells as seen in routine studies. The pattern of inflammatory cells deep within fascicles surrounding and sometimes invading myofibers is distinct from that of DM. What distinguishes IBM from PM in light microscopic examination is a sufficient number of rimmed vacuoles, though diagnostic and research criteria for what constitutes sufficient numbers of rimmed vacuoles have not been established. The presence of cytomembranous whorls and filamentous inclusions with electron microscopy are also highly supportive of a diagnosis of IBM. Difficulties with diagnosis occur in patients with typical clinical features but few inflammatory cells or with few rimmed vacuoles. Small numbers of rimmed vacuoles may be seen in patients with steroid-responsive PM syndromes.

**Polymyositis**

Patients with acquired myopathies whose weakness improves with immunosuppressive therapies and relapses with taper of such therapy, but lack the rash and pathological features of DM are challenging to classify. Depending on various criteria, such patients may be categorized as having PM, nonspecific myositis, necrotizing myopathy, overlap syndromes, or other diagnoses.

Patients with subacute progressive symmetrical proximal arm and leg weakness, without skin rash, and with muscle biopsy features of prominent inflammatory cells surrounding many muscle fibers, without perifascicular atrophy, are the patients that are most appropriately classified as having PM or nonspecific myositis. Various research diagnostic criteria have been considered with regard to the challenges of PM diagnosis. The practical issues are avoiding misclassification of certain muscular dystrophies, particularly limb-girdle muscular dystrophy (LGMD), and IBM as PM. Most patients with LGMD and IBM meet widely-used criteria for the diagnosis of PM.

As with DM, there is an association with interstitial lung disease, but not a well-established association with malignancy. Serum CK is almost always elevated in patients with progressing PM. Connective tissue diseases should be considered through clinical evaluation and antinuclear antibody testing.

The pathological diagnosis of PM is reasonable when there are abundant inflammatory cells surrounding multiple myofibers and an absence of rimmed vacuoles. There are considerable differences in opinion, ranging from support for diagnostic criteria that allow a diagnosis of definite PM with biopsy features that include some unspecified combination of muscle degeneration, regeneration, necrosis, and inflammatory cells, to positions that the diagnosis should require invasion by CD8+ T cells (which include cytotoxic and suppressor T cells) of non-necrotic muscle fibers with visible expression of major histocompatibility class 1 by immunohistochemistry on these fibers' sarcolemma. The former criteria may lead to misdiagnosis of genetically determined myopathies, which may have variable degrees of inflammation present (the association of calpain mutations with eosinophilic myositis is one excellent example of this problem), and IBM as PM, while the latter is restrictive enough that many patients with immune-mediated myopathies need an alternative diagnosis, such as non-specific or unspecified myositis.

**Pathogenesis of Dermatomyositis**

The pathophysiology of DM appears to be associated with the family of type I IFN cytokines. Microarray studies of muscle biopsy specimens generating over 2 million data points assaying gene expression of tens of thousands of genes in more than 100 muscle biopsy samples has found the marked overproduction of type I interferon (IFN)-inducible transcripts and proteins in muscle to be remarkably unique to DM in comparison to all other muscle diseases studied. Elevation of type I IFN-inducible transcripts has remarkable specificity for DM. For example, the transcript for the type I IFN-stimulated gene 15 (ISG15) was higher in muscle in all 28 biopsies from adults with DM and
perifascicular atrophy and children with JDM than in every one
of 199 non-DM biopsy samples from a wide range of neuromuscular
diseases.

Some type I IFN-inducible proteins also are highly specific bio-
markers of DM muscle. MxA, for example, is impressively and
uniquely (in comparison to other muscle diseases) abundant in
DM myofibers with perifascicular atrophy and in DM capillaries.
An ubiquitin-like modifier, ISG15 is conjugated to many other
proteins in DM muscle. In vitro models of human skeletal muscle
cell cultures, exposed to IFN-α or IFN-β, produces a similar
picture of ISG15 conjugation present in human DM samples.

Which specific type I IFN might be driving the marked type I
IFN-inducible response in DM muscle is uncertain but recent
evidence suggests that it is interferon-β.30

Pathogenesis of Inclusion Body Myositis

There are many theories of the pathogenesis of IBM. Toxicity theo-
ries of various molecules have dominated the field. Mitochondrial
pathology and infectious causes have also been considered. Other
considerations have included a potential infectious origin and a
mitochondrial disorder. Autoimmunity and nuclear degeneration
are perhaps the strongest theories.

Autoimmunity

The adaptive immune system is an arm of the immune system
capable of generating highly specific molecular targeting. Inclusion body myositis has a highly refined adaptive immune
response. Both T cells and B cells undergo affinity maturation,
selection, and clonal expansion through high-affinity interactions
of their receptors (the T cell antigen receptor and B cell surface
immunoglobulin receptor) with target antigen.

Cytoxic T cell invasion of myofibers has been emphasized
since the mid-1980s. Molecular analyses of the T cell receptor
(analyses of the nucleotide sequences of the variable regions of
their α and β chains) have demonstrated clonal restriction (a
limited population of distinct T cell receptor TCR transcript se-
quENCES), providing circumstantial evidence of clonal expansion
(that T cells have been activated by antigen and proliferated). In
IBM muscle, antigen-stimulated T cells develop highly specific
antigen-directed receptors during proliferation.

Inclusion body myositis also has a highly refined B cell response
with plasma cells31 with immunoglobulin gene rearrangements,
characteristic of clonal expansion in response to local antigen
stimulation,32 and a permissive environment for ectopic lymphoid
structures suggestive of local maturation of B cells in muscle.33
The differentiated B cells develop into clonally expanded, highly-
refined antigen directed plasma cells that produce and secrete
immunoglobulins within IBM muscle.

Recognition that a B cell-specific response was present in IBM
muscle and characterization of this response suggested that a
search for circulating IBM autoantibodies might be fruitful. In
2011, an autoantibody to a human muscle protein of approxi-
mately 43 kDa was identified in 52% (13/25) of IBM samples,
0% (0/25) of other autoimmune myopathy samples, and 0%
(0/15) of normal samples.34 The identity of this protein has not
been established.

Nuclear Degeneration

Rimmed vacuoles in IBM muscle derive from nuclei. They
are lined with the nuclear membrane proteins lamin A/C and
emerin.21 Lining of these vacuoles with histone H1 and with emerin
was reported in 200835 and with histone 2AX and DNA repair
regulatory components (DNA-PK, Hu70, and Hu80) in 2011.36

Inclusion body myositis muscle is also notable for the presence
of an aberrantly-localized sacroplastic protein with the capacity
to nonspecifically bind nucleic acids. The nucleic acid-binding
protein TDP-43 has been identified in IBM non-nuclear sarco-
plasm.20,37 TDP-43 is a predominantly nuclear heterogeneous
nuclear ribonucleoprotein that undergoes nucleocytoplasmic shut-
tling and associates with translation machinery in the cytoplasm.

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Myotonic Dystrophies

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CASE PRESENTATION

History

A 58-year-old man presented with a 10-year history of slowly increasing muscle weakness. He had difficulty standing from a sitting or squatting position, climbing stairs, and getting in his truck as well as mild hand grip, arm, and neck weakness. He had no speech, swallowing, or breathing difficulty. He denied any muscle stiffness, spasm, or twitches, except for having infrequent episodes of deep ache pain in the thighs, and less frequently in the shoulders and upper arms. The patient was seen by a local neurologist 2 years earlier, and reportedly his needle electromyography (EMG) showed a mix of positive waves and myopathic motor unit action potentials (MUAPs). He had declined a muscle biopsy.

The patient’s past medical history included diabetes mellitus, treated with metformin, bilateral cataracts removed 5 years prior, and an appendectomy at age 34 years. He smokes half a pack of tobacco per day and drinks two to three beers daily. The family medical history is positive for diabetes and his father died at age 61 years secondary to heart disease. He also was reported to have had muscle weakness. The patient had a living paternal aunt diagnosed with muscular dystrophy.

Examination

The patient’s general physical examination was unremarkable. The neurological examination revealed normal cognitive functioning. Cranial nerves II-XII were normal on examination, except for mild ptosis and subtle bilateral facial weakness. He had no diplopia or delayed eye opening after forceful closure. He was noted to have mild atrophy of the glutei and sternocleidomastoid muscles bilaterally. He had difficulty rising from a sitting position without pressing on the chair arms. Muscle strength examination using the Medical Research Council rating scale revealed weakness of neck flexors 4/5, shoulder abductors 4+/5, biceps 4+/5, long finger flexors 4+/5, hip flexors 4/5, hip abductors 4+/5 bilaterally, and ankle extensors 4+/5 and normal strength for all other remaining muscle groups. No muscle hypertrophy, fasciculations, stiffness, or hand grip myotonia were found; however, he was noted to have mild thenar muscle percussion myotonia. Tendon reflexes were symmetric rated 2+, and no pathological reflexes were elicited. Sensory testing, coordination, and gait examination were all normal.

Initial Differential Diagnosis

The patient presented with chronic, slowly progressive proximal muscle weakness of the shoulder, hip girdle, and neck. The differential diagnosis in patients with proximal weakness should include muscular dystrophies; metabolic, congenital, or mitochondrial myopathies; and acquired myopathies, such as inflammatory, toxic, or endocrine. Other diagnoses, such as late-onset spinal muscular atrophy (SMA) and generalized myasthenia gravis should also be considered. Motor neuron disease usually presents in a different anatomical distribution of muscle weakness, and it is not likely in this case given that the patient’s weakness remained mild after 10 years. An inherited autosomal dominant myopathy should be suspected, given that the patient’s father reportedly had muscle weakness and he has a living paternal aunt diagnosed with muscular dystrophy.
The predominantly proximal weakness suggests a diagnosis of muscular dystrophy (such as limb girdle muscular dystrophy), metabolic myopathy (such as adult onset acid maltase deficiency), myotonic dystrophy (or dystrophia myotonica) (DM), late onset SMA, or mitochondrial myopathy. Although adult onset acid maltase deficiency presents with a slowly progressive weakness over many years, it is usually associated with respiratory muscles weakness and with no clinical myotonia observed. Mitochondrial myopathy is a relatively static proximal weakness with poor endurance and can be associated with external ophthalmoplegia. It has a different inheritance pattern. Late onset SMA usually presents at an earlier age than this case, with insidious weakness and atrophy of the pelvic girdle and proximal leg muscles. It is followed by involvement of the shoulder girdle and upper arm muscles, associated with fasciculations and depressed tendon reflexes. Muscular dystrophy, especially DM, should be highly considered given that the patient has muscle weakness, diabetes, bilateral cataract, and percussion myotonia as well as a positive family history for weakness, diabetes, and heart disease. The classical myotonic muscular dystrophy type 1 (DM1) is unlikely with predominantly proximal weakness. However, the patient’s proximal weakness, percussion myotonia, associated systemic diseases, and family history are consistent with an autosomal dominant inheritance and are suggestive of myotonic muscular dystrophy type 2 (DM2), also called proximal myotonic myopathy (PROMM). Myasthenia gravis is not highly suspected given that the patient has no diplopia, ptosis bulbar weakness, increased fatigue, or weakness fluctuations.

Laboratory Tests and Electrodiagnostic Studies

Electrodiagnostic (EDX) studies were performed. A standard motor and sensory nerve conduction study and an F wave were all normal. Repetitive motor nerve stimulation of the ulnar and spinal accessory nerve at 3 Hz at rest and post-exhaustion exercise showed no neuromuscular junction abnormality. The needle EMG examination demonstrated runs of discharges with waxing and waning amplitude and frequency, in the form of positive waves more prominent in the distal muscles (Figure). In addition, the needle EMG demonstrated fibrillation potentials and frequent polyphasic MUAPs. Many of these were of short duration and small amplitude with early recruitment predominantly in the proximal limb muscles. Overall the EDX study was characteristic of myotonia with associated myopathic features predominantly in the proximal muscles, supportive of the clinical diagnosis of DM2. The diagnosis of DM2 was confirmed by a positive genetic test for expanded tetranucleide repeats mutation in the zing finger protein 9 (ZNF9) on chromosome 3.

DISCUSSION

Myotonic Dystrophy

Myotonic dystrophy type 1 is the most common form of muscular dystrophy, with an incidence of 13.5/100,000 based on Swiss data, and an estimated prevalence of around 5/100,000 for most European and North American populations. It is the most severe form among the myotonic disorders. Great variability of clinical expression exists, ranging from the severe congenital form to subclinical cases. Although DM1 can present at any age, in the majority of cases onset of symptoms and diagnosis occurs in the late teens or early adulthood. The most common presenting complaint is usually muscle weakness. Myotonia is often a “minor nuisance” compared with other symptoms. Less commonly, patients with DM1 may initially present with subnormal intelligence; premature cataracts; and pulmonary, endocrine, reproductive, gastrointestinal, skin, and cognitive involvement. The disease is classified into DM1 and DM2. There may be more genetically distinct forms yet to be identified.

Myotonic Dystrophy Type 1

Myotonic dystrophy type 1 is the most common form of muscular dystrophy, with an incidence of 13.5/100,000 based on Swiss data, and an estimated prevalence of around 5/100,000 for most European and North American populations. It is the most severe form among the myotonic disorders. Great variability of clinical expression exists, ranging from the severe congenital form to subclinical cases. Although DM1 can present at any age, in the majority of cases onset of symptoms and diagnosis occurs in the late teens or early adulthood. The most common presenting complaint is usually muscle weakness. Myotonia is often a “minor nuisance” compared with other symptoms. Less commonly, patients with DM1 may initially present with subnormal intelligence; premature cataracts; and pulmonary, endocrine, or gastrointestinal symptoms. Neck flexor and distal limb muscle weakness usually starts early in the disease course, especially in the forearm and finger flexors, and in the ankle dorsiflexors. It then slowly progresses to affect the proximal muscles, often associated with muscle atrophy. Facial features including mild ptosis, weakness of the eyes and mouth closure, frontal balding, a long face with hollowed cheeks, and temporalis and masseter wasting are other characteristics. Action myotonia, such as delayed relaxation of the fingers following a forceful hand grip, is a minor complaint, aggravated by cold weather. It will typically diminish with repeated attempts (“warm-up” phenomenon). Often patients deny having myotonia or appear to be unaware of it and it has to be actively elicited by percussion of the thenar eminence, the tongue, or during a needle EMG.

The extramuscular manifestations in DM patients include a number of frequent multisystemic clinical features. Posterior subcapsular cataracts of variable severity and lenticular opaci-
ties are invariably present in patients over the age of 20 years. These are best identified by slit lamp examination. Cardiomyopathy is rare and the cardiac abnormalities do not correlate with the severity of muscle dysfunction. With prolonged disease duration, fatal arrhythmias and sudden death may occur in DM1 patients. Insulin insensitivity, hyperglycemia, and hyperinsulinemia following a glucose tolerance test are common. The incidence of overt diabetes mellitus is not increased. Testicular failure, low serum testosterone, and impotence in males are seen in both DM1 and DM2. Cognitive and neuropsychological testing in DM frequently reveals mild cognitive deficits, poor insight, and behavioral and personality disorders. Magnetic resonance imaging nonspecific abnormalities of cerebral white matter and abnormal positron emission tomography have been reported. Smooth muscle involvement of the gastrointestinal tract may cause dysphagia, decreased motility, constipation, and fecal incontinence. Diaphragmatic dysfunction may account for the alveolar hypoventilation, frequently seen in DM patients. It is more striking in infants with the congenital form. Sleep apnea, hypersomnia, and disrupted sleep are also common.

**Myotonic Dystrophy Type 2 (or Proximal Myotonic Myopathy)**

Myotonic dystrophy type 2 was first identified in 1994 as an autosomal dominant disease, similar to DM1 in most of the clinical features, including muscle weakness, myotonia, and multisystem involvement. However, it has a characteristic pattern of muscle weakness and is genetically distinct from DM1. The incidence of DM2 is uncertain, but it is seemingly less common than DM1. The age of onset is usually between 20 and 60 years, although it may start at an earlier age. Anticipation is much milder than in DM1, and congenital forms have not been described. The disease may present with intermittent disabling pain and stiffness in the thighs, shoulders, or upper arms. The weakness is predominantly proximal and progresses to involve the neck flexors, long finger flexors, elbow extensors, hip flexors, and knees extensors. The main complaint of most affected patients is hip girdle and proximal lower limbs weakness. The weakness may fluctuate and/or worsen during pregnancy. Clinical myotonia is variably present and may be missed. It is associated with “warm-up” phenomena. In a case report it was evident only during pregnancy. However, in a large series electrical myotonia was demonstrable in the majority of patients. Cognitive and systemic abnormalities are generally milder than in DM1, and fatal cardiac arrhythmias or sudden death rarely occur.

**Congenital Myotonic Dystrophy**

Congenital myotonic dystrophy was the first myotonic disorder to be recognized. It is a distinctive and potentially fatal form of DM, with the affected parent always being the mother. Hydramnios and reduced fetal movements in the later part of pregnancy are common. The principal clinical features of the disease are recognized after birth. It is unusual for all features to be present in a single patient. Major clinical features include: bilateral facial weakness in over 85% of cases, accompanied by a “tented” upper lip, prominent jaw muscle weakness, hypotonia, and feeding and sucking difficulty of varying severity. The primary causes of mortality in affected infants are likely bronchial aspiration and neonatal respiratory distress due to diaphragmatic weakness and hypoplasia and intercostal muscle weakness. Talipes may occur in about half the cases and generalized arthrogryposis is reported in a small portion of patients. Myotonia is absent in infancy and becomes evident later in childhood. Surviving infants show delayed motor and speech development, swallowing difficulty, and mild-to-moderate cognitive deficits. Once adolescence is attained, the disease follows the same course as the later onset disease. The characteristic facial features and eliciting myotonia in the mother allow instant recognition of the diagnosis in many cases. Although the prenatal diagnosis of DM is readily accomplished by testing for cytosine-thymine-guanine (CTG) repeats in the amniotic fluid or chorionic villi, it is not possible to predict whether a fetus with an expanded mutation will have either congenital or later onset DM.

**Genetics and Pathogenesis**

Myotonic dystrophy type 1 is caused by an expansion of CTG trinucleotide repeats in the myotonin protein kinase (DMPK) gene on chromosome 19q13.2.23 The number of the CTG repeats may expand with the next generation due to anticipation phenomena and correlates with the muscle dysfunction severity. Myotonic dystrophy type 2 is caused by an expansion of a CCTG tetranucleotide repeat within intron 1 of the ZNF9 gene on chromosome 3. This very large repeat accumulates as RNA foci in the nuclei of the affected tissue. Muscle weakness and the multisystemic clinical features common to both DM1 and DM2 are caused by the toxic gain effect on cells subsequent to these repeat expansions in RNA.

**Diagnosis**

Myotonic dystrophy diagnosis can be achieved on clinical grounds and with needle EMG. Genetic testing confirms typical or atypical presentation and is commercially available for both DM1 and DM2. Minors should not be tested unless symptomatic or a diagnosis is necessary. Prenatal testing via amniocentesis or chorionic villous sampling assesses fetal risk in diagnosed parents. Serum CK may be normal or mildly elevated. Standard motor and sensory conduction studies are normal. Needle EMG demonstrates myotonic discharges often elicited by needle movements or voluntary contraction. Although at times several muscles may need to be tested before discharges can be found, they are less abundant in DM2. Diffuse fibrillations and positive waves, often masked by the myotonic discharges (as well as myopathic MUAPs and early recruitment), are detected in weak distal and/or proximal limb muscles. Electrical myotonia may not be elicitable in infants with the congenital form of DM, but it can be easily demonstrable in the mother’s hand muscles. Muscle biopsy, which is not required for diagnosis, shows characteristic type I fiber atrophy and occasional ring-band fibers in DM1. Type II fiber atrophy and pyknotic nuclei are common in DM2 with abundant central nuclei and intranuclear RNA inclusions. Necrotic muscle fibers are uncommon findings and increased connective tissue is usually mild. This is mostly seen in the late stages of the disease.
Therapy and Prognosis

There is no known effective treatment for muscle weakness or curative therapy for the multisystemic manifestations in DMs. Small clinical trials of creatine monohydrate and recombinant human growth hormone and controlled trials of dehydroepiandrosterone sulfate in DM1 patients showed no efficacy. Therapies are primarily focused on drug treatment of myotonia and muscle pain, along with management of the various systemic manifestations. Patients with DM rarely complain of myotonia, and drug management should be limited to those with bothersome myotonia due to the potential cardiac conduction side effects. Quinine sulfate 0.5 g twice daily, procainamide 0.5 three times daily, or tocainide 400 mg three times daily are effective treatments for myotonia, but they potentiate cardiac arrhythmias. None of these drugs should be used in the presence of any cardiac disturbances. Mexiletine 200 mg three times daily, with electrocardiogram (EKG) monitoring, or phenytoin 100 mg three times daily are helpful in relieving disabling myotonia. Muscle pain is usually secondary to weakness and deconditioning and can be treated with nonsteroidal anti-inflammatory drugs or other appropriate pain medications.

General management includes careful cardiac monitoring for conduction disturbances including screening with yearly EKGs. Cardiology referral, Holter monitoring, and echocardiograms are necessary if EKGs show conduction defect or arrhythmias. In patients with second or third degree heart block or in those for whom there is concern of unpredictable sudden death, pacemaker placement might be required. Pulmonary function tests and precautions to avoid respiratory problems, including increased risk of aspiration and pneumonia, are recommended. Noninvasive ventilatory assistance (bilevel positive airway pressure or continuous positive airway pressure) might be required in patients with clinically-significant hypoventilation, diaphragmatic weakness, and sleep apnea. Ophthalmologic evaluation and cataract surgery might be needed. Orthopedic measures might be needed in children with talipes and other joint deformities. Orthotic devices for patients with foot drop help to facilitate their gait. Swallowing assessment in patients with dysphagia is important to avoid risk of aspiration, pneumonia, and poor nutrition. Speech therapy in patients with dysarthria is helpful. Endocrine status and metabolic function assessment in symptomatic patients or those suspected with dysfunction is necessary. Anesthetists and surgeons should be made aware of the hazards associated with anesthesia and surgery in patients with DMs. Nonstrenuous exercise is safe and may improve physical fitness and endurance. Genetic counseling is essential and of particular value for individuals with an affected parent. It is also essential for those affected individuals who wish to have children or to have a prenatal diagnosis.

Most DM patients remain mobile throughout their life and are usually free from the contractures seen in most disabling neuromuscular disorders. It is important to recognize that life expectancy in DM1 patients is significantly reduced due to increased risk of fatal arrhythmias with sudden death, respiratory disease, neoplasia, and coronary artery disease. Longitudinal and cohort studies showed 7.3 times higher mortality rate than the age-matched control subjects with a mean age at death of 53 years.

Myotonic dystrophy type 2 has rarely been associated with fatal arrhythmias or respiratory insufficiency, and the congenital form has not been identified in DM2 cases.

REFERENCES


CASE PRESENTATION

History

A 60-year-old woman presents for evaluation of muscle stiffness and pain since age 7. She recalls that during winter in elementary school she would not be able to unzip her coat without the teacher’s help. In addition to the cold weather, her stiffness is worse with any repeated activity or exercise. She reports difficulty shoveling snow from the driveway and pulling weeds in the garden. She states, “I learned to live with it all these years, but lately I feel worse.” She describes fatigue and aching muscle pain affecting her arms and thigh muscles. Her past medical history includes remote history of idiopathic thrombocytopenic purpura, hypertension, and Hashimoto’s thyroid disease; she had hysterectomy and right carpal tunnel surgery. Her medications include hydrochlorothiazide, cozaar, atenolol, levothyroxine, and trazodone. She is allergic to sulfa and amoxicillin. She retired as a flight attendant and moved to Ohio recently. She has no siblings. She reports no similar history in the family, including her son and her two grandchildren.

Examination

She is afebrile and blood pressure is normal. Mental status is normal and language is intact. Her cranial nerves examination is unremarkable except for eyelid myotonia that worsens with repeated testing. She has normal muscle strength, 2+ and symmetric muscle stretch reflexes, and down going plantar responses. She has normal pin prick and vibratory sensation. Furthermore, she has hand-grip myotonia that worsens with repeated trials. She has no frontal balding, temporalis or masseter muscles atrophy, cataract, or thinning of the neck muscles.

Laboratory Studies

Serum creatine kinase (CK), complete blood count, electrolytes, liver function, and thyroid-stimulating hormone are all unremarkable. Electrodiagnostic (EDX) testing reveals normal sensory and motor nerve conduction studies. Needle electromyography (EMG) shows diffuse myotonic discharges.

Differential Diagnosis

The differential diagnosis for a patient with muscle stiffness, pain, and cold-induced weakness includes:

- Nondystrophic myotonia
- Myotonia congenita (MC)
- Paramyotonia congenita (PC)
- Sodium channel myotonias
- Myotonic dystrophy

The patient’s cardinal symptoms are muscle stiffness, pain, and cold-induced weakness since childhood. The presence of paradoxical myotonia (worsening with activity), eyelid myotonia, prominent upper limb and face involvement, extreme sensitivity to cold, and widespread myotonic discharges on needle EMG makes PC a likely diagnosis (see discussion). Specialized EDX testing (short exercise test) and genetic testing helped establish the diagnosis.

DISCUSSION

Myotonic disorders have in common a peculiar clinical phenomenon of delayed skeletal muscle relaxation following a trigger such as voluntary muscle contraction or percussion.
Clinical myotonia is associated with needle EMG recordings of runs of repetitive positive waves or fibrillation potentials representing repetitive muscle fiber action potentials. Typical myotonic discharges demonstrate waxing and waning of both amplitude and frequency, producing a peculiar sound that is compared to a dive bomber or a revving chain saw. Patients with myotonia usually report stiffness and difficulty relaxing muscles. Eyelid myotonia can lead to difficulty opening the eyes causing a squint that may last for minutes. Parents might report a child is having difficulty opening the eyes when crying. Lid lag phenomenon is noted with downward gaze after sustained upward gaze. The patient will appear as if staring or having a frightened look. Stiffness in the legs may cause tripping and falls.

On examination, action myotonia is elicited by having the patient forcefully close the eyes or make a tight fist while observing for difficulty relaxing the muscles. This is repeated successively three to four times. Usually repeated activity will improve the myotonia; a phenomenon referred to as “warm-up.” This is in contrast with paramyotonia (paradoxical myotonia) where repeated activity worsens the myotonia.

Percussion myotonia is evoked by tapping the thenar eminence or the posterior forearm (wrist extensor) muscles with a reflex hammer. Tongue myotonia is elicited by tapping the tongue lightly between two tongue blades while observing for a contraction resembling a ring.

Myotonic disorders are divided into myotonic dystrophies and nondystrophic myotonias. Myotonic dystrophies were described earlier in this course. The term “nondystrophic myotonias” is used to refer to an inherited group of skeletal muscle channelopathies characterized by muscle stiffness and EDX evidence of myotonic discharges. In contrast to the myotonic dystrophies, this group of disorders lack progressive weakness and extramuscular manifestations (cardiac, ocular, respiratory, gastrointestinal, and endocrine). Occasionally, differentiating an early dystrophy, particularly myotonic dystrophy type 2, from nondystrophic myotonia can be challenging. Subgroups of nondystrophic myotonia are identified based on the clinical and EDX phenotype, channel involved, and genetic mutation (Table). The advances in the understanding of the molecular and genetic pathogenesis have helped to simplify the approach to patients with these disorders. The clinical phenotype and EDX pattern are useful in determining the channel involved and thus guide the genetic testing.

The nondystrophic myotonias are divided into two major groups based on the type of ion channel involved: chloride and sodium channelopathies. The chloride channelopathies include patients with autosomal recessive (AR) MC (Becker’s disease) and patients with autosomal dominant (AD) MC (Thomsen’s disease). The sodium channelopathies encompass two groups of disorders: PC and sodium channel myotonias (SCMs). In addition to the muscle stiffness, PC is characterized by concomitant episodes of extreme cold sensitivity and cold-induced weakness. This helps differentiate it from the sodium channel myotonias, a group that shares lack of cold sensitivity and potassium aggravation, hence the name “potassium aggravated myotonia.” Several subtypes (myotonia fluctuans, myotonia permanens, and acetazolamide responsive myotonia) were described based on the clinical phenotype. Subsequently, sodium channel mutations were identified in patients with all the clinical phenotypes.

In addition to the primary myotonic disorders described above, other disorders with occasional myotonia were described. These are primarily myotonic discharges seen on needle EMG without clinical myotonia. Examples include acid maltase deficiency, hypothyroidism, and inflammatory myopathies as well as the effects of medications such as colchicine, statins, and clofibrate. However, it should be noted that in some of these cases, complex repetitive discharges might be mistaken for myotonic discharges.

### Chloride Channelopathies

#### Myotonia Congenita

Myotonia congenita is the most common skeletal muscle ion channelopathy. It is caused by mutation in the CLCN1 gene on chromosome 7q35, which encodes the skeletal muscle chloride channel 1. Chloride control resting membrane potential and impairment of chloride conductance in patients with MC shift.
needed, as one of the pitfalls for genetic testing is the presence of many uncommon pathogenic mutations. Thus, one should be cautious interpreting commercial testing limited only to common mutations. Also, a recent trial showed 6% of a MC cohort with a single recessive mutation has an exon deletion or duplication.14 It is important to counsel patients on the effect of the activity and cold exposure. Genetic counseling should be offered as well. Many patients might not require drug treatment for the myotonia. However, those with disabling symptoms will benefit from therapy. A Cochrane Review concluded a lack of good-quality data to allow for specific recommendations.13 Many specialists consider mexiletine, an anti-arrhythmic drug, as the drug of choice for treatment of myotonia. It is proven safe and well tolerated in a recent study by the Consortium for Clinical Investigation of Neuromuscular Channelopathies. The data was presented at the 2012 American Academy of Neurology annual meeting showing that mexiletine at a dose of 200 mg three times daily is effective therapy for symptoms and signs of myotonia in patients with nondystrophic myotonias.16 Because of the drug’s potential to cause prolonged QT and cardiac arrhythmia, an initial electrocardiogram and close cardiac monitoring for prolonged QT are needed. Other side effects include gastrointestinal, dizziness, and tremors. Other medications used with variable results are flecainide, dilantin, and carbamazepine.

**Sodium Channelopathies**

Paramyotonia Congenita

Paramyotonia congenita is an AD disease caused by a mutation in the SCN4A gene on chromosome 17q23, which encodes the alpha subunit of the voltage-gated sodium channel.17 It is allelic with hyperkalemic periodic paralysis, hypokalemic periodic paralysis type 2, and sodium channel myotonias. Though myotonia is seen in 75% of hyperkalemic periodic paralysis patients, the most prominent clinical picture is weakness.18 Described by Eulenberg in the 19th century,19 PC usually manifests in the first decade of life. The myotonia is more prominent in the arms, face, and tongue. Muscle hypertrophy is less common compared to patients with MC. Some of the main features that help differentiate PC from MC are paradoxical myotonia (worsens with repeated activity), extreme cold sensitivity, and cold-induced weakness lasting up to few hours (Table). Some patients complain of muscle pain, though it is usually mild. In general, clinical features are helpful in differentiating the various types of nondystrophic myotonias but there is significant overlap and thus mutation analysis is required to reach a specific diagnosis.

Serum CK is usually normal or mildly elevated. Needle EMG shows myotonic discharges. A recent study described other discharges, including dolphin-sounding low amplitude (100-600 μV), high frequency musical 150-250 Hz discharges in large limb muscles.13 Also higher amplitude tornadoe-shaped, neuromyotonia-like discharges are noted in some patients.13 The short exercise test shows a gradual and relatively prolonged decrement after brief exercise, indicative of pattern I.11 The decrement increases with repeated trials and with cooling reflective of the clinical worsening noted with repeated activity and cold.12 Confirmation of the diagnosis is made by establishing a pathogenic mutation in the SCN4A gene (www.genetests.org). Patients should receive
counseling on the effect of exercise, repeated activity, and cold as well as genetic counseling. Mexiletine can be used for symptomatic treatment.

Sodium Channel Myotonia

Sodium channel myotonia is caused by a mutation in the SCN4A gene on chromosome 17q23, which encodes the alpha subunit of the voltage-gated sodium channel. The disorder is allelic with PC, hyperkalemic periodic paralysis, and hypokalemic periodic paralysis type 2. It encompasses a group of various disorders, including myotonia fluctuans, myotonia permanens, and acetazolamide-responsive myotonia.\textsuperscript{20-23} All share the tendency to worsen with potassium ingestion and lack of cold sensitivity. In addition, other characteristics that help differentiate the group from MC patients are a delayed onset myotonia after exercise (10-30 min) and a more frequent occurrence of eye closure myotonia and muscle pain.\textsuperscript{3,10} Furthermore, transient weakness at initiation of movement reported with MC and cold-induced weakness reported with PC are not seen.\textsuperscript{2} Similar to other nondystrophic myotonia types, the clinical features are helpful in differentiating the subtypes; however, there is overlap, making genetic confirmation necessary.

Serum CK is normal to mildly elevated. Needle EMG showed diffuse myotonic discharges. The short exercise test shows a normal response, indicative of pattern III. Patients should receive genetic counseling and advice to avoid food rich in potassium. Mexiletine can be used for symptomatic treatment. Acetazolamide is helpful in some patients.

**CASE PRESENTATION FOLLOWUP**

The patient short exercise test showed a progressive CMAP decline with repeated trials. Genetic testing confirmed a sodium gene mutation SCN4 (threonine > methionine; codon 1313, nucleotide 3938) establishing the diagnosis of PC in the patient. The patient received mexiletine; however, she had difficulty tolerating the medicine because of dyspepsia and dizziness. The patient short exercise test showed a progressive CMAP decline with repeated trials. Genetic testing confirmed a sodium gene mutation SCN4 (threonine > methionine; codon 1313, nucleotide 3938) establishing the diagnosis of PC in the patient. In retrospect, the patient’s old records indicate a diagnosis of possible PC.

REFERENCES


**Neuromuscular Vignettes**

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Assistant Professor, Neurology  
Harvard Medical School  
Boston, Massachusetts

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**VIGNETTE ONE**

A 34-year-old man was evaluated for pain in feet. He described the sensation as if a hot towel were wrapped around his feet. There was no weakness. Review of systems revealed dry eyes, blurred vision, and lightheadedness. He was evaluated for intermittent abdominal pain and vomiting without nausea. He has also had episodes of erectile dysfunction.

His cranial nerve examination was normal. He has normal tone, bulk, and strength. Sensory examination revealed normal light touch, pinprick, vibration, and joint position sense. Reflexes were absent in ankles only. Cerebellar examination was normal.

Questions

1A. What is the clinical pattern of his symptoms and signs?
   - B. Sensory with upper motor neuron signs.
   - C. Severe proprioceptive deficit.
   - D. Sensory and autonomic.

1B. What other information would be helpful?
   - B. Ethnic background.
   - C. Family history.
   - D. All of the above.

1C. What other studies would be MOST useful?
   - A. Genetic testing.
   - B. Cardiac echocardiogram.
   - C. Autonomic testing.
   - D. Serum immunofixation.

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**VIGNETTE TWO**

A 43-year-old man, with a history of papillary thyroid cancer, developed right arm abduction weakness after surgical resection. He was referred to the EMG Laboratory for evaluation. He has weakness in right abduction only. Sensory examination and reflexes were normal.
Questions

2A. What is the cause of his weakness?
   A. Spinal accessory neuropathy.
   B. Axillary neuropathy.
   C. Brachial plexopathy.
   D. Cervical radiculopathy.

Routine nerve conduction studies (NCSs) and needle electromyography (EMG) of the right arm is normal.

2B. What other studies should be performed?
   A. Spinal accessory nerve motor study.
   B. Needle examination of the trapezius.
   C. Needle examination of the sternocleidomastoid.
   D. All of the above.

Below are the results of the patient’s electrodagnostic (EDX) studies.

Motor NCSs

<table>
<thead>
<tr>
<th>Nerve and site</th>
<th>Lat (ms)</th>
<th>Amp (mV)</th>
<th>Dur (ms)</th>
<th>Area (mVms)</th>
<th>Temp (°C)</th>
<th>Lat diff (ms)</th>
<th>Dist (mm)</th>
<th>CV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median R to abductor pollicis brevis R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>3.5</td>
<td>12.7</td>
<td>6.2</td>
<td>48.3</td>
<td>33.5</td>
<td>3.5</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Elbow</td>
<td>8.2</td>
<td>12.3</td>
<td>6.3</td>
<td>46.6</td>
<td>33.3</td>
<td>4.7</td>
<td>240</td>
<td>51</td>
</tr>
<tr>
<td>Ulnar R to abductor digiti minimi (manus) R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>3</td>
<td>8.4</td>
<td>7.8</td>
<td>27.1</td>
<td>33.3</td>
<td>3</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Below elbow</td>
<td>7</td>
<td>7.6</td>
<td>7</td>
<td>23.6</td>
<td>33.7</td>
<td>4</td>
<td>235</td>
<td>59</td>
</tr>
<tr>
<td>Above elbow</td>
<td>9.5</td>
<td>7.2</td>
<td>7.1</td>
<td>23.6</td>
<td>33.8</td>
<td>2.5</td>
<td>160</td>
<td>64</td>
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<td>Accessory (spinal) R to trapezius R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>2.5</td>
<td>3.1</td>
<td>14.8</td>
<td>26</td>
<td>33.2</td>
<td>2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accessory (spinal) L to trapezius L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck</td>
<td>2.2</td>
<td>7.3</td>
<td>15.2</td>
<td>72.2</td>
<td>33.1</td>
<td>2.2</td>
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</table>

F-Wave studies

<table>
<thead>
<tr>
<th>Nerve</th>
<th>M-Lat (ms)</th>
<th>F-Lat (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median R</td>
<td>3.7</td>
<td>29.2</td>
</tr>
<tr>
<td>Ulnar R</td>
<td>3.1</td>
<td>30.6</td>
</tr>
</tbody>
</table>

2C. What are the consequences of injury to the spinal accessory nerve?
   A. Lateral and upward displacement of the scapula.
   B. Drooping of the shoulder.
   C. Asymmetric shoulder shrug.
   D. All of the above.
### Sensory NCSs

<table>
<thead>
<tr>
<th>Nerve and site</th>
<th>Onset lat (ms)</th>
<th>Peak lat (ms)</th>
<th>Amp (μV)</th>
<th>Temp (°C)</th>
<th>Lat diff (ms)</th>
<th>Dist (mm)</th>
<th>CV (m/s)</th>
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</thead>
<tbody>
<tr>
<td>Median R to digit II (index finger) R</td>
<td>2.3</td>
<td>3.1</td>
<td>33</td>
<td>33.9</td>
<td>2.3</td>
<td>130</td>
<td>57</td>
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<tr>
<td>Ulnar R to digit V (little finger) R</td>
<td>1.9</td>
<td>2.7</td>
<td>23</td>
<td>34</td>
<td>1.9</td>
<td>110</td>
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<tr>
<td>Radial R to anatomical snuff box R</td>
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<td>2.3</td>
<td>25</td>
<td>33.9</td>
<td>1.8</td>
<td>100</td>
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<td>Lateral antebrachial cutaneous R to forearm R</td>
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<td>2.8</td>
<td>18</td>
<td>33.8</td>
<td>2.2</td>
<td>130</td>
<td>59</td>
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<tr>
<td>Medial antebrachial cutaneous R to forearm R</td>
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<td>2.8</td>
<td>10</td>
<td>33.8</td>
<td>2.3</td>
<td>130</td>
<td>57</td>
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<tr>
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<td>2.8</td>
<td>15</td>
<td>33.3</td>
<td>2.3</td>
<td>130</td>
<td>57</td>
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<tr>
<td>Medial antebrachial cutaneous L to Forearm L</td>
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<td>2.9</td>
<td>9</td>
<td>33.3</td>
<td>2.5</td>
<td>130</td>
<td>52</td>
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### Needle EMG Examination

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Insertion activity</th>
<th>Spontaneous activity</th>
<th>Volitional MUAPs</th>
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<tr>
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<tr>
<td>Biceps brachii R</td>
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<td>None</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Pronator teres R</td>
<td>Normal</td>
<td>None</td>
<td>None</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>First dorsal interosseous R</td>
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<tr>
<td>Trapezius R</td>
<td>2+</td>
<td>None</td>
<td>Normal</td>
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<td>Many</td>
</tr>
<tr>
<td>Sternocleidomastoid R</td>
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<td>Normal</td>
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</table>
VIGNETTE THREE

A 66-year-old man was evaluated for progressive walking difficulty over several months. He noticed the onset of tingling in his toes. He felt like he was walking as if he was drunk. He had intermittent falls.

His examination revealed normal tone, bulk, and strength. Vibration was absent in toes and joint position sense was mildly reduced in toes. His reflexes were 3+ in the upper extremities and 2+ in the lower extremities. His toes were upgoing.

Questions

3A. What is the clinical pattern of his symptoms and signs?
   A. Distal sensory loss.
   B. Sensory with upper motor neuron signs.
   C. Severe proprioceptive deficit.
   D. Sensory and autonomic.

3B. Which conditions lead to subacute combined degeneration?
   A. Nitrous oxide abuse.
   B. Vitamin B12 deficiency.
   C. Copper deficiency.
   D. All of the above.

Laboratory and examination results showed the following:
- EDX studies: Absent bilateral sural responses only.
- C-spine magnetic resonance imaging: Mild degenerative changes.
- Vitamin B12, homocysteine, and methylmalonic acid levels: Normal.
- Copper: 62 (normal 85-155) mcg/dL.
- Ceruloplasmin: 30 (normal 22-58) mg/dL.
- Zinc: 120 (normal 50-155) mcg/dL.

3C. What other history would be helpful?
   A. Gastric surgery.
   B. Excessive zinc ingestion.
   C. Malabsorptive enteropathies.
   D. All of the above.

VIGNETTE FOUR

A 53-year-old man had insidious onset of difficulty speaking and swallowing. He complains of a hoarse voice, along with loss of muscle mass in all his limbs. He was originally told by another neurologist (who was not a member of the American Association of Neuromuscular and Electrodiagnostic Medicine) that he had amyotrophic lateral sclerosis (ALS) and had “only a few years to live.” He is referred to you for a second opinion and some management issues.

Physical examination showed diffuse muscle wasting and multiple fasciculations. You also note hyporeflexia and what appears to be an intention tremor. There was also diminished fine motor movement, and a “floppy head.”

Questions

3A. Which additional finding is he also MOST LIKELY to have?
   A. Ashworth grade II spasticity.
   B. Cogwheel rigidity in his extremities.
   C. Gynecomastia.
   D. Oculomasticatory myorhythmia.

Hyperhidrosis and allodynia

The patient is not able to elevate the soft palate and has markedly atrophy and decreased tongue movement. Having recently passed the American Board of Electrodiagnostic Medicine examination, you are confident in your needle EMG skills and decide to restudy this man. Needle EMG showed acute and chronic denervation with fasciculations; peripheral NCSs showed decreased amplitude of compound motor action potentials but no conduction slowing.

CERVICAL COLLARS IN NEUROMUSCULAR DISEASE

Individuals with neck extensor muscle weakness may complain of neck stiffness, heaviness, and fatigue in holding the head up, and they may also notice difficulties in keeping the head upright with unexpected movements. In the later stages, and in cases of severe muscle weakness, the head drops forward, the cervical spine is completely flexed, and the patient experiences severe neck pain and anterior muscle tightness.

Several different types of collars that can support the head, protect the weakened muscles, and prevent further deformity are available. For mild-to-moderate weakness a soft foam collar is usually recommended. Soft collars are usually comfortable and well-tolerated, and neck movements are limited to a certain degree.

For moderate-to-severe weakness, a semi-rigid collar, such as the traditional Philadelphia™ collar, is required. Patients find these collars very warm, may experience discomfort at points of contact and pressure over the trachea, or may feel confined. If the individual has a tracheostomy, a Miami-J®, Aspen, or Malibu collar that allows for anterior neck access are prescribed. Warmth, discomfort, and a sense of confinement are also common with these collars. The Headmaster, Executive, and Canadian collars have an open air design, but do not control as well for lateral instability as the Miami-J®, Aspen, or Malibu collars. In practice, the Headmaster collar is well accepted by many patients and is a compromise.
or block. However, you had great difficulty obtaining any sensory nerve action potentials.

4B. What is his LIKELY diagnosis?
A. Amyotrophic lateral sclerosis.
B. Multi-focal motor neuropathy.
C. Spinal muscular atrophy III (Kugelberg-Welander syndrome).
D. Spinobulbar muscular atrophy (Kennedy disease).
E. Guillain-Barré syndrome

4C. The patient has tremendous difficulty holding his head up and really wants help with this. What type of collar might work BEST in this situation?
A. Freeman or Headmaster type cervical orthosis.
B. Minerva brace.
C. Halo type orthosis.
D. The “Iron Maiden” neck stabilizer.

VIGNETTE FIVE

A 9-year-old boy presents to the neuromuscular clinic for evaluation and management. The family is from Mexico and the parents do not speak English. The boy speaks limited English. You are able to ascertain through an interpreter that he had an older brother who died of pneumonia when he was 18 years old. He also had a maternal uncle who died “very young” from some type of heart problem. The boy is now having progressive difficulties walking and is falling all the time at school now. On examination you note reflexes are 1+ in the arms and absent in the legs, with pinprick and vibratory sensation intact. The boy has a distinct waddle when he walks and is up on his toes.

Questions

5A. Based on the photograph above, what additional findings does he also have?
A. Hyperlordotic positioning of the spine with heel cord tightness.
B. Severe pectus excavatum.
C. Kyphosis with a secondary curve less than 20 degrees.
D. Scoliosis with a curve that likely exceeds 50 degrees and forced vital capacity (FVC) is < 25% predicted value, which is not corrected with spinal instrumentation.

5B. Knowing that he has a serum creatine kinase level of 20,000 U/L at rest, what is the BEST next test to perform in order to arrive at a definitive diagnosis?
A. EDX evaluation including single fiber EMG.
B. Forearm ischemic exercise testing.
C. DNA evaluation.
D. Muscle biopsy through needle aspiration.

5C. One year later spinal radiographs reveal scoliosis with a primary curve exceeding 25 degrees and FVC is < 50% predicted value. What is the next management course?
A. Aggressive spinal manipulation to reduce the curvature.
B. Referral to a pediatric spine surgeon for spinal fusion and instrumentation.
C. Fitting with a custom molded spinal orthosis.
D. Proprioceptive neuromuscular stretching through a neurodevelopmental therapist.

5D. When is spinal instrumentation in boys like this indicated?
A. Any time before the age of skeletal maturity.
B. When the primary curve exceeds 25 degrees and FVC is < 50% predicted value.
C. When the primary curve is less than 25 degrees.
D. Never because scoliosis is not corrected with spinal instrumentation.
E. Never because scoliosis is best corrected with bracing.

VIGNETTE SIX

A 28-year-old man presents with a 5-7 year history of slowly progressing weakness beginning in the distal limb muscles but now affecting his hands. He is starting to notice muscle wasting. He also remembers that as a child he was always clumsy or not very athletic.

He now notes that he is having great difficulty walking and he frequently trips due to catching his feet. Frequent ankle sprains and falls are also a problem for him.

On examination, his reflexes are absent throughout. He demonstrates 4/5 strength in most major muscle groups. After walking for several minutes he does start to drag his feet.
Questions

6A. Which type of bracing modality is MOST LIKELY to improve his gait?

A. Custom fit shoe orthotics with metatarsal pads.
B. Bilateral double metal upright ankle-foot orthotics (AFOs).
C. Lightweight, low profile AFOs with dorsiflexion assist.
D. Bilateral long leg, double metal upright knee ankle-foot orthotics (KAFOs).
E. Bilateral universal foot orthotics (UFOs).

6B. Which factor is MOST LIKELY to contribute to loss of ambulation in a patient with peripheral neuropathy?

A. Progressive dyspnea.
B. Weakness in the quadriceps muscles (< 3/5 on manual muscle testing).
C. Severe atrophy in the cerebellum.
D. Loss of pain sensation.
E. Weakness (< 4/5) in tibialis anterior muscles.

6C. Which gait description BEST characterizes his walking?

A. Toe walking.
B. A steppage gait, where the patient lifts their legs in an exaggerated fashion to clear the feet off the ground.
C. A reverse Trendelenberg gait caused by gluteus medius weakness.
D. A shuffling gait due to impaired proprioception.
E. A VIP gait often noted in executives and politicians.

6D. Regarding orthotics in peripheral neuropathy, which statement is the MOST appropriate and correct?

A. Custom fit shoe orthotics with metatarsal pads are most helpful in terms of improving balance.
B. Bilateral KAFOs are generally too heavy and cumbersome to be of much use.
C. UFOs cannot be used outside of Area 51.
D. Bilateral double metal upright AFOs are often preferred by patients as they provide excellent medial-lateral ankle support and stability.
E. Upper extremity orthotics are easy to use and very helpful for patients with peripheral neuropathy.

A 57-year-old woman is referred to your office with slowly progressive weakness in both proximal and distal muscles. She is much weaker on the left side of her body with striking asymmetry. She has remarkable weakness of the wrist and finger flexors, disproportionate to that of her extensors (see image). Hence, she has loss of finger dexterity and grip strength.

Questions

7A. All of the following are likely additional symptoms, EXCEPT:

A. Dysphagia.
B. “Floppy neck” syndrome.
C. Myalgias and cramping.
D. Sensory and autonomic dysfunction.

DEVICES TO ASSIST WITH WALKING: MOBILITY AIDS

Muscle weakness and resultant balance problems will eventually necessitate that a patient use an aid to enhance mobility and safety. The type of assistive device recommended is determined by the degree of lower extremity (LE) and trunk weakness and spasticity, range of motion and strength of the upper extremities (UEs), extent and rate of progression of the disease, acceptance of the aid by the individual, and economic constraints. In addition to taking into account which device will ensure optimal function and safety, the weight of the mobility aid is an important factor to consider in decisionmaking, as individuals with amyotrophic lateral sclerosis (ALS) experience muscle fatigue.

Canes

Canes are usually recommended in the early stages of ALS for mild LE weakness or balance problems, as they provide the least amount of support. A cane is carried in the hand opposite to the most affected leg, requires good UE strength, and can be used on stairs. The standard wooden cane is the least expensive, has a curved handle, and can be made shorter but not longer. An adjustable aluminum cane easily adapts for various heights and is lightweight. An aluminum cane may have a curved handle or an offset handle. An offset handle allows the weight to be directed over the cane tip when in contact with the floor, rather than anteriorly, as is the case with a curved handle. Quad canes are aluminum canes with four points of floor contact. Quad canes provide greater stability than straight canes, but all tips must be in contact with the ground for stability. The size of base can vary and these canes are heavier to lift. Aluminum and quad
Canes come in a variety of styles and sizes of handgrips. Patients with hand muscle weakness may be better able to grip an enlarged or molded handle.

Crutches

In general, crutches are rarely recommended for individuals with ALS, as the patient must have very good UE and trunk strength as well as adequate balance to use them. If crutches are recommended, Lofstrand or Canadian crutches are preferred. These crutches consist of a single upright, a forearm cuff, and a handgrip; the hands can be freed for standing tasks without having to release the crutch.

Walkers

Walkers provide greater support than canes and crutches, but are more bulky and may be cumbersome in confined spaces. Various types of walkers are available (e.g., folding, with or without wheels, with brakes, with seating surfaces, etc.) and some walkers can be modified to suit the individual’s walking environment and needs; for example, they may be fitted with a basket, food tray, or forearm trough. Standard aluminum walkers are the least expensive, very stable, and can be adjusted for various heights. However, they must be picked up and lowered during ambulation, and patients may find them heavy to lift. Walkers with wheels do not need to be lifted and they roll forward easily, thus they are usually recommended for patients with ALS; however, the stability of wheeled walkers is decreased and they may move forward too quickly. Some walkers come equipped with brakes. Push down brakes secure a walker when the patient loads his or her weight on the walker and are preferred over squeeze type brakes for patients with hand weakness. Specialized wheeled walkers are the most expensive. They have large wheels that can move over a variety of terrains.

7B. She continues to have slow but relentless progression of muscle weakness and is now having difficulty with ambulation and frequent falls. What one examination/test should you be sure to perform?

A. Bone density scan to assess for osteoporosis.
B. Hemoglobin A1c blood test to rule out diabetes.
C. Ophthalmology examination to assess for cataracts.
D. Hepatobiliary iminodiacetic acid scan to assess for gall bladder sludging.

7C. What is the MOST LIKELY cause of her difficulty in walking?

A. Weakness in her spinal extensor musculature.
B. Loss of proprioception.
C. Weakness in her quadriceps muscles.
D. Loss of full field of vision.

7D. You want to prescribe something to assist her in walking. What would be BEST to reduce her risk of falling?

A. Single point cane.
B. Front wheeled walker.
C. Quad (four-point) cane.
D. A hemi walker.

VIGNETTE EIGHT

A 40-year-old woman presents with 2 weeks of burning and tingling pain in her fingers and toes followed by progressive leg weakness. She also has a 2-year history of repetitive vomiting and diffuse abdominal pain. On examination, she has severe distal lower extremity weakness with bilateral foot drop, distal sensory loss in a stocking-glove pattern, and absent deep tendon reflexes. Her skin is diffusely hyperpigmented. Laboratory studies are significant for a hematocrit of 28% with a mean corpuscular volume of 85 fl. Basophilic stippling is present. Chest X-ray shows an ill-defined hyperdensity overlying the gastric bubble. Nerve conduction studies show symmetrically reduced peroneal and tibial CMAP amplitudes with normal conduction velocities, reduced sural SNAP amplitudes with normal conduction velocities, and normal NCSs in the arms. Needle EMG shows fibrillation potentials and reduced recruitment in tibialis anterior, extensor hallucis longus, and gastrocnemius, but is otherwise normal.

Questions

8A. Which of the following is the MOST LIKELY diagnosis?

A. Acute intermittent porphyria.
B. Arsenic intoxication.
C. Guillain-Barré syndrome.
D. Fabry’s disease.
E. Polyarteritis nodosa

8B. Which of the following statements concerning this patient is TRUE?

A. She is likely to have diffuse hair loss.
B. Her transaminases should be normal.
C. Mees’ lines (leukonychia) are a frequent finding.
D. Motor symptoms are more likely to precede sensory symptoms.
E. Recent fish consumption may result in an increase in the measured arsenic level.

8C. Which of the following is the MOST appropriate for this patient?

A. Chelation with dimercaprol.
B. Gastrointestinal lavage.
C. Hematin and glucose.
D. Intravenous immunoglobulin.
E. Prednisone.

VIGNETTE NINE

An 18-month-old girl (see photo) presents for evaluation of weakness. She has a previous history of neonatal hypotonia, with respiratory failure requiring intubation and developmental delay. On physical examination, she has a long face, bilateral facial weakness, open jaw, bilateral ptosis, and moderate distal-greater-than-proximal muscle weakness. Hand-grip and percussion myotonia are present.
Questions

9A. What is the MOST LIKELY diagnosis?

A. Facioscapulohumeral dystrophy.
B. Myotonic dystrophy type 1.
C. Myotonic dystrophy type 2.
D. Myotonia congenita.
E. Slow-channel syndrome.

9B. How did this patient MOST LIKELY inherit this disorder?

A. Autosomal dominant, from her father.
B. Autosomal dominant, from her mother.
C. Autosomal recessive, from her father.
D. Autosomal recessive, from her mother.
E. It is X-linked recessive.

9C. What is the LIKELY number of CTG repeats in the DMPK gene in this patient?

A. < 30.
B. 50.
C. 100.
D. 250.
E. 1,000.

VIGNETTE TEN

A 63-year-old man presents with left shoulder pain and atrophy. Two years ago, while lifting weights, he noticed the sudden onset of left shoulder pain without radiation. The pain did not improve on its own, so he began physical therapy. After 20 sessions, his pain had improved, but he also noticed that his left deltoid was becoming atrophic. Directed neurological examination shows atrophy of the left deltoid. Strength is normal with the exception of left shoulder abduction which is 4/5 and left external shoulder rotation which is 5−/5. There were no reflex asymmetries. Sensation was minimally decreased over the lateral left shoulder. Needle EMG and NCSs show the following:

**Sensory NCSs**

<table>
<thead>
<tr>
<th>Nerve/sites</th>
<th>Recording site</th>
<th>Onset (ms)</th>
<th>Peak (ms)</th>
<th>NP amp (μV)</th>
<th>Temp (°C)</th>
<th>Dist (cm)</th>
<th>Vel (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left median</td>
<td>Wrist Digit II</td>
<td>2.7</td>
<td>3.5</td>
<td>20.1</td>
<td>14</td>
<td>51.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wrist Digit V</td>
<td>2.35</td>
<td>3.65</td>
<td>14.3</td>
<td>32.4</td>
<td>12.4</td>
<td>52.8</td>
</tr>
</tbody>
</table>

NP amp = negative peak amplitude, Dist = distance, Temp = temperature, Vel = velocity

**Motor NCSs**

<table>
<thead>
<tr>
<th>Nerve/sites</th>
<th>Recording Site</th>
<th>Lat (ms)</th>
<th>Amp (mV)</th>
<th>Area (mVms)</th>
<th>Temp (°C)</th>
<th>Dist (cm)</th>
<th>Vel (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left median, APB</td>
<td>Wrist APB</td>
<td>3.65</td>
<td>11.6</td>
<td>43.4</td>
<td>32</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elbow APB</td>
<td>7.95</td>
<td>11.6</td>
<td>41</td>
<td>22.4</td>
<td>52.1</td>
<td></td>
</tr>
<tr>
<td>Left ulnar, ADM</td>
<td>Wrist APB</td>
<td>2.7</td>
<td>14.9</td>
<td>45.9</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Below Elbow APB</td>
<td>6.7</td>
<td>13.9</td>
<td>45.5</td>
<td>22.9</td>
<td>57.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Above Elbow APB</td>
<td>7.85</td>
<td>12.4</td>
<td>41.9</td>
<td>7.2</td>
<td>62.6</td>
<td></td>
</tr>
</tbody>
</table>

ADM = abductor digiti minimi, Amp = amplitude, APB = abductor pollicis brevis, Dist = distance, Lat = latency, Temp = temperature, Vel = velocity

**F Wave Studies**

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Fmin (ms)</th>
<th>Fmax (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left median, APB</td>
<td>31.15</td>
<td>31.65</td>
</tr>
<tr>
<td>Left ulnar, ADM</td>
<td>30.55</td>
<td>33.6</td>
</tr>
</tbody>
</table>

ADM = abductor digiti minimi, APB = abductor pollicis brevis

**Needle EMG Summary Table**

<table>
<thead>
<tr>
<th>Spontaneous</th>
<th>MUAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertional</td>
<td></td>
</tr>
<tr>
<td>Fib</td>
<td>Fasc</td>
</tr>
<tr>
<td>Left deltoid</td>
<td>Increased</td>
</tr>
<tr>
<td>Left biceps</td>
<td>Normal</td>
</tr>
<tr>
<td>Left triceps</td>
<td>Normal</td>
</tr>
<tr>
<td>Left teres minor</td>
<td>Normal</td>
</tr>
<tr>
<td>Left infraspinatus</td>
<td>Normal</td>
</tr>
<tr>
<td>Left rhomboid major</td>
<td>Normal</td>
</tr>
<tr>
<td>Left C5 PSP</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Amp = amplitude, CRD = complex repetitive discharges, Dur = duration, Fib = fibrillation, Fasc = fasciculation, PSP = paraspinal, PSW = positive sharp wave
Questions

10A. What is the MOST LIKELY localization of this lesion?
   A. Axillary nerve.
   B. C5 nerve root.
   C. Lateral cord of brachial plexus.
   D. Musculocutaneous nerve.
   E. Upper trunk of brachial plexus.

10B. Which of the following sensory NCSs would help to distinguish this condition from an upper trunk brachial plexopathy?
   A. Lateral antebrachial cutaneous nerve.
   B. Medial antebrachial cutaneous nerve.
   C. Median nerve, recording at digit III.
   D. Ulnar nerve.
   E. None of the above.

10C. What is the MOST LIKELY site of nerve entrapment in this case?
   A. Arcade of Frohse.
   B. Quadrilateral space.
   C. Spinoglenoid notch.
   D. Suprascapular notch.
   E. Thoracic outlet.

When the patient’s medical records arrive, you learn that he had been given bortezomib to treat his multiple myeloma.

11B. Which of the following is TRUE about the development of polyneuropathy secondary to this medication?
   A. It is an acute-onset neuropathy characterized by paresthesias, allodynia, and cold hypersensitivity.
   B. Symptoms resolve immediately upon discontinuation of bortezomib.
   C. The neuropathy usually presents within the first five cycles of administration.
   D. The neuropathy appears several months after completion of chemotherapy.
   E. It is difficult to distinguish from POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome on electrophysiologic grounds.

11C. Which of the following agents is effective in prophylaxis of bortezomib-induced neuropathy?
   A. Calcium.
   B. Magnesium.
   C. Amitryptiline.
   D. Alpha lipoic acid.
   E. None of the above.