

Neuromuscular Update I: Updates on Genetics of Nerve and Muscle Disease

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Objectives

Objectives - Participants will acquire skills to (1) Explain how to manage respiratory symptoms in NM conditions, (2) evaluate and treat autonomic disorders, and (3) quickly assess and answer questions about common clinical NM scenarios.

Target Audience:

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

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Neuromuscular Update I: Updates on Genetics of Nerve and Muscle Disease

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Neuromuscular Update I: Updates on Genetics of Nerve and Muscle Disease

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Respiratory Muscle Aids to Avert Respiratory Failure and Tracheostomy: A New Patient Management Paradigm

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INTRODUCTION: A CASE STUDY

In 1990, an 18-year-old boy with Duchenne muscular dystrophy (DMD) documented by biopsy and DNA analysis, and who was wheelchair dependent at age 10, developed acute respiratory failure during an otherwise benign chest infection and was intubated in a local hospital. This occurred although he had been previously instructed in how to use a mouthpiece and nasal intermittent positive pressure ventilation (IPPV) and he air stacked daily. While intubated his vital capacity (VC) decreased from an 800 ml baseline to 200 ml which meant that he was unweanable and was told that he had to undergo tracheotomy. At this point he was extubated directly to continuous noninvasive IPPV for ventilatory support and aggressive use of mechanically assisted coughing (MAC). Because he knew how to receive IPPV via a simple mouthpiece it was unusually easy. With aggressive MAC, his VC immediately increased to 400 ml but he continued to have no breathing tolerance and airway secretions remained profuse for 5 days, at which point he weaned to nocturnal nasal IPPV and went home using MAC as needed.

In 1996, at age 24, he began to require an ongoing daytime mouthpiece as well as nocturnal nasal IPPV. He had thus far had five chest infections which had been managed at home with the oximetry, respiratory aid protocol (noninvasive IPPV and MAC) and no further hospitalizations. During one such episode, nasal congestion rendered nasal IPPV ineffective and he developed respiratory distress with a PaCO₂ of 55 mmHg. When given the choice between switching to lipseal IPPV or using nasal decongestants, he chose the latter and had no further elevations of EtCO₂ or significant dSaO₂s. Hospitalization was avoided despite temperature elevations to 104°F and leucocytosis during at least three of the five infections and continuous respirator

dependence. He died from his cardiomyopathy at age 48 at home, suddenly, after breakfast, without apparent distress after 24 years of continuous noninvasive ventilatory support.

WHAT ARE PHYSICAL MEDICINE RESPIRATORY MUSCLE AIDS?

Inspiratory and expiratory muscle aids are devices and techniques that involve the manual or mechanical application of forces to the body, or intermittent pressure changes to the airway, to assist inspiratory or expiratory muscle function. The devices that act on the body include body ventilators that create pressure changes around the thorax and abdomen. Negative pressure applied to the airway during expiration assists coughing, just as positive pressure applied to the airway during inhalation (noninvasive intermittent positive pressure ventilation [NIV]) assists the inspiratory muscles. Continuous positive airway pressure (CPAP) does not assist ventilation and is not useful for patients with primarily ventilatory impairment.

PATIENT EVALUATION

Patients with diminished ventilatory reserve who are able to walk commonly complain of exertional dyspnea. Eventually, morning headaches, fatigue, sleep disturbances, and hypersomnolence develop.¹ For wheelchair users, symptoms may be minimal except during intercurrent respiratory infections when they complain of anxiety, inability to fall asleep, and dyspnea. Evaluation necessitates four items: spirometer, peak flow meter, capnograph, and oximeter. VC is measured in sitting and supine positions and

the difference should be less than 7%. Because hypoventilation is worse during sleep, the supine rather than sitting position VC is the most important indicator of ventilatory dysfunction. When it is greater than 20%, orthopnea often indicates the need for nocturnal NIV. Spirometry is also used for monitoring progress with glossopharyngeal breathing (GPB) and air stacking (i.e., retention of a maximum lung volume of aid delivered by manual resuscitator or volume cycling ventilator that can be held by the glottis). The maximum volume is termed the maximum insufflation capacity (MIC). Patients who learn GPB can often air stack consecutive GPB gulps to or beyond the MIC.²

Cough peak flows (CPFs) are measured using a peak flow meter (Access Peak Flow Meter, Healthscan Products Inc., Cedar Grove, New Jersey). CPFs of 160 l/m are the minimum needed to cough effectively,² and this is the best indicator for tracheostomy tube removal irrespective of remaining pulmonary function. Indeed, 40% of patients with amyotrophic lateral sclerosis (ALS) can survive despite continuous ventilator dependence using strictly noninvasive aids.³ Patients with VCs less than 1,500 ml have assisted CPFs measured from a maximally stacked volume of air and with an abdominal thrust delivered simultaneously with glottic opening.⁴ Coughing from a deep air stacked volume with a concomitantly applied abdominal thrust is termed a manually assisted cough.

For the stable patient without intrinsic pulmonary disease, arterial blood gas sampling is unnecessary. Besides the discomfort, 25% of patients hyperventilate as a result of anxiety or pain during the procedure.⁵ Noninvasive continuous blood gas monitoring, including capnography and oximetry, yield more useful information, particularly during sleep for any questionably symptomatic patient.⁶ With decreased VC, multiple nocturnal oxyhemoglobin desaturations below 95%, and elevated nocturnal PaCO₂, a trial of nocturnal NIV is warranted. Since, in general, only patients improperly treated with supplemental O₂ develop CO₂ narcosis, and acute respiratory failure (ARF) is generally caused by ineffective cough and airway secretion management, any patient finding that NIV use is more burdensome than symptoms of ventilatory insufficiency is told that it is alright to discontinue NIV and return for a re-evaluation in 3-6 months.

THE INTERVENTION OBJECTIVES

The intervention goals are to maintain lung and chest-wall compliance as well as to promote normal lung and chest-wall growth for children, maintain normal alveolar ventilation around the clock, and maximize CPFs. The longterm goals are to avert episodes of ARF, especially during intercurrent chest infections; avoid hospitalizations; and prolong survival without resorting to tracheotomy. Unweanable intubated and cannulated patients can be extubated and decannulated to NIV and MAC. All goals can be facilitated by evaluating, training, and equipping patients in the outpatient setting and at home.

LONGTERM MANAGEMENT

Goal One: Maintain Pulmonary Compliance, Lung Growth, and Chest-Wall Mobility

Pulmonary compliance is diminished because the patient can not expand the lungs to predicted inspiratory capacity. As the VC decreases, the largest breath one can take only expands a fraction of lung volume. Like limb articulations, regular mobilization is required to prevent chest-wall contractures and lung restriction. This can only be achieved by providing deep insufflations, air stacking, or nocturnal NIV.⁷ The extent to which the MIC exceeds VC (MIC-VC) objectively quantitates glottic and bulbar-innervated muscle integrity and correlates with the capacity to use noninvasive aids rather than tracheostomy.⁴ Patients who cannot close the glottis and, therefore, cannot air stack, must be passively insufflated using a CoughAssist™ (Respironics International Inc., Murrysville, Pennsylvania), a pressure-cycling ventilator at pressures of 40-70 cmH₂O, or a manual resuscitator with the exhalation valve blocked. The maximum passive insufflation volume can be termed the “lung insufflation capacity.”⁸

The primary objectives of lung expansion therapy are to increase the VC and maximize CPFs, maintain or improve pulmonary compliance, diminish atelectasis, and master NIV.⁸ The deeper lung volumes achieved by air stacking also permit patients to raise voice volume as desired.

Because patients who can air stack are also able to use NIV, any patient who is intubated for respiratory failure can more easily be extubated directly to continuous NIV regardless of ventilator-free breathing ability (VFBA). Before a patient’s VC decreases to 70% of predicted normal, they are instructed to air stack 10-15 times, at least two or three times daily usually using a manual resuscitator. Because of the importance of air stacking, NIV is provided via ventilators using volume rather than pressure cycling, on assist/control mode.

Infants cannot air stack or cooperate with passive insufflation therapy. All babies with spinal muscular atrophy (SMA) type 1, infants with SMA type 2, and others with infantile neuromuscular disease (NMD) who have paradoxical chest-wall movement require nocturnal NIV to prevent pectus excavatum and promote lung growth, as well as for ventilatory assistance.⁹ In addition to nocturnal aid, deep insufflations may be possible by delivering air from a manual resuscitator via an oral-nasal interface and timing the air delivery to the child’s breathing.

Goal Two: Maintain Normal Alveolar Ventilation by Inspiratory Muscle Assistance

Although the inspiratory muscles can be assisted by applying pressures to the body, negative pressure body ventilators cause obstructive apneas, are less effective than NIV, and become less effective with age.¹⁰ Blood gases improve dramatically when switching patients from them to NIV. The intermittent abdominal pressure ventilator, however, is still useful for daytime support.¹¹

Noninvasive Intermittent Positive Pressure Ventilation

NIV can be noninvasively delivered via lipseals, nasal, and oral–nasal interfaces for nocturnal ventilatory support. Mouthpiece and nasal IPPV are open systems that require the user to rely on central nervous system reflexes to prevent excessive insufflation leakage during sleep,^{1,12} thus, supplemental oxygen and sedatives can render NIV ineffective. NIV should be introduced in the clinic or home setting.

There are numerous commercially available nasal interfaces (CPAP masks). Several should be tried and the patient should be encouraged to alternate their use. Excessive insufflation leakage can be avoided by switching to the use of a closed noninvasive system such as a lipseal–nasal prong system. Such interfaces deliver air via mouth and nose during sleep and require minimal strap pressure. This optimizes skin comfort and minimizes air (insufflation) leakage. Excessive leakage is also prevented by sustaining ventilatory drive by maintaining normal daytime CO₂ and avoiding supplemental O₂ and sedatives.

NIV via a 15-mm angled mouthpiece is the most important method of daytime ventilatory support. Some patients keep the 15-mm angled mouthpiece between their teeth all day.¹³ Most have the mouthpiece held near the mouth. A metal clamp attached to a wheelchair can be used for this purpose, or the mouthpiece can be fixed onto motorized wheelchair controls—most often sip and puff, chin, or tongue controls. The ventilator is set for large tidal volumes, often 800–1,500 ml. The patient grabs the mouthpiece with his mouth and supplements or substitutes for inadequate autonomous breath volumes. The patient varies the volume of air taken from ventilator cycle to ventilator cycle and breath to breath to vary speech volume and cough flows as well as to air stack to fully expand the lungs. Some neck movement and lip function are needed to grab the mouthpiece and use it without leaking air. The soft palate must move in the posterocranial direction to seal off the nasopharynx. In addition, the patient must open the glottis and vocal cords, dilate the hypopharynx, and maintain airway patency. These normally reflex movements may require a few minutes to relearn for patients who have been receiving ventilation via a tracheostomy tube.¹⁴

Nasal NIV is most practical for nocturnal use but it is also indicated for infants and for those who can not grab or retain a mouthpiece because of oral muscle weakness, inadequate jaw opening, or insufficient neck movement. Continuous nasal NIV is, nevertheless, a viable and desirable alternative to tracheostomy.^{1,15} Nasal NIV users learn to close their mouths or seal off the oropharynx with their soft palates and tongues to prevent oral insufflation leakage.

Abdominal distention tends to occur sporadically in NIV users. The air usually passes as flatus once the patient is mobilized in the morning. When severe, however, it can increase ventilator dependence and necessitate a rectal tube to decompress the colon or a nasogastric or gastrostomy tube to burp out the air.

Despite aggressive lung mobilization and expansion three times daily—often to over 60 cmH₂O pressures—along with NIV support lasting for over 50 years in many cases, this author has had only one case of pneumothorax in over 1,000 NIV users.

Although often described as a complication or limiting factor for NIV, secretion encumbrance most often results from failure to use MAC.

Goal Three: Assist Expiratory Muscles to Augment Cough Flows

Manually assisted coughing is the use of air stacking for any patient with less than 1,500 ml of VC to precede an abdominal thrust timed to glottic opening.^{4,16} The inability to generate 160 l/m of assisted CPFs despite having a VC or MIC greater than 1 liter indicates upper-airway obstruction often due to severe bulbar-innervated muscle dysfunction and should be evaluated by laryngoscopy and reversible lesions corrected surgically.

MAC is the combination of the use of mechanical insufflation–exsufflation (CoughAssist™) with an exsufflation-timed abdominal thrust. Deep insufflations followed immediately by deep exsufflations at pressures of 40 to –40 cmH₂O are usually the most effective and preferred. MAC can be provided via an oral–nasal mask, a simple mouthpiece, or via a translaryngeal or tracheostomy tube. When delivered via the latter, the cuff, when present, should be inflated. The CoughAssist™ can be manually or automatically cycled. Manual cycling facilitates caregiver–patient coordination of inspiration and expiration with insufflation and exsufflation, but it requires hands to deliver an abdominal thrust, to hold the mask on the patient, and to cycle the machine.

One treatment consists of about five cycles of MAC. In general, 2–4 s are required. Treatment continues until no further secretions are expelled and secretion-related oxyhemoglobin desaturations are reversed. Use can be required as frequently as every 30 min around the clock during chest infections. The use of mechanical insufflation–exsufflation (MI–E) via the upper airway can be effective for children as young as 11 months of age. Routine airway suctioning misses the left main stem bronchus about 90% of the time.¹⁷ MAC provides the same exsufflation flows in both left and right airways without the discomfort or airway trauma of tracheal suctioning. Patients prefer MAC to suctioning for comfort and effectiveness, and they find it less tiring.¹⁸ Deep suctioning, whether via airway tube or via the upper airway, can be discontinued for most patients. VC, pulmonary flow rates, and SpO₂ when abnormal improve immediately with clearing of airway secretions and mucus by MI–E.^{19–21}

Of the three muscle groups required for effective coughing, MI–E can only take the place of the inspiratory and expiratory muscles. Thus, it cannot be used to avert tracheotomy very long if bulbar-innervated muscle function is inadequate to prevent airway collapse and continuous saliva aspiration as often becomes the case in advanced bulbar ALS. On the other hand, patients with completely intact bulbar muscle function, such as most ventilator users with traumatic tetraplegia, can usually air stack to volumes of 3 liters or more, and, unless very scoliotic or obese, a properly delivered abdominal thrust can result in assisted CPFs of 6–9 l/s. These flows should be more than adequate to clear the airways and prevent pneumonia and ARF without need for MAC. Thus, the patients who benefit most from MAC have moderately impaired bulbar muscle function that limits assisted CPFs to less than 300 l/m. This is typical of most non-ALS NMD patients, especially

those with DMD who benefit greatly from MAC.¹⁶ Patients with respiratory muscle weakness complicated by scoliosis and the inability to capture the asymmetric diaphragm by abdominal thrusting also greatly benefit from MI-E.

GLOSSOPHARYNGEAL BREATHING

Both inspiratory and, indirectly, expiratory muscle function can be assisted by GPB.²² GPB can provide an individual with weak inspiratory muscles and no VC or breathing tolerance with normal alveolar ventilation when not using a ventilator or in the event of sudden ventilator failure day or night.^{22,23} The technique involves the use of the glottis to add to an inspiratory effort by pistoning (gulping) boluses of air into the lungs. The glottis closes with each “gulp.” One breath usually consists of 6-9 gulps of 40-200 ml each. During the training period, the efficiency of GPB can be monitored by spirometrically measuring the milliliters of air per gulp, gulps per breath, and breaths per minute. A training manual²⁴ and numerous videos are available,²⁵ the best of which was produced in 1999.²⁶

Although severe oropharyngeal muscle weakness can limit the usefulness of GPB, this author and colleagues have managed 13 DMD ventilator users who had no breathing tolerance other than by GPB.²⁷ Approximately 60% of ventilator users with no autonomous ability to breathe and good bulbar muscle function can use GPB and discontinue ventilator use for minutes to up to all day.^{22,28} GPB is rarely useful in the presence of an indwelling tracheostomy tube. The safety and versatility afforded by GPB are additional reasons to eliminate tracheostomy in favor of noninvasive aids.

Because of their generally intact bulbar musculature, high level spinal cord injury (SCI) patients are ideal candidates to master GPB for ventilator-free breathing and be decannulated to NIV. In some centers, these patients are decannulated to free them from the fear of ventilator failure or accidental ventilator disconnection.^{1,28}

Oximetry Monitoring and Feedback Protocol

For a hypercapnic patient with desaturation due to chronic alveolar hypoventilation or the patient being weaned from tracheostomy ventilation, introduction to and use of mouthpiece or nasal NIV is facilitated by oximetry feedback. An SpO₂ alarm set at 94% signals the patient to normal SpO₂ by taking deeper breaths and to maintain SpO₂ over 94% all day.¹⁶ When it is no longer possible to achieve this by unassisted breathing, it is accomplished by mouthpiece or nasal NIV. With time, the patient requires increasing periods of NIV to maintain normal SpO₂. In this manner, central ventilatory drive can be reset.

Continuous SpO₂ feedback is especially important during respiratory tract infections. The cough of infants and small children who can never sit is inadequate to prevent chest cold-triggered pneumonia and ARF. The patients use MAC for any dip in SpO₂ below 95%. When using NIV continuously, such dips are usually due to bronchial mucous plugging. If not quickly cleared, atelectasis and pneumonia can quickly result. Thus, patients are instructed to use NIV and MAC to maintain normal SpO₂ to avert pneumonia, ARF, and hospitalization. For adults with infrequent chest colds, rapid access to MAC may be all that is necessary.

INVASIVE VENTILATORY SUPPORT

Tracheotomy is only needed when continuous saliva aspiration results in a decrease in baseline SpO₂.²⁹⁻³³ Patients with DMD, even those who are continuously ventilator dependent on noninvasive NIV, can avoid hospitalizations, pulmonary morbidity and mortality for decades, and tracheotomy indefinitely when properly managed by using respiratory muscle aids.¹⁶

LONGTERM OUTCOMES

Spinal Muscular Atrophy Type 1

This author and colleagues reported 17 SMA-1 patients using ventilation via tracheostomy tubes alive at a mean age of 78.2 (range: 65-179) months and 10 who died at 61.6 (range: 16-270) months; 25 of the 27 lost all autonomous breathing ability immediately upon tracheotomy. None of the 21 who had not developed the ability to verbalize before undergoing tracheotomy did so after tracheotomy. On the other hand, 62 SMA-1 patients using NIV were alive at the mean age 86.1 (range: 13-196) months; 13 died at 52.3 (range: 13-111) months. Sixty-seven of the 75 could communicate verbally. Fifteen SMA-1 patients are now over age 10 and six over age 15 without tracheostomy tubes, despite requiring continuous NIV in most cases.³³ Others have also reported continuous NIV dependence for patients with SMA-1.³⁴

Duchenne Muscular Dystrophy

One hundred-one of our nocturnal-only NIV users eventually became continuously NIV dependent for 7.4±6.1 years to the age of 30.1±6.1 years, with 56 patients still alive. Twenty-six of the 101 became continuously dependent without requiring hospitalization. Eight continuous tracheostomy ventilation users were decannulated to noninvasive NIV. Thirty-one consecutive “unweanable” intubated patients were extubated to NIV/MAC. Seven of this author and colleagues’ DMD patients have lived to over age 40, including four who have required NIV continuously for 28, 19, 21, and 24 years to ages 41, 44, 48, and 47. Others have also reported prolongation of life for DMD by continuous NIV.³⁵

Amyotrophic Lateral Sclerosis

Of 176 of this author and colleagues’ ALS patients using nocturnal NIV, 109 (42%) went on to require continuous NIV for about 10 months before their SpO₂ baseline decreased below 95% because of saliva aspiration due to bulbar-innervated muscle impairment. At the 69th Congress of the Mexican Society of Respiratory and Thoracic Surgeons, 20 centers from 14 countries presented data on more than 1,500 SMA-1, DMD, and ALS patients who required continuous ventilatory support without tracheostomy tubes. Four of the centers routinely extubated unweanable DMD patients so that none of their over 250 continuously ventilator dependent or any other patients have undergone tracheotomy.

EXTUBATION OF UNWEANABLE PATIENTS

NMD-specific extubation criteria and a new extubation protocol were developed and are summarized in the Table. Once the criteria are met, the oro or nasogastric tube is removed to facilitate postextubation nasal NIV. The patient is then extubated directly to NIV on assist/control of 800-1,500 ml at a rate of 10-14/min in ambient air. The NIV is provided via a combination of nasal, oro–nasal, and mouthpiece interfaces. Assisted CPFs—CPFs obtained by abdominal thrust following air stacking—were measured within 3 hours as the patient receives full volume-cycled NIV support. Patients keep 15-mm angled mouthpieces accessible and wean themselves, when possible, by taking fewer and fewer IPPVs as tolerated. Diurnal nasal NIV is used for those who cannot secure the mouthpiece. They use nasal or oro–nasal interfaces for night time ventilation. For episodes of SpO₂ less than 95%, ventilator positive inspiratory pressure (PIP), interface or tubing air leakage, CO₂ retention, ventilator settings, and MAC are considered. Patients are then taught air stacking and manually assisted coughing. Then assisted CPFs are measured.

Therapists, nurses, and, in particular, family and personal care attendants provide MAC via oro–nasal interfaces up to every 30 min until SpO₂ no longer dips below 95% and the patients feel clear of secretions. In seven cases, postextubation oral intake was considered unsafe so open modified Stamm gastrostomies were performed under local anesthesia using NIV without complication.

Data were reported on 157 consecutive “unweanable” patients with the following conditions: SMA 25 (16%), DMD 20 (13%), non-Duchenne muscular dystrophies 22 (14%), spinal cord injury 17 (11%), ALS 16 (10%), and other NMDs 57 (37%). Eighty-three who refused tracheostomies were transferred from other hospitals. They could not pass spontaneous breathing trials before or after extubation. Once SpO₂ was maintained ≥95% in ambient air they were extubated to continuous NIV and aggressive MAC. Extubation success was defined as not requiring re-intubation during the hospitalization. Before hospitalization 96 (61%) patients had no experience with NIV, 41 (26%) used it part-time, and 20 (13%) were continuously NIV dependent. First attempt protocol extubation success rate was 95% (149 patients). All 98 extubation attempts on patients with assisted CPFs ≥160 l/m were successful. Six of eight patients who initially failed extubation succeeded on subsequent attempts, so only two bulbar ALS patients with no measurable assisted CPFs underwent tracheotomy.³⁶

Table. Extubation criteria for unweanable ventilator-dependent patients

Fully alert, cooperative, afebrile, and normal white blood cell count
PaCO ₂ 40 mmHg or less at peak ventilation pressures less than 35 cmH ₂ O
Oxyhemoglobin saturation (SpO ₂) baseline ≥95% in ambient air
All oxyhemoglobin desaturations below 95% reversed by mechanically-assisted coughing
Chest radiograph abnormalities cleared or clearing
Air leakage via upper airway sufficient for vocalization upon cuff deflation

DECANNULATION OF UNWEANABLE PATIENTS

In 1996, this author and colleagues reported the decannulation of 50 unweanable patients with neuromuscular weakness.² Earlier, in 1990 and 1991, they and others reported the routine decannulation of high level traumatic SCI patients to NIV.^{23,28} The principles of decannulating unweanable patients are essentially the same as those for extubation. Any ventilator-dependent patient whose bulbar-innervated musculature is adequate such that saliva aspiration does not cause a continuous decrease in baseline SpO₂ is a candidate for decannulation to NIV. Patients with tracheostomy tubes who had no VFBA with VCs of 250 ml or greater invariably developed VFBA following decannulation. Most weaned to nocturnal-only NIV within 3 weeks of decannulation. Tube removal also facilitated speech and swallowing. All decannulated patients preferred NIV to tracheostomy ventilation for convenience, speech, swallowing, cosmesis, comfort, and safety, and they preferred NIV overall.³

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The Evaluation and Treatment of Autonomic Disorders: Postural Orthostatic Tachycardia Syndrome and Autoimmune Autonomic Neuropathy

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PART I: EVALUATION OF AUTONOMIC DISORDERS

In the late 19th century, Jean Marie Charcot, Pierre Marie, and Howard Henry Tooth described a group of individuals with high arched feet, legs shaped like inverted champagne bottles, and distal weakness as well as sensory loss. These patients with inherited hypertrophic neuropathy of the demyelinating type now known as Charcot–Marie–Tooth (CMT) type 1 often had characteristically enlarged peripheral nerve trunks. Since that era, it is now known that the peripheral nerve is populated by three main morphological types of fibers: large myelinated fibers, small myelinated fibers, and unmyelinated fibers. While needle electromyography (EMG) and nerve conduction studies have for decades provided volumes of useful data on the function and dysfunction of large myelinated fibers, the small myelinated and unmyelinated fibers, which mediate autonomic nerve traffic as well as carrying out important functions in relaying pain, have been mostly ignored. How can the lowly unmyelinated fiber be better ushered into the light of 21st century electrodiagnostic (EDX) practice? A number of diagnostic techniques are now readily available which help us decipher the autonomic nervous system and diagnose people afflicted with disorders affecting these complex neural pathways.

Commonly used autonomic test strategies include sudomotor testing such as quantitative sudomotor axon reflex testing (QSART, Fig. 1),⁵ cardiovagal testing including heart rate variation with cyclic deep breathing (HRV, Fig. 2)⁸ and the Valsalva ratio (Fig. 3),⁴ cardiac sympathetic testing using the Valsalva maneuver

to measure blood pressure and heart rate responses to increased abdominal and intrathoracic pressures (Fig. 3),⁷ and passive tilt table testing to assess adrenergic, vasomotor, and cardiac responses to head up tilt (Fig. 4).⁶

One way to illustrate the use of these various diagnostic tests in a practical clinically relevant way is to see them applied to a typical patient.

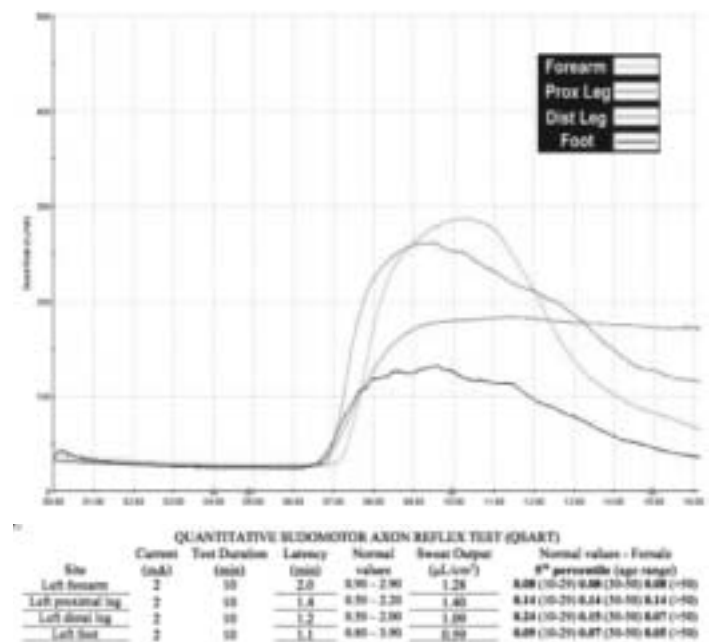


Figure 1. Quantitative sudomotor axon reflex test (QSART).



Figure 2. Heart rate variation (HRV) to deep breathing.



Figure 3. Valsalva maneuver.

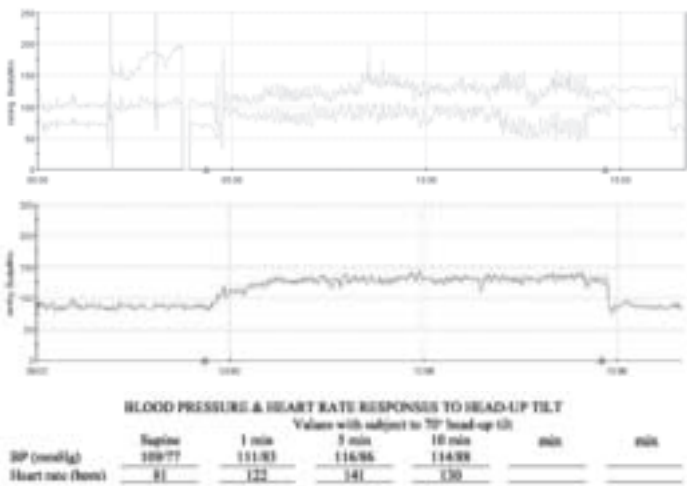


Figure 4. Passive head up tilt (HUT) testing.

Case Report

A 36-year-old wife and mother of two without prior medical problems 1 month prior to neurological evaluation suffered a miscarriage; this was 6 weeks into her pregnancy. Her obstetrician performed an examination and prescribed a 5-day course of ciprofloxacin. These events occurred in South Africa.

Eight days after this event she developed generalized joint pains but no redness or swelling. The right side of the abdomen began to hurt. Because of pain, sleep was all but impossible for the next 2 nights. She was admitted for 1 night to the hospital and underwent abdominal computed tomography (CT) scan and ultrasound examinations, neither of which led to a diagnosis. She was dismissed and presented to a second hospital where she remained for 3 nights. Liver function tests were elevated and she

was studied with a hepatobiliary iminodiacetic acid (HIDA) scan, esophagogastroduodenoscopy (EGD), and another ultrasound. Again, without a specific diagnosis, she was dismissed. This occurred a week after these symptoms had begun with continued arthralgias and abdominal pain. A few days later she developed numbness of the upper abdomen which wrapped around the torso to the mid back accompanied by brief “electric shock-like” sensations leading to a diagnosis of possible zoster sine herpette. A 5-day course of acyclovir therapy was given. The truncal numbness ascended to the chest above breast level on both sides and she began to experience decreased urge to void even when the bladder was full. For the first time in her life she became constipated.

Four weeks after these symptoms had begun she was readmitted for possible myelitis, although spinal magnetic resonance imaging (MRI) showed no abnormalities. Lumbar puncture demonstrated a mildly increased protein but no pleocytosis; the cerebrospinal fluid glucose was normal. She received a 5-day course of intravenous (IV) methylprednisolone at 1 g daily. Following the empiric steroids, the abdominal pain seemed to lessen but the numbness was only minimally improved. Bladder function worsened and she began to retain urine. The numbness came to involve the lower limbs in a circumferential pattern affecting the legs and ankles. At this point she returned to the United States and was admitted for further evaluation.

Symptoms plateaued at this juncture. On further questioning, she reported racing of the heart, postural lightheadedness, pre-syncope symptoms, and more prominent axillary sweating all coming on since the current episode began 6 weeks previously.

Her social history included no tobacco or recreational drugs and minimal alcohol use. Her CAGE substance abuse screening tool score was 0.

Laboratory evaluation at the U.S. tertiary medical center showed a number of tests to be normal including complete blood count, vitamin B12, erythrocyte sedimentation rate, electrolytes, albumin, C-reactive protein, sensitive thyroid-stimulating hormone, human immunodeficiency virus serology, paraneoplastic panel, urinalysis, and CSF studies. Reports from Africa noted elevated Cocksackie B5 antibodies and borderline Cocksackie B2 antibody titers. Borrelia serologies were negative.

MRI scans of the cervical thoracic and lumbosacral spine with and without contrast were unremarkable without evidence of abnormal signal in the spinal cord or nerve roots. Median and tibial somatosensory evoked potentials were normal as was needle EMG.

Neurologic Examination

- Vital signs: Right arm: blood pressure 94/56, supine heart rate 76. Left arm: blood pressure 94/72, supine heart rate 100.
- Mental status: Language and speech normal.
- Cranial nerves: Normal including pupillary function.
- Strength: Normal throughout.
- Sensation: Normal to pinprick, light touch, vibration, and joint position sense with no demonstrable deficits in the torso. Subjectively diminished cold sensation in the feet.
- Deep tendon reflexes: Symmetric and slightly brisk, no ankle clonus.
- Plantar responses: Flexor.
- Feet: Normal color, turgor, sweating, and pulses.
- Gait and coordination: Normal, without ataxia of torso or limbs.

Impression

- Autoimmune mediated neurologic process: the history and symptoms of paresthesia, orthostatic intolerance, and urinary dysfunction raise the possibility of autonomic neuropathy with or without myelitis associated with Cocksackie virus antibody titers which may or may not be related.
- Incidental pineal cyst on brain MRI.

Plan

- Autonomic reflex screen (Figs. 1-4).
- Echocardiogram.
- Standing catecholamine testing.
- Further immunotherapy with a second course of IV methylprednisolone over 5 days.
- Gabapentin to be administered with gradual titration for neuropathic pain.

Outcome

- Not much change after the second course of steroids.

Plan

- Conservative nonpharmacologic measures: raise the head of bed 4-6 in, liberalization of fluid intake to 2.5 liters daily, increase salt intake to 10 g daily, exercise to strengthen lower extremities and core muscles, daily walking to begin at 10-15 min daily, use of compression stockings
- IV immunoglobulin course 0.4 g/kg for 5 days.
- Empiric course of midodrine.
- Alternatives in the future: fludrocortisone, methylphenidate, venlafaxine, and droxidopa (the latter not yet available in the United States).

Outcome

- Symptoms continued to improve. Autonomic reflex testing (tilt testing) showed a progressive improvement until orthostatic tachycardia resolved completely (Fig. 5).

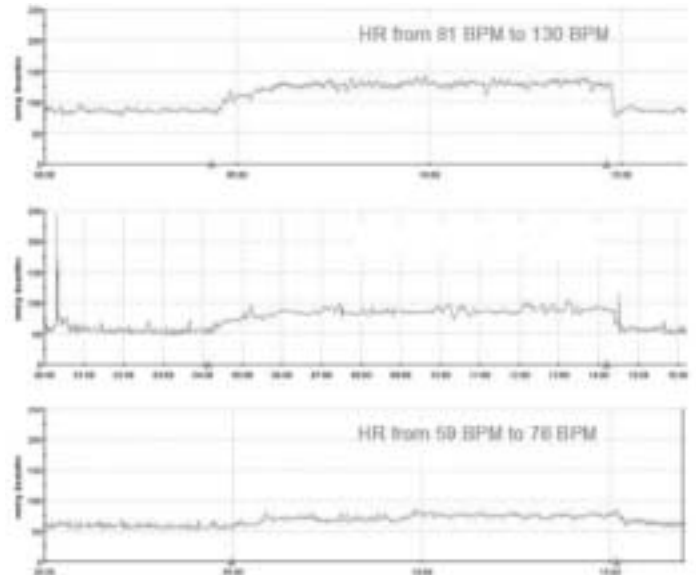


Figure 5. Resolution of symptomatic orthostatic tachycardia with immunotherapy (intravenous methylprednisolone followed by intravenous immunoglobulin) for postural orthostatic tachycardia syndrome with mild autonomic neuropathy.

Common Autonomic Symptoms

- Heat, cold intolerance
- Blurred vision
- Orthostatic lightheadedness: 0 never, 1 mild, 2 frequent, 3 consistent, 4 with syncope
- Palpitations
- Anxiety, tremulousness
- Unsteadiness
- Dry eyes, mouth
- Vasomotor discoloration of hands and feet
- Reduced/excessive sweating
- Postprandial symptoms: 0 never, 1 mild, 2 frequent, 3 consistent—anorexia, early satiety, weight loss
- Abdominal pain/cramping
- Nocturnal diarrhea
- Sexual dysfunction, loss of libido

The treatment is largely dependent upon the presumed mechanism of autonomic dysfunction. For instance, patients with orthostatic hypotension may respond to volume enhancement with 2-3 liters of water daily, salt supplementation, and compression stockings. Patients with postural tachycardia without hypotension may respond to beta blockers and exercise with recumbent bicycle. A critical component of treatment is daily exercise. Over 90% of patients with postural orthostatic tachycardia syndrome (POTS) are deconditioned.⁹ Levine and colleagues have demonstrated that a graded exercise program beginning with a recumbent bicycle and progressing over several months to standing exercise is more effective than beta blockers at restoring function and quality of life.¹⁰

More controversial is the role of autoimmunity in the pathogenesis and treatment of autonomic disorders. Autoimmune autonomic neuropathy/ganglionopathy is a multicentric illness involving sudomotor, adrenergic, and cholinergic symptoms, about half

TREATMENT OF AUTONOMIC DISORDERS

The treatment of autonomic disorders is largely symptomatic, with few disease-modifying therapies. Symptomatic therapies are both nonpharmacologic and pharmacologic (Tables 1 and 2). The most common autonomic symptom is orthostatic intolerance, either due to hypotension or tachycardia or both. Urinary retention, gastroparesis, and sexual dysfunction are also common. Patients often have multiple complaints bordering on somatization disorder, a phenomenon which has been termed somatic hypervigilance.⁹ It is often cathartic for patients to vent their complaints by using a standard autonomic review of systems.

Table 1. Nonpharmacologic therapies for dysautonomia/orthostatic hypotension

Maneuver	Mechanism
Raise the head of the bed 4-6 inches	Prevents supine hypertension, reduces nocturnal diuresis
Increase fluid intake 2-3 l/day	Volume expansion, possible hormonal mechanism
Increase salt intake (5-10 g/day)	Volume expansion
Knee high 20-30 mmHg stockings	Enhanced venous return
Abdominal binder	Enhanced venous return
Counter maneuvers: leg crossing, toe curling, toe lifts, etc.	Enhanced venous return
Orthostatic standing	Postural conditioning
Avoidance of drugs likely to worsen orthostatic hypotension	Antihypertensives, diuretics, anticholinergics, tricyclic antidepressants

Table 2. Pharmacologic therapies for dysautonomia/orthostatic hypotension

Fludrocortisone	0.1-0.5 mg daily, mineralocorticoid promotes fluid retention
Midodrine*	5-20 mg three times daily, direct alpha agonist
Pyridostigmine	30-90 mg three times daily improves acetylcholine release from ganglia, reducing risk of supine hypertension
SSRIs (fluoxetine, sertraline, paroxetine)	May reduce syncope in young people
Caffeine 100-250 mg twice daily	Blockade of vasodilatory adenosine receptors
Erythropoietin	Expanded blood volume, correction of anemia
Methylphenidate, pseudoephedrine, ephedrine, phenylpropanolamine	Direct and indirect agonists, sympathomimetic amines
Droxidopa, DOPS, octreotide, others	variable mechanisms

*the only Food and Drug Administration-approved agent for orthostatic hypotension¹

have evidence of ganglionic nicotinic acetylcholine receptors (nAChR-G). In addition, a small percentage (10%) of patients with POTS will have nAChR-G. This is a specific but insensitive marker of autoimmunity. If patients with dysautonomia present in an acute/subacute fashion and have an inciting event such as recent surgery or viral syndrome, further investigation for autoimmunity with lumbar puncture; serologies for anti-nuclear antibody, rheumatoid factor, C-reactive protein, erythrocyte sedimentation rate, extractable nuclear antigens, paraneoplastic antibodies, and Sjögren antibodies (SSA/Ro and SSB/La); salivary gland biopsy; and tests of celiac disease may be warranted.³ There are no controlled studies using immunotherapies such as plasma exchange, steroids, or IV immunoglobulin, but they may be appropriate in certain cases.² Further study of large groups of patients using standardized protocols and treatment trials are needed to address this question.

Impression

1. Orthostatic intolerance
2. Probable postural orthostatic tachycardia syndrome (POTS)
3. Dysautonomia

Comment: POTS is thought most commonly to be a post-viral dysautonomia marked by selective denervation of the capacitance vessels in the legs, leading to decreased venous return and reactive tachycardia with standing. There are several variants of POTS, including neuropathic, hyperadrenergic, and autoimmune.

The treatment includes volume expansion, exercise, and medication. Critical to success is a lifestyle change that includes vigorous daily exercise and weight training of the legs, to restore venous return.

For symptomatic improvement, consider the following:

1. Use countermeasures such as leg crossing, toe lifts, and orthostatic standing to improve postural tolerance.
2. 20-30 mmHg knee high stockings.
3. Abdominal binder to be worn while standing and as needed.
4. Intake 2-3 liters water daily.
5. Thermotabs® 4-8 daily. The goal is to gain between 3-6 lb of water weight. Can use 3-5 teaspoons salt in a self seal plastic bag, then distribute on food throughout the day.
6. Obtain a heart rate monitor.
7. Begin a graded exercise program 2-4 days/week with a recumbent bicycle, swimming, or rowing machine.
8. Perform 10 min of warmup prior to exercise.
9. Then perform 20-40 min of vigorous activity to maintain heart rate at 80% of maximum.
10. Heart rate of 80% of maximum can be calculated using the following: $(220 - \text{age}) \times 0.8$.
11. After 2 weeks, increase exercise program to 5-7 days/week.
12. Add weight lifting with modest weights to the regimen.
13. After 1-3 months, begin to introduce gravity sports: running, treadmill, spinning classes, etc.

The sidebar provides a template for the evaluation and education of the patient with POTS that includes treatment. This can be copied and placed in an electronic medical record and used as an after-visit summary.

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Neuromuscular Vignettes

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VIGNETTE ONE

A 59-year-old man with a 6-month history of small cell carcinoma of the lung treated with palliative radiation and chemotherapy presents with 6 weeks of difficulty walking. On examination, he has normal oculobulbar function, moderate symmetric proximal muscle weakness, diminished reflexes, and subtle sensory loss in a stocking pattern. Nerve conduction studies (NCSs) and needle electromyography (EMG) show the following:

Sensory Nerve Conduction Studies

Nerve/sites	Recording site	Onset (ms)	Peak (ms)	Amplitude (μ V)	Distance (cm)	Velocity (m/s)
Left ulnar, little finger						
1. Wrist	Little finger	2.15	3.05	35.0	11	51.2
Left radial, snuffbox						
1. Forearm	Snuffbox	1.75	2.35	37.9	10	57.1
Left sural, lateral malleolus						
1. Calf	Lateral malleolus	2.25	3.15	8.3	12	53.3
Right sural, lateral malleolus						
1. Calf	Lateral malleolus	2.50	3.35	10.4	12	48.0

Motor Nerve Conduction Studies

Nerve/sites	Recording site	Latency (ms)	Amplitude (mV)	Area (mVms)	Distance (cm)	Velocity (m/s)
Left median, APB						
1. Wrist	APB	4.85	0.5	2.1	7	
2. Elbow	APB	8.10	0.4	1.5	20	61.5
Left ulnar, ADM						
1. Wrist	ADM	2.85	1.1	3.8	7	
2. Below elbow	ADM	6.45	0.9	3.5	18.5	51.4
3. Above elbow	ADM	7.85	0.8	3.1	7.5	53.6
Left ulnar, ADM						
1. Wrist	ADM	3.60	0.4	2.6	7	
2. Below elbow	ADM	NR	NR	NR		
Left deep peroneal, EDB						
1. Ankle	EDB	5.60	0.8	2.3	9	
2. Fibular head	EDB	11.20	0.7	2.4	26.5	47.3
3. Knee	EDB	12.65	0.7	2.2	8	55.2
Left Tibial, AH						
1. Ankle	AH	5.80	2.2	4.8	8.5	
2. Knee	AH	13.40	1.6	3.9	37	48.7

ADM=abductor digiti minimi, AH=abductor hallucis, APB=abductor pollicis brevis, EDB=extensor digitorum brevis

Questions

- 1A. Which of the following is the MOST LIKELY diagnosis?
- Chemotherapy-induced sensorimotor polyneuropathy.
 - Lambert–Eaton myasthenic syndrome (LEMS).
 - Multifocal motor neuropathy with conduction block.
 - Sensory ganglionopathy due to anti-Hu antibodies.
 - Thoracic spinal cord compression due to metastatic tumor.

The combination of proximal muscle weakness with diminished reflexes in the presence of diffusely decreased compound muscle action potentials is highly suggestive of LEMS. Chemotherapy-induced neuropathies are more typically sensory predominant and do not lead to proximal muscle weakness. Radiation necrosis may lead to a motor neuron disease, but this complication almost always follows radiation therapy by several years or more. This patient does not present with prominent or rapidly progressive sensory loss that would be expected in the sensory ganglionopathy due to anti-Hu antibodies. There is no back pain, myelopathic pattern of weakness, hyperreflexia, or sensory level to support a diagnosis of thoracic cord compression due to metastasis.

- 1B. Which of the following treatment options is MOST LIKELY to be effective for this patient?
- Alpha lipoic acid.
 - Bevacizumab.
 - Hyperbaric oxygen.
 - Naphazoline.
 - Pyridostigmine.

Pyridostigmine may be a modestly effective treatment for patients with LEMS. Alpha lipoic acid has been investigated as a treatment for a variety of polyneuropathies. Bevacizumab and hyperbaric oxygen have been found to be effective for some patients with radiation-induced motor neuron disease, but not for those with LEMS. Ephedrine may be effective for some patients with congenital myasthenic syndrome caused by acetylcholinesterase deficiency. Naphazoline is an alpha-adrenergic agonist that has been used to treat patients with ptosis secondary to myasthenia gravis.

1C. The patient fails to respond completely to pyridostigmine, so 3,4-diaminopyridine (3,4-DAP) is initiated. Which of the following is the MOST LIKELY side effect of this treatment?

- Blindness.
- Cardiac bradyarrhythmia.
- Excessive salivation.
- Paresthesias.
- Seizure.

Paresthesias are the most likely side effect of 3,4-DAP. Important toxicities of 3,4-DAP, including cardiac bradyarrhythmia and seizures, occur at high medication doses, and they are both less common than paresthesias. Blindness is not likely to be secondary to treatment with 3,4-DAP, but may be seen with bevacizumab or hyperbaric oxygen. Excessive salivation is a more typical side effect of pyridostigmine than of 3,4-DAP.

VIGNETTE TWO

A 54-year-old woman has a history of right breast cancer 8 years prior to presentation. She was treated with lumpectomy, chemotherapy, and radiation therapy of the involved field. She presents with 6 weeks of tingling in the right hand followed by progressive weakness in the right arm and hand. Examination shows mild atrophy of the intrinsic muscles of the hand on the right and moderate distal arm weakness on the right.

Questions

- 2A. What provocative activity would increase the probability of finding a diagnostic needle EMG discharge in this patient?
- Brief, intense muscle contraction.
 - Calcium infusion.
 - Cold exposure.
 - Hyperventilation.
 - Startle.

The patient's history and examination are consistent with radiation-induced injury of the brachial plexus. Myokymia is the most characteristic abnormal needle EMG discharge in the setting of radiation-induced injury, and hyperventilation is the activity that will most likely provoke this discharge. Brief muscle contractions are most effective in eliciting myotonic discharges, not myokymic discharges. Cold exposure is most likely to produce myotonic discharges, especially in patients with paramyotonia congenita. Intravenous calcium infusion reduces the chance of detecting myokymia. Startling a patient may elicit a variety of abnormal movements, especially myoclonus, but should not change the yield of needle EMG in detecting myokymic discharges.

- 2B. Despite careful needle EMG examination, characteristic electrical discharges could not be demonstrated in this patient. What is the likelihood of finding these discharges upon needle EMG of patients with radiation-induced plexopathy?
- 25%.
 - 40%.
 - 60%.
 - 80%.
 - 95%.

Harper and colleagues¹ investigated 34 patients with radiation-induced plexopathy and found myokymic discharges in 22. Thus, 60% most closely approximates the probability of finding myokymic discharges in patients with radiation-induced plexopathy.

- 2C. What other abnormal needle EMG discharges are MOST LIKELY to accompany this patient's myokymia?
- Complex repetitive discharges.
 - Cramps.
 - Fibrillations.
 - Myotonia.
 - Neuromyotonia.

Fasciculations and fibrillations often accompany myokymic discharges associated with radiation injury. Neuromyotonia and myokymia are found together in Isaac's syndrome, but neuromyotonic discharges are not characteristic of radiation-induced injury.

- Harper CM, Thomas JE, Cascino TL, Litchy WJ. Distinction between neoplastic and radiation-induced brachial plexopathy, with emphasis on the role of EMG. *Neurology* 1989;39:502-506.

VIGNETTE THREE

An 84-year-old man with amyotrophic lateral sclerosis (ALS) diagnosed 1 year ago presents for routine followup. He has complaints of dysphagia and dyspnea, and he is now wheelchair bound.

Questions

- 3A. Initiating noninvasive positive-pressure ventilation (NPPV) is being considered. Which of the following pieces of data meet Medicare criteria for NPPV?
- Arterial blood gas analysis showing pCO₂ of 40 mmHg.
 - Fall in vital capacity of 15% upon supine testing.
 - Forced vital capacity (FVC) measuring 60% predicted.
 - Overnight sleep study demonstrating desaturation to 85% for 5 min.
 - Rise in Epworth sleepiness scale score of 3 points.

In order for an ALS patient to meet Medicare criteria for initiation of noninvasive positive pressure ventilation, they must have one of the following: (1) arterial blood gas PaCO₂ greater than or equal to 45 mmHg on the patient's usual FiO₂, (2) sleep oximetry with an O₂ saturation level less than or equal to 88% for 5 continuous minutes on room air, (3) maximal inspiratory pressure less than 60 cm H₂O, or (4) FVC less than or equal to 50% predicted. Falls in FVC upon assuming a supine position or changes in the Epworth sleepiness scale score are not included in the Medicare criteria.

- 3B. Which of the following is TRUE concerning the initiation of NPPV in patients with ALS?
- There are benefits to survival and to quality of life.
 - There is a benefit to survival but no benefit to quality of life.
 - There is no benefit to survival but there is a benefit to quality of life.
 - There are no benefits to survival or to quality of life.
 - The effects of NPPV to survival and quality of life have not been tested.

NPPV has been shown to increase survival, reduce the rate of FVC decline, and enhance quality of life in patients with ALS. Because the patient reported dysphagia, a swallowing study was ordered. This study showed delayed swallowing and penetration of liquids of all consistencies. The decision is made to place a percutaneous endoscopic gastrostomy tube.

- 3C. According to the most recent American Academy of Neurology (ANN) Practice Parameter on the care of the patient with ALS, an FVC of AT LEAST which of the following values would be considered to be low risk for percutaneous endoscopic gastrostomy (PEG) tube placement:
- 30% predicted.
 - 40% predicted.
 - 50% predicted.
 - 60% predicted.
 - 70% predicted.

Based on the 2009 AAN Practice Parameter, PEG tube placement is considered low risk when the FVC is at least 50% of the predicted value. Although in clinical practice, many patients have PEG tubes placed with FVC predicted of 30% (or even lower), the retrospective data on which the recommendation was made indicate that peri-procedural complication and mortality rates are lowest when the FVC is at least 50%.

VIGNETTE FOUR

A 36-year-old female presents for evaluation of weakness. She describes a lifelong history of progressive weakness and gait difficulties. She was weak as an infant and had frequent falls as a child. Muscle biopsy at age 4 was nondiagnostic. Most recently, she has had difficulty arising from a chair and cannot get up from the floor or go up stairs. She denies cardiac, cognitive, sensory, bulbar, or respiratory symptoms. She has two boys and a girl of which both boys are also affected, as well as her father and sister. (A video showing the neurological examination will be presented during the live course.)

Questions

- 4A. Which feature MOST suggests the underlying disorder?
 - A. Elbow contractures.
 - B. Finger flexor contractures.
 - C. Autosomal dominant inheritance.
 - D. The gait abnormalities.
- 4B. Note the skin changes on examination as seen below. What is the MOST LIKELY diagnosis?



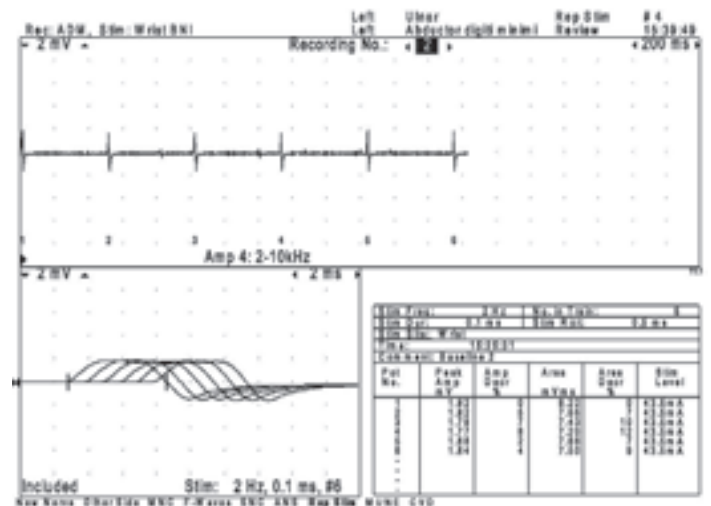
- A. Facioscapulohumeral dystrophy.
 - B. Myotonic dystrophy.
 - C. Bethlem myopathy.
 - D. Limb-girdle muscular dystrophy type 1A.
- 4C. Which of the following is MOST LIKELY to confirm the diagnosis?
- A. Collagen type VI (COL6) mutation analysis.
 - B. Muscle trichrome staining.
 - C. Lamin A/C mutation analysis.
 - D. Serum phytanic and pristanic acid levels.

VIGNETTE FIVE

A 52-year-old white male presents to the hospital with 1 week of progressive swallowing difficulties and lower extremity weakness. He subsequently develops shortness of breath and is found to have a FVC of ~60% normal. There are no skin rashes, sensory symptoms, or myalgias. General examination reveals sluggish pupillary responses and dry mucous membranes. Neurological examination shows normal mentation. Cranial nerves are normal except for mild flaccid dysarthria. No ptosis or dysconjugate gaze is seen. Motor examination reveals proximal muscle weakness in the legs greater than the arms with areflexia. Sensation and coordination are normal. Gait is unsteady due to weakness.

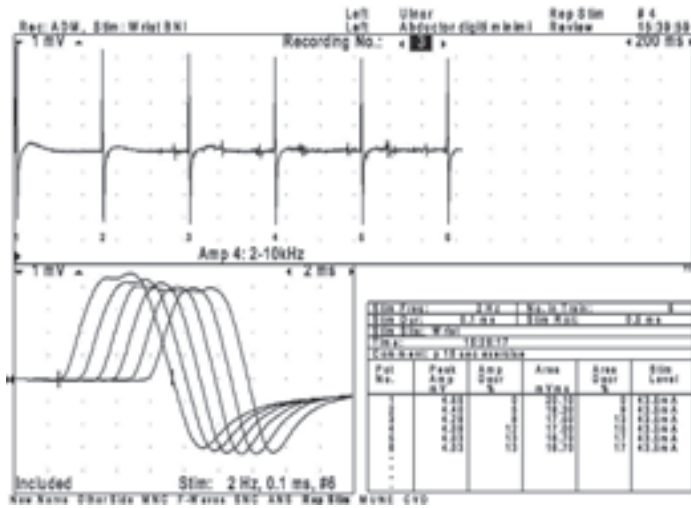
Questions

- 5A. Which of the following is the MOST LIKELY etiology?
 - A. Toxic myopathy.
 - B. Immune mediated neuropathy.
 - C. Endocrine myopathy.
 - D. Neuromuscular junction defect.
- 5B. Upon further questioning he endorses dry mouth, new erectile dysfunction, and swallowing difficulty. He also admits a history of diabetes, hypertension, and life-long tobacco use. Which would be the MOST useful next diagnostic study to reveal the diagnosis?
 - A. Repetitive nerve stimulation.
 - B. Single fiber EMG.
 - C. Edrophonium test.
 - D. Acetylcholine receptor antibodies.
- 5C. The results of an ulnar motor NCS with 2-Hz repetitive nerve stimulation are shown below. What is the next electrophysiologic study to perform?



- A. The long exercise test of the ulnar nerve.
- B. Ulnar antidromic sensory NCS.
- C. Tell the patient that the diagnosis is confirmed and treatment will be initiated.
- D. Repeat the repetitive nerve stimulation after 15 s of exercise.

5D. The repetitive nerve stimulation is repeated after 15 s of exercise. Which of the following are possible diagnoses based on the neurophysiology?



- A. Botulism and myasthenia gravis
- B. Myasthenia gravis and LEMS
- C. LEMS and botulism
- D. Myotonia congenita and LEMS
- E. Myotonia congenita and myasthenia gravis

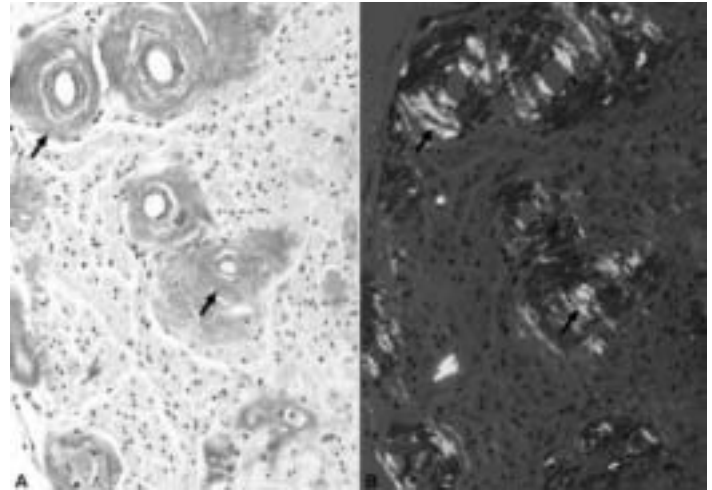
VIGNETTE SIX

A 54-year-old Hispanic male presents for evaluation of weakness and numbness. He has had progressive weakness and stiffness over the last 4 years. Two years ago he began to develop burning paresthesias and a sense of “coldness” in the feet. During the same time period he developed severe diarrhea with voluminous watery stool. This was believed to be responsible for his recent 70 lb weight loss and orthostatic hypotension although other autonomic symptoms such as erectile dysfunction were also present. Neurological examination reveals normal mentation; a cranial nerve examination was also performed. There is proximal greater than distal weakness in the setting of well-developed overly firm muscles. Pan-modality length-dependent sensory loss and hyporeflexia is present.

Questions

- 6A. Which diagnostic test is the MOST appropriate to order next?
- A. Computed tomography chest/abdomen/pelvis.
 - B. Serum immunofixation.
 - C. Antineutrophil cytoplasmic antibodies (ANCA) panel.
 - D. Ganglionic acetylcholine receptor antibody titers.
- 6B. The tests in question 6A are all normal. It is discovered that his father and brother both had burning dysesthesias and died of congestive heart failure in their 50s. Which of the following is LEAST LIKELY to provide the diagnosis?
- A. Liver biopsy.
 - B. Sural nerve biopsy.
 - C. Skin biopsy.
 - D. Prostate biopsy.

6C. The results of a sural nerve biopsy are shown below. Which of the following is the MOST helpful to aid in prognosis?



- A. The specific transthyretin mutation.
- B. Epidermal nerve fiber density.
- C. Absent sural NCS responses.
- D. Presence of a family history of congestive heart failure.

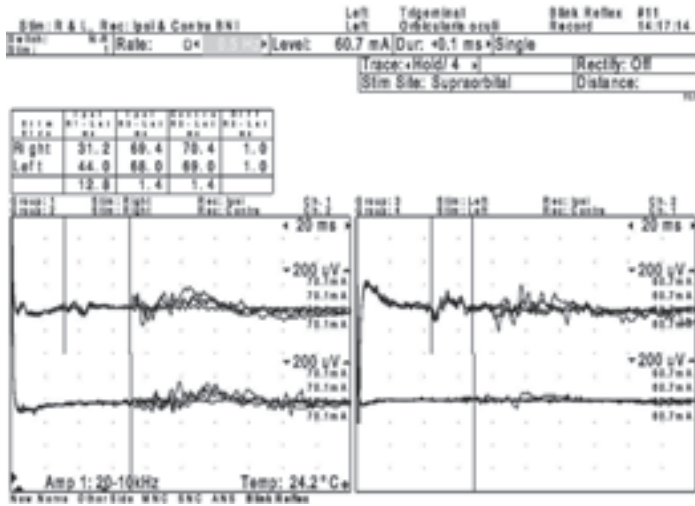
VIGNETTE SEVEN

A 59-year-old white male presents to the emergency room with 6 weeks of progressive weakness. He first noted falls because his legs would “buckle” underneath him. He has intermittent paresthesias in the hands and feet. No bulbar symptoms are present. His medical history is significant for a deep vein thrombosis 3 weeks ago resulting in current treatment with warfarin. His neurological examination is significant for severe weakness of the proximal arm and leg muscles with moderate distal weakness. Sensation is mildly diminished to vibration in the feet. Reflexes are absent in the legs and hypoactive in the arms.

Questions

- 7A. What is the next MOST appropriate step in the workup?
- A. Lumbar puncture.
 - B. Sural nerve biopsy.
 - C. Needle EMG and NCSs.
 - D. Skeletal survey.

7B. The needle EMG and NCSs show no sensory or motor responses in the upper and lower extremities. Given these findings, the extremities are re-examined and surprisingly no atrophy is found. Blink reflex testing is performed and shows the following. What is the MOST LIKELY diagnosis based on these findings?



- A. Paraneoplastic ganglionopathy.
- B. Chronic inflammatory demyelinating polyradiculopathy.
- C. Lyme disease.
- D. Hereditary motor sensory neuropathy type 2A.
- E. Unrelated. The abnormal blink reflex results are technical and due to cold skin temperature.

VIGNETTE EIGHT

A 36-year-old man who works on a commercial fishing boat has insidious onset of difficulty extending his right wrist. He complains of a burning in his mid-forearm and right lateral elbow pain for about 4 months. He attributed this to the heavy work he does on the boat.

On physical examination he has pain on passive range of motion (ROM) at the elbow and wrist. Weakness in wrist extension with dorsal wrist pain is noted. There is subtle radial deviation with active extension.



Questions

- 8A. Which additional examination finding is he also MOST LIKELY to have? (See picture for subtle hint.)
- A. Weakness in the first dorsal interosseous muscle.
 - B. Weakness of finger metacarpal extension.
 - C. Atrophy in the pronator teres muscle.
 - D. Hyperhidrosis and allodynia.

He reports that his pain is markedly increased when resistance is applied to supination of the forearm.

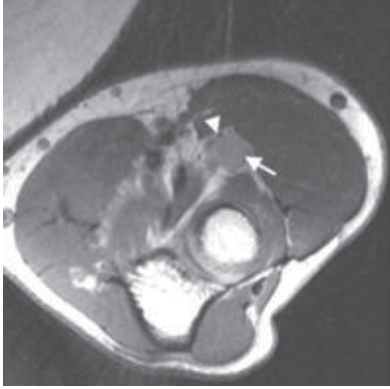
- 8B. What is the MOST LIKELY diagnosis?
- A. Lateral epicondylitis.
 - B. Multifocal motor neuropathy.
 - C. C7 radiculopathy.
 - D. Posterior interosseous nerve syndrome (PINS).
 - E. Trigger finger with extensor tendon rupture.

His examination also reveals tenderness over the lateral epicondyle. When he puts his forearm into full pronation he reports a marked increase in his pain. Active supination from a pronated position reproduces his symptoms. Isolated weakness is also noted in the extensor indicis proprius (see photo).



- 8C. Given these examination results, what else might be considered?
- A. That PINS is not present.
 - B. That, in addition to PINS, there also may be a concomitant extensor tendon injury.
 - C. That the patient may have a concomitant C6 radiculopathy.
 - D. That the patient may have systemic neurovasculitis.

Magnetic resonance imaging (MRI) of the forearm reveals abnormal thickening in the arcade of Frohse and edema in the supinator.



- 8D. What is the **LIKELY** cause of the thickening in the arcade of Frohse in this man?
- Traction on the radial head by the leash of Henry.
 - A redundancy in the arcade of anastomosing branches of the radial recurrent artery.
 - Tendinous thickening, which occurs in 30-100% of people, most likely due to repetitive pronation-supination.
 - The arcade of Frohse was not thickened.
- 8E. Why does full pronation of his forearm cause so much pain?
- Because full pronation of the forearm produces pressure on the posterior interosseous nerve (PIN) by the sharp tendinous edge of the origin of extensor carpi radialis brevis muscle.
 - Because full pronation of the forearm creates longitudinal tension on the PIN.
 - Because there also is likely a component of tenosynovitis.
 - Because the patient is a malingerer; this maneuver should not cause any pain.
- 8F. Electrodiagnostic (EDX) testing is initiated. Which muscle(s) will be abnormal on needle EMG?
- Brachioradialis.
 - Extensor carpi radialis longus.
 - Extensor carpi ulnaris.
 - Supinator.
 - Extensor carpi radialis brevis.

VIGNETTE NINE

A 6-year-old boy diagnosed with DNA-confirmed Duchenne muscular dystrophy (DMD) presents to the neuromuscular clinic for management. There is no family history of DMD, and the boy has otherwise had a very typical course for DMD. The parents report that their son is now having difficulties walking and he is falling more at home. He begins school soon and the parents, understandably, say that “they want the best possible treatment for their son” and that they “have many questions.” You begin to examine the boy, who is quite pleasant and cooperative. On examination reflexes are absent in the extremities, with pinprick and vibratory sensation intact. The boy has a distinct waddle when he walks and is up on his toes.

Questions

- 9A. The family asks if he should be treated with glucocorticoids. What is the **MOST APPROPRIATE** response?
- There is only anecdotal evidence from case series showing any beneficial effects of glucocorticoid therapy in DMD.
 - There is evidence from randomized controlled studies that glucocorticoid corticosteroid therapy improves muscle strength and function in the short-term (6 months to 2 years) in DMD.
 - Longterm benefits and hazards of glucocorticoid treatment are clearly evaluated from the currently published randomized studies. There is no hesitation recommending glucocorticoid in this setting.
 - Glucocorticoids work and the most effective regimen appears to be prednisone, dosing at 3 mg/kg/day.
- 9B. The family continues to ask more questions regarding glucocorticoids for their son. Attempting to offer further advice, which of the following statements could be given to the family with reasonable confidence?
- The median prolongation of ambulation for boys treated with intermittent glucocorticoid therapy is the same as those treated with daily therapy.
 - Boys treated with intermittent glucocorticoid therapy do not demonstrate any real benefit.
 - Boys treated with intermittent glucocorticoid therapy do show prolongation of ambulation, with fewer side effects, compared to daily dosing, although the beneficial effect is not as great.
 - Boys treated with daily glucocorticoid therapy show greater prolongation of ambulation, with similar degree of side effects, compared to intermittent treatment.
 - Given the possibility of severe side effects (e.g., Cushingoid features, adverse behavior, hypertension, weight gain), glucocorticoids are not recommended at all.

The boy is appropriately referred to a neurodevelopment program through physical and occupational therapy and speech language pathology. Soon there are requests regarding bracing from the therapists and parents. The therapist is reporting hyperlordotic positioning of the spine with heel cord tightness. Contractures of the Achilles tendons and the gastrocnemius muscle may deteriorate performance in daily living activities in patients with neuromuscular diseases.

- 9C. What should the parents be advised when they ask about resting night splints (nocturnal ankle-foot orthotics [AFOs]) for their son?
- AFOs prevent the progression of joint deformities in DMD and it is recommended that they obtain a set immediately.
 - Optimal position of the joints to support standing is a pointless goal in DMD as the boy will lose walking ability ultimately.
 - The available studies investigating the relationship between orthotic usage and functional activities in boys with DMD arrive at conflicting results.
 - The use of night time AFOs has not been found to be effective in improving functional performance in boys with DMD, despite a modest benefit in protecting the ankle from contractures and helping to correct gait.

Spinal radiographs are obtained for a baseline assessment of possible scoliosis. The films do not show any evidence of scoliotic curvature.

- 9D. What is the next management course?
- Aggressive spinal manipulation to reduce the curvature.
 - Referral to a pediatric spine surgeon for spinal fusion and instrumentation.
 - Fitting with a custom molded spinal orthosis.
 - Proprioceptive neuromuscular stretching through a neurodevelopmental therapist.
 - Close clinical monitoring with intermittent radiographic evaluation as indicated.

VIGNETTE TEN

A 39-year-old, otherwise healthy female patient is referred by her family physician for EDX evaluation for “cervical radiculopathy.” She complains of a vague periscapular pain in her right shoulder. Pressing her for more detail she described this as a “burning”, nagging pain that is increased with exercise, but may persist for hours after she stops activities. More recently, it is present at rest. She also notes the pain is increased by continuous overhead activity, such as swimming, doing her hair, and downward traction, like carrying heavy objects.

On physical examination, there is a normal ROM in her right shoulder. There are no signs of subacromial or glenohumeral pathology. Her neurological examination was also unremarkable, with normal reflexes and sensory examination.

To shed more light on her condition, she is asked to demonstrate what initiates her symptoms. She proceeds to raise her arm overhead with her upper arm abducted to 90 degrees and shoulders externally rotated to 90 degrees. She now says that she starts to feel weakness in her grip, along with generalized right arm pain and fatigue. This does not occur in the left arm.

Questions

- 10A. What is the next diagnostic test of choice?
- Anterior scalene block.
 - EDX testing.
 - Radiological investigations of the cervical spine X-rays.
 - Arteriography and venography to rule out aneurysm or venous thrombosis.
 - MRI of the brachial plexus to rule out a Pancoast tumor or metastatic involvement of the brachial plexus.

The radiographs (shown below) show a congenital cervical rib.



- 10B. What is now included in the differential diagnosis for this patient?
- Ankylosing spondylitis.
 - Thoracic outlet syndrome.
 - Parsonage–Turner syndrome.
 - Cheney–Rumsfeld syndrome.
 - Marfan syndrome with achondroplasia.
- 10C. On closer inspection, it is noted that she has some subtle wasting in the fleshy base of her thumb. What is the significance of this examination finding?
- This is Gilliatt–Sumner hand, suggesting neurogenic thoracic outlet syndrome (TOS).
 - This is proud flesh, suggesting complex regional pain syndrome, type II.
 - By itself, this finding has no significance.
 - This confirms Marfan syndrome with achondroplasia.

- 10D. EDX abnormalities are required to objectively confirm the diagnosis of neurogenic TOS. Which of the following EDX abnormalities would help confirm a diagnosis of neurogenic TOS in this patient?
- Temporal dispersion in the median nerve compound motor action potential (CMAP) on the right.
 - Absent sensory nerve action potentials (SNAPs) in the bilateral medial antebrachial cutaneous nerves, using antidromic stimulation.
 - Absent or reduced amplitude in the right ulnar antidromic SNAP.
 - Prolonged minimum latency (>33 ms) of the median F wave (with or without abnormalities in the ulnar F wave), and with normal F waves in the contralateral (unaffected) upper extremity.
 - Needle EMG showing denervation (e.g., fibrillation potentials, positive sharp waves) in at least one muscle supplied by each of two different nerves from the upper trunk of the brachial plexus, with normal needle EMG of at least one muscle supplied by a nerve from the middle or lower trunk of the brachial plexus.

VIGNETTE ELEVEN

A previously healthy 24-year-old male, recently inducted into the National Guard, is referred for an EDX evaluation with complaints of left shoulder abduction weakness. He denies neck pain or radicular pain but he does note some progressive loss of bulk and definition in his left deltoid muscle, as well as weakness, and slight sensory deficit over the lateral shoulder.

The physical examination revealed obvious atrophy of the left deltoid compared to the right (see photo).



With volitional contraction of the left deltoid, the posterior head of the deltoid was noted to become more prominent. There was no visible activation of the middle or anterior heads of the muscle. Left shoulder ROM and distal upper extremity strength was otherwise unremarkable. Sensory examination of the left shoulder showed slightly decreased sensation compared to the right. Deep tendon reflexes were 2+ at the bilateral biceps brachii, 1+ at the brachioradialis, and 1+ at the triceps in a symmetric fashion.

Questions

- 11A. What is the MOST LIKELY diagnosis?
- Brachial plexitis with selective involvement of the radial nerve.
 - C6 radiculopathy.
 - Regionalized myofascial pain syndrome.
 - Brachial plexitis with selective involvement of the axillary nerve.
 - Myositis.

On further inquiry about possibly injuries, he does report receiving a series of inoculations via intramuscular injections in his left deltoid muscle about a month earlier. At the time of injection, he did recall experiencing an immediate sharp, electric-like sensation radiating down to his fingers, which did not last.

EDX evaluation is initiated. Using a recording surface electrode placed over the most prominent portion of the middle deltoid, with a stimulating cathode placed in the supraclavicular fossa lateral to the sternocleidomastoid muscle, the evoked CMAP amplitude on the left is 1.5 mV (14.4 mV on the right).

- 11B. What results are expected on needle EMG of the left deltoid muscle at this point?
- Markedly reduced motor unit recruitment pattern with no abnormal spontaneous activity (i.e., fibrillations and positive sharp waves).
 - Marked (3-4+) abnormal spontaneous activity (i.e., fibrillations and positive sharp waves) with relatively normal motor unit recruitment pattern.
 - Marked (3-4+) abnormal spontaneous activity (i.e., fibrillations and positive sharp waves) with reduced motor unit recruitment pattern.
 - Marked (3-4+) abnormal spontaneous activity (i.e., fibrillations and positive sharp waves) with increased motor unit recruitment pattern.

It is now suspected that this is an isolated axillary nerve injury following an intramuscular injection to the left deltoid muscle. Although the practice of intramuscular injection in to the deltoid muscle is performed routinely, there is significant risk of a neurovascular injury if performed incorrectly.

- 11C. In addition to the axillary nerve, which other neurovascular structures are at most risk to be affected by intramuscular injection to the deltoid muscle?
- Subacromial bursa.
 - Circumflex humeral artery.
 - Recurrent brachial nerve.
 - There are no other structures at risk.
- 11D. What would be the BEST treatment at this point?
- Referral to an orthopedic surgeon for surgical exploration and decompression.
 - Modification of activities that put excessive strain on the left deltoid or exacerbate the symptoms, education, postural exercises, physical therapy, and anti-inflammatory drug therapy.
 - Immobilization of the left shoulder for 4-6 weeks followed by physical therapy.
 - Functional electrical stimulation to improve nerve regeneration.

