

Approach To Patients with Neuromuscular Disorders

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Evaluating the Patient with Generalized Weakness

- ❖ Where is the lesion?
- ❖ What is the pattern of weakness?
- ❖ What is the age of onset?
- ❖ What is the time course?
- ❖ Is this a hereditary or acquired process?
- ❖ Are there any associated symptoms, medical problems, medications/drugs?



Where is the Lesion?

- ❖ Central (Corticospinal)
- ❖ Anterior Horn Cell
- ❖ Peripheral Nerve (motor, sensory, sensorimotor, autonomic)
- ❖ Neuromuscular junction (pre- or post-)
- ❖ Muscle



What is the Pattern of Involvement?

- ❖ Motor, sensory, and/or other systems
- ❖ Symmetric or asymmetric
- ❖ Cranial, axial, and/or limb
- ❖ Proximal, distal, generalized
- ❖ Peculiar Patterns (e.g., ocular, facioscapulohumeral, scapulohumeral, forearm flexor and knee extensor)



What is the Age of Onset?

- ❖ Congenital or infancy
- ❖ Early childhood or adolescence
- ❖ Early or middle adulthood
- ❖ Late adulthood



What is the Time Course?

- ❖ Acute (hours or a few weeks) , subacute (4 weeks to 2 months), or insidious onset (over 2 or more months)
- ❖ Monophasic, relapsing-remitting, chronic progressive course



Is this a Hereditary or an Acquired Disorder?

- ❖ Obtain a family history
- ❖ Examine affected and asymptomatic family members if a hereditary disorder is suspected
- ❖ Draw the pedigree (x-linked, autosomal recessive or dominant, maternal (mitochondrial) inheritance pattern)



Are there Associated Medical Disorders?

- ❖ Cardiomyopathy
- ❖ Pulmonary
- ❖ Rheumatologic
- ❖ Renal
- ❖ Liver
- ❖ Infectious
- ❖ Malignancy



Can the disorder be toxin-related?

- ❖ Medications
- ❖ ETOH
- ❖ Illicit Drugs
- ❖ Other environmental exposures



Differential Dx of the Floppy Infant

- ❖ CNS (most common)
- ❖ Anterior horn cell
 - SMA I and II
- ❖ Peripheral Nerve
 - CMT III
 - congenital hypomyelinating / amyelinating neuropathy
 - CMTI and II (rare)
 - giant axonal neuropathy
- ❖ NMJ
 - infantile botulism
 - infantile MG
 - congenital myasthenia
- ❖ Muscle
 - congenital myopathy
 - muscular dystrophy
 - mitochondrial
 - metabolic (glycogen and lipid storage defects)
 - endocrine (hypothyroid)



Weakness Presenting in Childhood or Early Adulthood

- ❖ Anterior Horn Cell
 - SMA II and III
 - juvenile muscular atrophy
 - poliomyelitis
 - ALS
- ❖ Peripheral Nerve
 - AIDP / CIDP
 - vasculitis
 - hereditary neuropathies
- ❖ NMJ
 - Botulism
 - LES
 - congenital myasthenia
 - myasthenia gravis
- ❖ Muscle
 - congenital myopathy
 - muscular dystrophy
 - mitochondrial myopathy
 - metabolic myopathy (glycogen and lipid storage diseases)
 - periodic paralysis
 - electrolyte imbalance
 - endocrine myopathies
 - toxic myopathies
 - inflammatory myopathies
 - ◆ dermatomyositis
 - ◆ polymyositis (after 20 yrs)



Weakness Presenting in Middle or Late Adulthood

❖ Anterior Horn Cell

- SMA III
- poliomyelitis
- Kennedy's disease
- ALS

❖ Peripheral Nerve

- AIDP / CIDP
- vasculitis
- toxic neuropathies
- endocrine (DM)
- paraneoplastic
- hereditary neuropathies

❖ NMJ

- Botulism
- LES
- myasthenia gravis


❖ Muscle

- sarcopenia (e.g., disuse atrophy related to age, systemic illness, steroids)
- muscular dystrophy
- mitochondrial myopathy
- metabolic myopathy (e.g., acid maltase, debrancher deficiencies)
- electrolyte imbalance
- endocrine myopathies
- toxic myopathies
- amyloid myopathy
- inflammatory myopathies
 - ♦ inclusion body myositis (most common)
 - ♦ dermatomyositis
 - ♦ polymyositis (after 20 yrs)



Disorders Presenting with Acute or Subacute Proximal Weakness

- ❖ Anterior Horn Cell
 - poliomyelitis
- ❖ Peripheral Nerve
 - AIDP
 - Tick paralysis
 - porphyria
 - vasculitis
 - paraneoplastic
 - carcinomatous infiltration
 - toxic neuropathies
- ❖ NMJ
 - Botulism
 - LES
 - myasthenia gravis
- ❖ Muscle
 - periodic paralysis
 - electrolyte imbalance
 - endocrine myopathies
 - toxic myopathies
 - ICU myopathy
 - metabolic myopathies (e.g., glycogen and lipid storage disorders associated with myoglobinuria)
 - inflammatory myopathies
 - ◆ dermatomyositis
 - ◆ polymyositis
 - ◆ infectious myositis



Disorders Presenting with Chronic Progressive Proximal Weakness

- ❖ Anterior Horn Cell
 - post-polio syndrome
 - SMA III and Kennedy's disease
 - ALS (usually more distal)
- ❖ Peripheral Nerve
 - CIDP and variants
 - amyloidosis
 - vasculitis
 - endocrine
 - paraneoplastic
 - carcinomatous infiltration
 - toxic neuropathies
- ❖ NMJ
 - LES
 - myasthenia gravis
- ❖ Muscle
 - muscular dystrophy
 - periodic paralysis (progressive fixed weakness)
 - endocrine myopathies
 - toxic myopathies
 - metabolic myopathies (e.g., glycogen and lipid storage disorders)
 - inflammatory myopathies
 - ♦ IBM (proximal and distal)
 - ♦ dermatomyositis
 - ♦ polymyositis
 - ♦ infectious myositis



Disorders Presenting with Distal Weakness

- ❖ Anterior Horn Cell
 - ALS
 - distal SMA
- ❖ Radiculopathies (low cervical and LS), syring, tumors of cord
- ❖ Plexopathies (e.g., lower trunk)
- ❖ Peripheral Nerve
 - CMT
 - MMN and MADSAM
 - vasculitis
 - cancer
 - toxic/metabolic/endocrine
- ❖ NMJ
 - myasthenia gravis (rare)
 - congenital myasthenia
- ❖ Muscle
 - distal myopathies
 - Myofibrillary myopathy
 - some dystrophies (e.g., FSH, scapuloperoneal, EDMD)
 - glycogen storage diseases (acid maltase, debrancher, branching enzyme, PBK)
 - congenital myopathies (e.g., central core, centronuclear, nemaline)
 - inclusion body myositis



Disorders Presenting with Ptosis or Ophthalmoparesis

❖ Central Disorders

- PSP
- MS
- CVA/aneurysm
- tumor

❖ Cranial/peripheral neuropathy

- AIDP
- Miller-Fisher syndrome
- Cavernous sinus syndrome

❖ NMJ

- botulism
- LES
- myasthenia gravis
- congenital myasthenia

❖ Muscle

- mitochondrial myopathies
- oculopharyngeal MD
- congenital myopathy (myotubular, nemaline)
- myotonic dystrophy (ptosis)
- Grave's disease



Evaluating the Patient with Generalized Weakness

- ❖ Look, Listen, and Feel
- ❖ Obtain a detailed History, Past Medical History, Family History, ROS, and Physical Examination
- ❖ EMG/NCS are an extension of the exam
- ❖ Directed Laboratory work-up



Symptoms

❖ Distribution of weakness

- Cranial nerve involvement (droopy eyelids, blurred or double vision, speech , chewing, or swallowing difficulties)
- Neck weakness
- Proximal weakness (difficulty arising from floors/chairs, climbing stairs, lifting objects overhead)



Symptoms

❖ Distribution of weakness

- Distal (grip, twisting/turning door knobs, opening jaws, tripping, standing on tip toes)
- Fluctuating weakness (fatigability)
- Symmetric or Asymmetric (at onset and at present)



Symptoms

- ❖ Associated neuromuscular symptoms?
 - Myalgias, cramps, muscle stiffness (e.g., myotonia, neuromyotonia, spasticity), fasciculations, muscle atrophy or hypertrophy, history of myoglobinuria, bowel or bladder involvement, sensory complaints



Symptoms

❖ Sensory Involvement

- Distribution or pattern
 - ◆ sensory level
 - ◆ root, plexus, nerve, multiple nerves
 - ◆ stocking-glove or generalized
 - ◆ symmetric or asymmetric
- Associated pain, paresthesia, burning, or aching
- Ataxia or coordination problems



Clinical Examination

- ❖ Inspection (look and listen)
 - cranial nerve involvement (ptosis, ophthalmoparesis, jaw opening and closing, facial weakness, dysarthria)
 - shoulder girdle weakness (scapular winging, horizontal displacement of the anterior axillary line, trapezius hump, internal rotation of the shoulders)

FSHD



Becker Muscular Dystrophy



Miyoshi Myopathy





Clinical Examination

❖ Inspection

- lower extremity weakness (Gower's sign, wide-based waddling gait, genu-recurvatum, steppage gait)
- muscle atrophy or hypertrophy
- fasciculations, myokymia, tremor, ataxia
- skeletal defeormities (scoliosis, pes cavus, hammer toes)
- skin lesions



Clinical Examination

❖ Cranial Nerve Examination

- Ophthalmoscopy (optic atrophy, pigmentary retinopathy), visual acuity
- Pupils (reactivity, autonomic involvement)
- Hearing
- Ptosis or ophthalmoparesis (fatigue?)
- Facial weakness (orbicularis oculi and oris)
- Jaw opening and closing, palate, and tongue



Clinical Examination

❖ Motor Examination

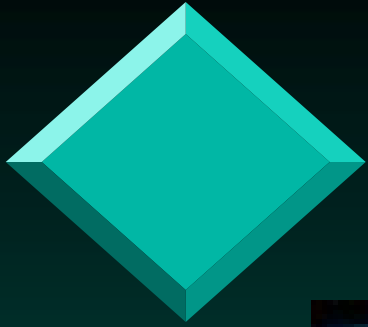
- tone (normal, hypotonic, spastic)
- muscle bulk (atrophy, hypertrophy)
- fasciculations, myokymia
- myotonia (percussion and action, proximal, distal, or bulbar), paramyotonia, myoedema, rippling muscles

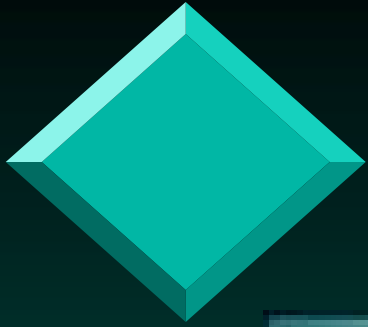


Clinical Examination

❖ Motor Examination

- Assess Muscle Strength
- Medical Research Council (MRC) Scale
- Distribution of weakness, atrophy
 - ◆ symmetric or asymmetric,
 - ◆ proximal or distal
 - ◆ peculiar pattern (e.g., ocular, facioscapulohumeral, scapuloperoneal, forearm flexors and knee extensors))







Clinical Examination

❖ Sensory Examination

- Pin prick, temperature, light touch, vibratory perception, proprioception, Romberg sign (large and/or small fiber involvement ?)
- Distribution
 - ◆ sensory level
 - ◆ symmetric or asymmetric,
 - ◆ root, plexus, mono- or multiple mononeuropathies, stocking-glove, generalized



Clinical Examination

- ❖ Functional and Complex Motor Function
 - assess station and gait
 - arise from chair, climb steps
 - hop on either foot
 - heel, toe, and tandem
 - coordination, ataxia (heel-toe, finger-nose, fine motor control and rapid alternating movements)



Clinical Examination

- ❖ Deep Tendon or Muscle Stretch Reflexes
 - 0 Absent
 - 1 diminished , requires reinforcement
 - 2 normal
 - 3 hyperactive with spread
 - 4 clonus
- ❖ Plantar Response (flexor or extensor)



Electrodiagnostic Examination

- ❖ EMG/NCS is an extension of the neurological examination
- ❖ helps localize the lesion when not apparent by the H&P or confirm the clinical impression
- ❖ provides insight into the underlying pathophysiology of the lesion



Electrodiagnostic Examination

❖ Motor and Sensory Nerve Conduction Studies (NCS)

- ◆ Study at least 2 motor and sensory nerves in one arm and leg
- ◆ Sensory NCS should be normal in central disorders, motor neuron disease, neuromuscular junction disorders, and myopathies
- ◆ Motor NCS are usually normal in above disorders, but amplitudes may be reduced in atrophic muscles and in LES/botulism



Electrodiagnostic Examination

❖ NCS

- Most informative in patients with peripheral neuropathy
- Can help assess whether the pathological process primarily effects the cell body, axon, or myelin
- Useful in determine if the neuropathy multifocal or generalized, hereditary or acquired, and treatable or not

Conduction block

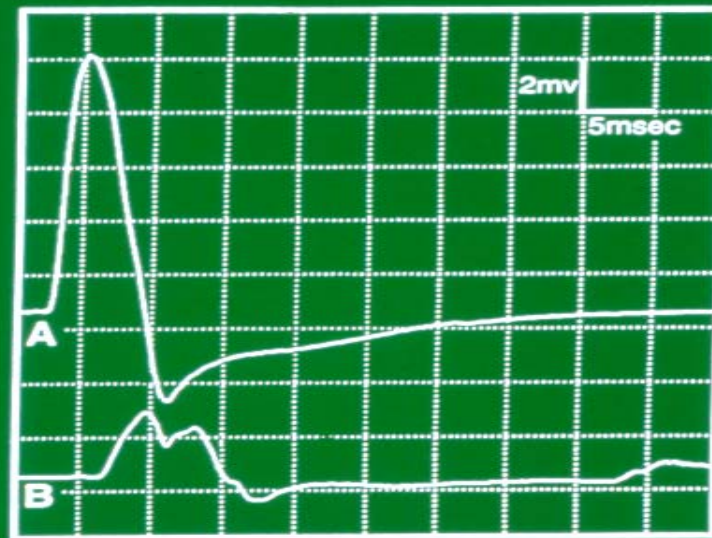


Figure 1. Conduction block on motor nerve conduction study of the left median nerve (patient 5), stimulating at the wrist (A) and elbow (B). There is an amplitude reduction of 75% and an area reduction of 69%. The negative peak duration increases by 23%.

Temporal Dispersion





Electrodiagnostic Examination

- ❖ F-waves and H-reflex
 - useful in suspected demyelinating neuropathies
 - not helpful in the majority of neuropathies which are axonal
- ❖ Blink Reflex
- ❖ Masseter Reflex



Electrodiagnostic Examination

❖ Repetitive Nerve Stimulation

- useful for assess for neuromuscular junction defects
- stimulate distal (ADM), proximal (trapezius), or facial (nasalis) muscles
- distal muscles are better tolerated with less artifact but facial and proximal muscles are usually more sensitive

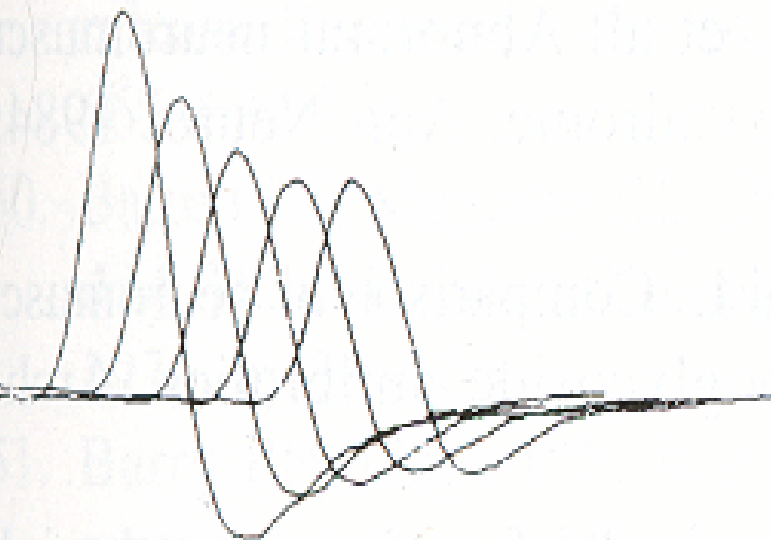


Electrodiagnostic Examination

- Myasthenia Gravis
 - ◆ 2-3 Hz stimulation at rest
 - ◆ If decrement ($>10\%$) at rest, have patient exercise for 10 sec and repeat looking for post-exercise facilitation
 - ◆ If no decrement evident at rest, have patient exercise for 1 minute and repeat repetitive stimulation every minute X 5 minutes looking for post-exercise exhaustion

R. Abd Hal

Resp (#)	NPamp (%chg)	NParea (%chg)	NPdur (%chg)	PPamp (%chg)
1	0.0	0.0	0.0	0.0
2	-22.9	-23.6	2.2	-23.5
3	-34.3	-36.0	4.3	-35.6
4	-42.2	-41.4	-2.2	-44.0
5	-41.4	-41.9	2.2	-43.2

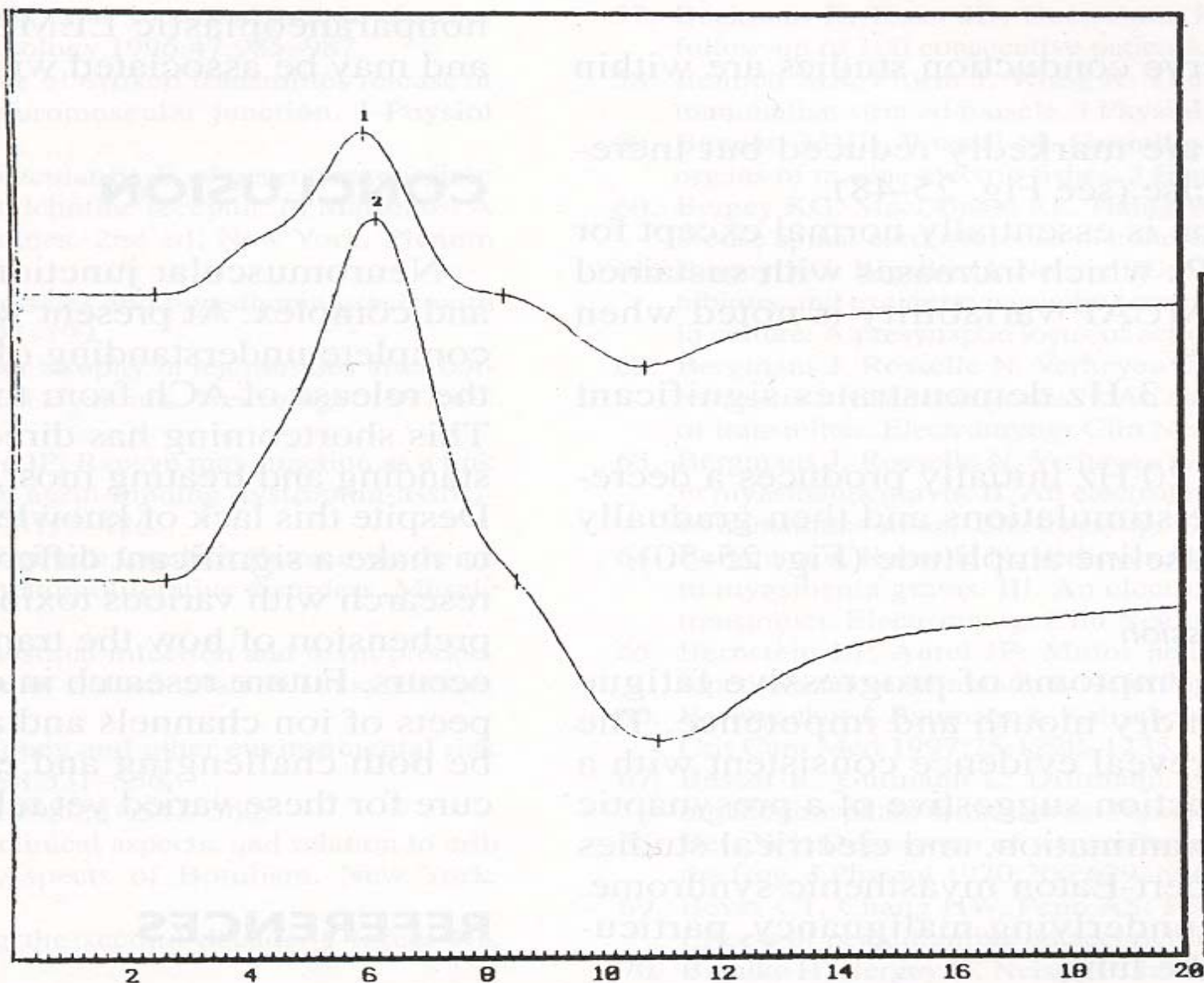


Train 1



Electrodiagnostic Examination

- Lambert- Eaton Myasthenic Syndrome
 - ◆ Baseline CMAP amplitudes are often diminished: ADM 95%, APB 85%, EDB 80%, trapezius (55%) [Tim et al; Neurology 2000;54:2176]
 - ◆ Exercise muscle for 10-15 sec and look for abnormal increment in amplitude
 - ◆ >100% increment noted in ADM (77%), APB (62%), EDB (59%), trapezius (10%)



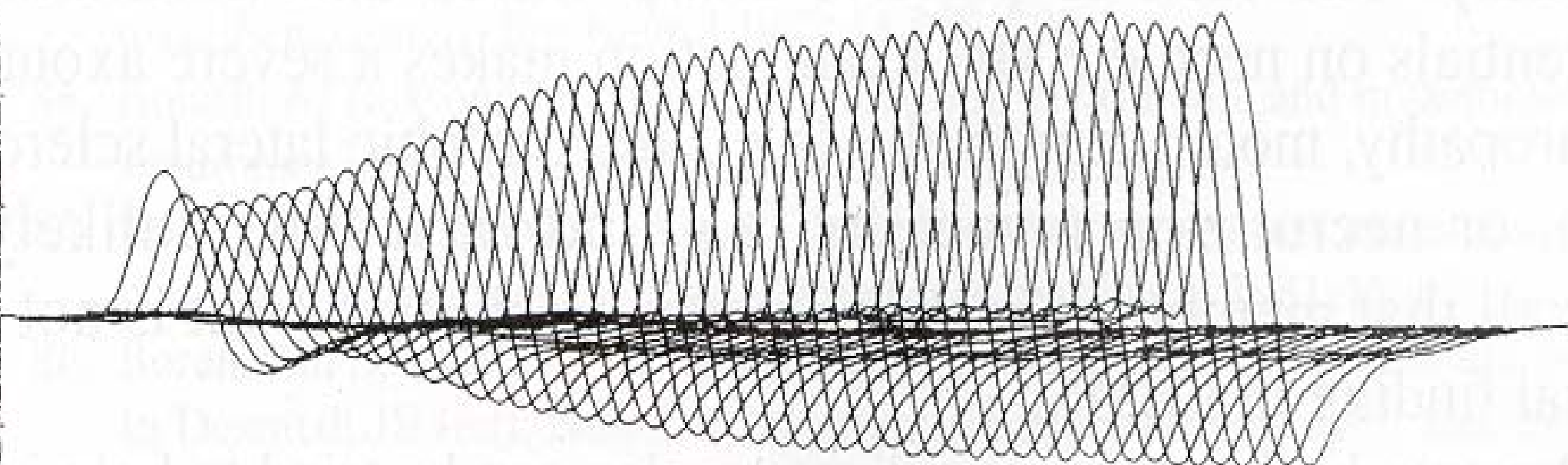
L Ulnar
 Seg 1 - Wrist to Hypothear en'in
 L ulnar
 Seg 2 - wrist to ADM p 10 sec ex

Seg #	Dist (mm)	Lat (ms)	P Lat (ms)	CU (m/s)	NPamp (mV)	NPamp %	NParea (mVms)	NParea %	NPdur (ms)	NPdur %	PPamp (mV)	Scale (mV/d)	LowF (Hz)	HighF (kHz)	Temp (°C)
1		2.5	6.0	N/A	3.43	N/A	7.96	N/A	5.9	N/A	4.93	2.0	2	10	
2		2.6	6.2	N/A	7.63	N/A	19.74	N/A	6.8	N/A	11.05	2.0	2	10	



Electrodiagnostic Examination

- Lambert- Eaton Myasthenic Syndrome
 - ◆ 2-3 Hz repetitive stimulation usually reveals a decrement: ADM and APB 98%, EDB 84%, trapezius 89%
 - ◆ post-exercise facilitation after 10-15 sec of exercise
 - ◆ post -exercise exhaustion after 1 minute of exercise
 - ◆ Abnormal increment may be noted on 20-50 Hz repetitive stimulation



2.0 mV
2 ms

Train 1



Electrodiagnostic Examination

- ❖ Electromyography (EMG)
 - Evaluate proximal and distal muscles in at least 1 arm and leg (also thoracic paraspinals and tongue may be useful)
 - ◆ insertional activity
 - ◆ spontaneous activity
 - ◆ motor unit action potential (MUAP) morphology (duration, amplitude, phases, and variability)
 - ◆ recruitment pattern



Electrodiagnostic Examination

❖ EMG

- Useful in differentiating neuropathic from myopathic disorders, acute/active versus chronic processes, NMJ disorders (variable MUAPs)
- Abnormal insertional or spontaneous activity (e.g., myotonic discharges, CRDs, myokymic discharges, PSWs, fibrillation and fasciculations potentials) may help narrow down the differential diagnosis

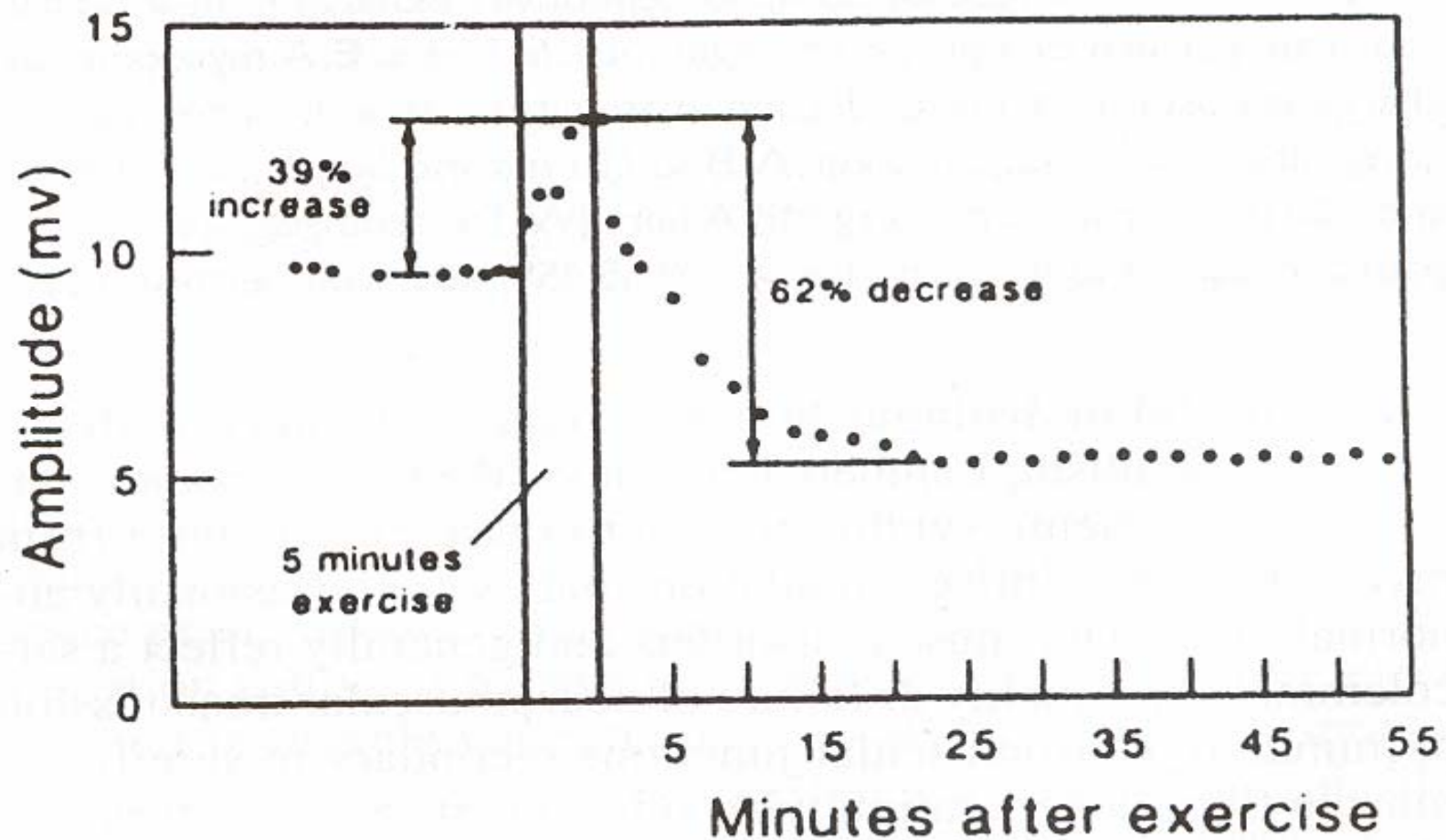


Electrodiagnostic Examination

❖ Special Studies

- short and long exercise test
- quantitative EMG
- volitional and axonal-stimulated single fiber EMG
- magnetic stimulation
- somatosensory evoked potentials
- autonomic studies

Long Exercise Test





Laboratory Evaluation

❖ Motor Neuron Disease

- sporadic: CBC, routine chemistries, TFTs, SPEP
- family history of ALS: DNA for SOD1 mutation
- symmetric proximal and distal LMN weakness: SMN mutation for SMA
- X-linked bulbospinal involvement: DNA of androgen receptor gene for Kennedy's disease
- early onset or atypical features: hexosamidase, CJD



Laboratory Evaluation

❖ Motor Neuron Disease

- heavy metal screen only if exposure history
- parathyroid hormone levels: **not helpful**
- anti-ganglioside antibodies (e.g., GM1, antisulfatide, anti-MAG) are **not useful**
- PFTs
- swallowing study



Laboratory Evaluation

❖ Peripheral Neuropathy

- symmetric sensorimotor: CBC, routine chem, TFTs, SPEP, UPEP, ESR, ANA, RF, B12, UA
- smoker: CXR
- multiple mononeuropathies: above plus cryoglobulins, hepatitis serology, ANCA
- sensory ataxia: anti-Hu, ANA, SSA, SSB, antigliadin, anti-endomysial (also Schirmer's test, Rose-Bengal stain, lip or parotid biopsy, chest CT, pelvic CT/US)



Laboratory Evaluation

❖ AIDP or CIDP

- Routine labs plus serum IFE
- If LFTs are elevated : hepatitis, CMV, EBV
- CSF : usually see albuminocytologic dissociation.
- If CSF is cellular: HIV, Lyme disease, lymphoproliferative disorder/leukemia, sarcoidosis
- AIDP: PFTs

Errors of Commision

PERIPHERAL NEUROPATHY PROFILES

- ☐ **SensoriMotor Neuropathy Profile** *-xp* (MAG 'Dual Antigen'TM, GM1TriadTM, Hu, Sulfatide, GALOP)
(1 Red top tube) ☐ Check box only to order previous version without current upgrade
- ☐ **Sensory Neuropathy Profile** *-xp* (MAG 'Dual Antigen'TM, Hu, Sulfatide, GALOP)
(1 Red top tube) ☐ Check box only to order previous version without current upgrade
- ☐ **Motor Neuropathy/Motor Neuron Disease Profile** (MAG 'Dual Antigen'TM, GM1TriadTM)
(1 Red top tube)
- ☐ **Chronic Demyelinative Neuropathy Profile** (MAG 'Dual Antigen'TM, CMT1 Evaluation Profile, GD1b) (1 Red top tube/serum, 3 Yellow top tubes ACD Solution A)
- ☐ **Small Fiber Painful Axonal Profile** (TTR met 30 Amyloidosis DNA Test, Sulfatide, Hu) (1 Red top tube/serum, 1 Lavender – EDTA)

☐ **MAG 'Dual Antigen'TM Antigen Panel 1 Test** (GGPO/MAG) (1 Red top tube)



Errors of Commision

- ❖ GM1 antibodies are seen in some patients with multifocal motor neuropathy and GBS –NOT IN GENERALIZED SENSORY NEUROPATHIES
- ❖ Anti-MAG is seen in distal, large-fiber, demyelinating sensory > motor neuropathy
- ❖ Anti-Hu is seen in paraneoplastic sensory ganglionopathies (patients manifest with large fiber loss and sensory ataxia)
- ❖ Anti-sulfatide antibodies have poor sensitivity and specificity
- ❖ heavy metal screen ordered only if there is an exposure history

Cure for Panelopathy

PERIPHERAL NEUROPATHY DIAGNOSIS SERVICE

PERIPHERAL NEUROPATHY PROFILES

- ☐ **SensoriMotor Neuropathy Profile**-xp (MAG 'Dual Antigen'TM, GM1TriadTM, Hu, Sulfatide, GALOP)
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☐ **MAG 'Dual Antigen'TM Autoantibody Test** (GGDC/MAG) (1 Red top tube)



Laboratory Evaluation

❖ Neuropathies

– hereditary neuropathies

- ◆ DNA analysis available for most forms of CMT, HNPP, familial amyloidosis (transthyretin), some mitochondrial disorders
- ◆ Porphobilinogen and delta-aminolevulinic acid if porphyria is suspected
- ◆ Vitamin E, phytanic acid, and DNA for frataxin, and some SCAs for spinocerebellar syndromes



Laboratory Evaluation

❖ Myasthenia Gravis

- acetylcholine receptor or muscle specific kinase (MuSK) antibodies, ANA, TFTs
- Chest CT
- EKG
- PFTs



Laboratory Evaluation

❖ Lambert-Eaton Syndrome

- voltage-gated calcium channel antibodies, ANA, TFTs
- chest CT

❖ Botulism

- assay serum and stool for botulinum toxin
- PCR organism in biological specimens and food
- infantile or wound botulism: may also culture stool or wound for the organism



Laboratory Evaluation

❖ Myopathies

- serum creatine kinase (CK): most sensitive and specific lab for muscle destruction
- AST, ALT, LDH, aldolase (present in muscle and liver) may also be elevated; GGT (specific for liver) should be normal
- routine chemistries (electrolyte imbalance), TFTs, ANA, RF, ESR, SPEP



Laboratory Evaluation

- ❖ Hereditary myopathies
 - DNA analysis is commercially available for dystrophinopathies, some LGMDs, myotonic dystrophy 1 and 2, FSHD, oculopharyngeal dystrophy, EDMD, some types of periodic paralysis, some glycogen storage disorders, and some forms of mitochondrial myopathies



Histological Evaluation

❖ Muscle Biopsy

- needle or open biopsy under local anesthesia
- Biopsy a weak muscle , but MRC grade 4 or above
- EMG helpful to guide muscle to biopsy
- helpful in providing definitive diagnosis in patients with objective abnormalities
- not useful in patients with only subjective complaints (e.g., myalgias, fatigue)



Muscle Biopsy

❖ Diagnosis

- ◆ inflammatory myopathy (PM, DM, IBM)
- ◆ fasciitis
- ◆ toxic myopathy
- ◆ dystrophy
- ◆ congenital myopathy
- ◆ mitochondrial myopathy
- ◆ metabolic myopathy (lipid or glycogen storage disease)
- ◆ neurogenic atrophy, including SMA



Nerve Biopsy

- ❖ Unlike muscle biopsy, nerve biopsy has limited utility
- ❖ usually abnormalities are non-specific
- ❖ most neuropathies can be diagnosed by less invasive measures



Nerve Biopsies

- ❖ Sural, superficial peroneal , or rarely superficial radial nerve biopsies
- ❖ indications: vasculitis, amyloidosis, evaluate for lymphoma/leukemic infiltrate, toxic neuropathy without typical HNPP mutation
- ❖ Not helpful in most cases of sensory and sensorimotor neuropathies



Skin Biopsies

- ❖ Punch biopsy of skin
- ❖ Measure the density of small unmyelinated nerves innervating the epidermis
- ❖ Allows for objective measurement of abnormalities in patients with mainly subjective sensory symptoms (e.g., small fiber neuropathies)
- ❖ may be useful in monitoring the natural history and response to future therapies



Skin Biopsy

- ❖ Can perform punch biopsy of skin at proximal and distal sites in legs and arms
- ❖ Stain for amyloid
- ❖ Measure intraepidermal nerve fiber density (abnormal in 50-88%) of patients with sensory neuropathy
- ❖ Increased percentage of abnormalities if include morphological abnormalities: abnormal axonal swellings and branching pattern