PATIENT WITH PROGRESSIVE GENERALIZED MUSCLE WEAKNESS

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NEUROLOGY

BENEFIS MEDICAL GROUP
• Peripheral Nervous System
  • Nerve
    • Motor neuron disorder
    • Polyneuropathy (axonal, demyelinating, mixed)
      • Acute
      • Subacute
      • Chronic
  • Neuromuscular junction
    • Myasthenia Gravis
    • Eaton Lambert Syndrome
  • Muscle
    • myopathies
MOTOR NEURON DISORDERS

• Amyotrophic Lateral Sclerosis
• Primary lateral sclerosis
• Primary muscular atrophy
AMYOTROPHIC LATERAL SCLEROSIS (ALS)

• Sporadic 90-95%
• Incidence 1.5-2.7 per 100,000/year
  • Incidence increases with the age
• Male to female ration of 1.3 to 1.5
DIAGNOSIS

• Diagnosis is based upon clinical criteria
  • Upper Motor Neuron signs
  • Lower Motor Neuron signs
    • There is no single diagnostic tests that can confirm or entirely exclude the diagnosis of ALS
DIAGNOSIS

- Lower motor neuron signs
  - Weakness
  - Atrophy
  - Fasciculation
DIAGNOSIS

• Upper motor neuron signs
  • Increased tone and increased DTR.
  • The presence of DTR in muscles that are very weak or atrophic
  • Pathologic reflexes, Babinski, Hoffman
  • Pseudobulbar affect
DIAGNOSIS

• Practically the diagnosis is made based on
  • History
  • Physical exam
  • Supported by the EMG/NCS
  • Not excluded by the neuroimaging and laboratory studies
DIAGNOSIS

By the revised El Escorial criteria, diagnosis of ALS requires the presence of:

• Evidence of lower motor neuron degeneration by clinical, electrophysiological, or neuropathological examination

• Evidence of upper motor neuron degeneration by clinical examination

• Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination.
RISK FACTORS

• Smoking
• Military service
• Other environmental factors
• Genetic susceptibility
PATHOLOGY

- Motor neuron degeneration and death
- Frontal and temporal neurons can be affected
- Intracellular inclusions are frequent
- Altered RNA processing and aggregation
- Excitotoxicity (excess of glutamate)
- Deranged neurofilaments
- Mitochondrial dysfunction
- Apoptosis
- Growth factors
MYASTHENIA GRAVIS

• Neuromuscular transmission defect
  • One of the best understood autoimmune disorder
  • Weakness is the result of an antibody mediated immunological attack direct at the postsynaptic membrane
MYASTHENIA GRAVIS

• Ocular myasthenia
• Generalized myasthenia
• Seronegative
• Seropositive
• 10% have a thymoma
EPIDEMIOLOGY

• Incidence 7-9 new cases per million
• Prevalence of 70-165 per million
• Bimodal age distribution
CLINICAL FEATURES

• Fluctuating muscle weakness
• True muscle fatigue
• 50% present with ocular symptoms
  • Patients with ocular onset, about 50% will develop generalized symptoms within 2 years
• 15% present with bulbar symptoms
• Less than 5% present with proximal muscle weakness alone
• The progression of Myasthenia peaks within the first 2 years or so.
DIAGNOSIS

- Typical history and physical exam
- Tensilon test and ice pack test have a high incidence of false positive
- Serologic tests for the antibodies
- Repetitive nerve stimulation
- SFEMG
SEROLOGIC TESTING

• AChR antibodies
  • Binding Ab are highly specific, rare false positive
  • Blocking Ab very specific and no significant false positive
  • Modulating Ab has false-positive results that can problematic
  • Titer does not predict well disease severity
    • Titer can be used as a measure of immunotherapy response and in this case titer does correlate with symptoms severity

• MuSK, muscle specific tyrosine kinase
  • Has a much better predictive value
Differential Diagnosis

- Thyroid ophthalmopathy
- Chronic progressive external ophthalmoplegia (CPEO) or Kearns-Sayre syndrome (KSS)
- Myotonic dystrophy and oculopharyngeal muscular dystrophy
- Brainstem and motor cranial nerve pathology

The differential also includes conditions that mimic generalized myasthenia:

- Generalized fatigue ("tiredness")
- Motor neuron disease (ALS)
- Lambert-Eaton myasthenic syndrome (LEMS)
- The Miller Fisher and pharyngeal-cervical-brachial variants of Guillain-Barré syndrome
- Botulism
- Penicillamine-induced myasthenia
- Congenital myasthenic syndromes
TREATMENT

• Symptomatic treatment
  • Pyridostigmine
    • Ratio oral/IV is 30:1
TREATMENT

• Immunomodulating treatment
  • Rapid
    • IVIG
    • Plasmapheresis
  • Chronic
    • Prednisone, Azathioprine, Cyclosporine and Mycophenolate mofetil
TREATMENT

- **Surgical treatment**
  - **Thymectomy**
    - Usually for patients under 60 years old
    - The time of onset of clinical effect is usually years
DRUGS THAT MAY UNMASK OR WORSEN MG

• Anesthetic agents
• Neuromuscular blocking agents*
• Antibiotics Aminoglycosides* - eg, gentamicin, neomycin, tobramycin
• Clindamycin
• Fluoroquinolones - eg, ciprofloxacin, levofloxacin, norfloxacin
• Ketolides¶ - eg, telithromycin
• Vancomycin
• Cardiovascular drugs Beta blockers - eg, atenolol, labetalol, metoprolol, propranolol
• Procainamide
• Quinidine
• Other drugs
  • Botulinum toxin, Chloroquine, Hydroxychloroquine, Magnesium, Penicillamine, Quinine
DEMYELINATING POLYNEUROPATHIES

• Acute
• Chronic
ACUTE DEMYELINATING POLYRADICULONEUROPATHY

• Guillane Barre Syndrome
  • Several variant forms
EPIDEMIOLOGY

- Incidence 1 to 2 per 100,000 per year
- Incidence increases with age
- Incidence is greater in males
CLINICAL FEATURES

• Progressive over a period of about 2 weeks, by 4 weeks 90% reaches the nadir of the disease
• Symmetric
• Absent or depressed DTR
• Usually starts in the legs
• Severe respiratory muscles weakness occurs in 10 to 30% of patients
• Paresthesias are present in 80% of cases
• Pain in the back and extremities occurs in 66%
• Dysautonomia occurs in 70%
LABORATORY FEATURES

• CSF shows elevated protein with normal cell count, up to 66% of patients have this feature in the first week of disease.

• EMG/NCS can show acute demyelination (AIDP), motor axonal or sensory axonal variants.
DIAGNOSTIC EVALUATION

• Clinical presentation

• Supported by:
  • CSF
  • EMG/NCS
DIAGNOSTIC CRITERIA

• Progressive weakness of more than one limb, ranging from minimal weakness of the legs to total paralysis of all four limbs, the trunk, bulbar and facial muscles, and external ophthalmoplegia

• Areflexia. While universal areflexia is typical, distal areflexia with hyporeflexia at the knees and biceps will suffice if other features are consistent.

• Supportive features include:
  • Progression of symptoms over days to four weeks
  • Relative symmetry
  • Mild sensory symptoms or signs
  • Cranial nerve involvement, especially bilateral facial nerve weakness
  • Recovery starting two to four weeks after progression halts
  • Autonomic dysfunction
  • No fever at the onset
  • Elevated protein in CSF with a cell count <10/mm³
  • Electrodiagnostic abnormalities consistent with GBS

• The following features make the diagnosis of GBS doubtful:
  • Sensory level (decrement or loss of sensation below a spinal cord root level as determined by neurologic examination)
  • Marked, persistent asymmetry of weakness
  • Severe and persistent bowel and bladder dysfunction
  • More than 50 white cells in the CSF
DIFFERENTIAL DIAGNOSIS

• CIDP (progression over more than 4 weeks)
• Acute polyneuropathy,
  • B1 deficiency, poisoning, vasculitis, porphyria, sarcoidosis, leptomeningeal disease, paraneoplastic disease, critical illness, Lyme disease
• Spinal cord disorders
• Neuromuscular junction disorders
• Muscle Disorders
TREATMENT

• Frequent monitoring of respiratory function (NIF or VC), DO NOT rely on pulse oximetry
• Monitor swallowing function
• IVIG
• Plasmapheresis
• DO NOT USE steroids
CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY (CIDP)

- Concept of CIDP was introduced in 1975
- Similar features with Guillane Barre but patients continue to progress beyond 8 weeks.
- GBS onset is usually easily identified
- GBS has more frequent antecedent events
EPIDEMIOLOGY

• Prevalence is about 0.8 to 8.9 per 100,000
• More progressive for older patients
CLINICAL MANIFESTATIONS

• Fairly symmetric
• Motor involvement is greater than sensory
• Sensory involvement is more severe for vibration and more severe distally
• Weakness is present in proximal and distal muscles
• Cranial and bulbar is involved in about 10 to 20%
• Globally diminished and/or absent DTR
EMG/NCS

• Partial conduction block
• Conduction velocity slowing by at least 30%
• Prolonged distal motor latencies by at least 50%
• Delay or disappearance of F waves
• Dispersion and distance dependent reduction of compound motor action potential (CMAP) amplitude
EVALUATION

• Electrodiagnostic testing is recommended for all patients with suspected CIDP

• Additional studies that may be indicated in select patients include:
  • Cerebrospinal fluid analysis
  • Nerve biopsy
  • MRI of spinal roots, brachial plexus, and lumbosacral plexus
  • Laboratory studies
  • Evaluation for inherited neuropathies
DIAGNOSTIC CRITERIA

• Progression over at least two months
• Weakness more than sensory symptoms
• Symmetric involvement of arms and legs
• Proximal muscles involved along with distal muscles
• Reduced deep tendon reflexes throughout
• Increased cerebrospinal fluid protein without pleocytosis
• Nerve conduction evidence of a demyelinating neuropathy
• Nerve biopsy evidence of segmental demyelination with or without inflammation
TREATMENT

• Immunotherapy
  • Prednisone can be used in this condition and is the first line therapy
  • Other immunotherapy can be used if prednisone is not effective and/or has side effects.