MOTOR NEURON DISEASE

I. Introduction

A. There are several diseases of the anterior horn cell for which there is no known etiology.

1. The onset is insidious and the course slowly progressive.
2. In general, classification is based upon the patient's age at onset and the associated clinical findings.
3. Several of the disorders, based upon time of onset, are listed below:

B. Clinical Classification.

1. Infants.
   a. Infantile muscular atrophy (Werdnig-Hoffman).

2. Childhood/adolescence.
   b. Progressive bulbar palsy of childhood (Fazio-Londe).

3. Adults.
   a. Progressive muscular atrophy or spinal muscular atrophy (SMA).
   b. Progressive bulbar-spinal muscular atrophy (Magee).
   c. Adult progressive bulbar palsy.
   d. Upper limb SMA (Aran-Duchenne).
   e. Amyotrophic lateral sclerosis.
   f. Primary lateral sclerosis (Erb).
   g. Pseudobulbar palsy.
   h. Hereditary spastic paraplegia.

4. The most common form of motor neuron disease is amyotrophic lateral sclerosis (ALS).
   a. Classification overlaps with categories described above.
   b. Subtypes are based upon combination of LMN & UMN involvement of bulbar and spinal motor neurons.
      (1) LMN-bulbar: progressive bulbar palsy.
      (2) LMN-spinal: progressive muscular atrophy.
      (3) UMN-bulbar: progressive pseudobulbar palsy.
      (4) UMN-spinal: progressive lateral sclerosis.
   c. Comparison of initial and terminal clinical manifestations in 70 patients with "ALS" (from Mackay).

Initial Manifestations in 70 Patients

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<tbody>
<tr>
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<td>24%</td>
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<tr>
<td>UMN</td>
<td>4%</td>
<td>10%</td>
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<tr>
<td>LMN &amp; UMN</td>
<td>7%</td>
<td>29%</td>
<td>16%</td>
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<td>15%</td>
<td>63%</td>
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Terminal Manifestations in Same 70 Patients

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<tbody>
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<tr>
<td>UMN</td>
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<td>TOTAL</td>
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C. Additional Forms of Motor Neuron Disease.

1. "Degenerative" disorders including:
   a. HMSN type II.
   b. Shy-Drager Syndrome.
   c. Friedreich's ataxia.
   d. Scapuloperoneal syndrome.
2. Infectious disorders, all of which may demonstrate multifocal anterior horn cell destruction.
   a. Poliomyelitis.
   b. Herpes zoster.
   c. Coxsackia virus.
   d. Jacob Creutzfeld disease.
3. Paraneoplastic syndrome.
5. MND associated with juvenile asthma.
6. MND associated with diabetes mellitus.
   a. Diabetic amyotrophy.
   b. ? relationship to hypoglycemia.
7. Toxic motor neuronopathies.
   a. Dapsone.
   b. Disulfiram.
8. MND associated with structural lesions.
   a. Syringomyelia or syringobulbia.
   b. Cervical spondylotic.
      (1) Motor neuron loss above level of lesion may relate to venous stasis.

II. Electrodiagnostic Evaluation

A. The patient with weakness and normal sensation may have abnormality of:

1. Upper motor neurons.
2. Anterior horn cells.
3. Ventral roots.
5. Neuromuscular junction.

B. In all of these disorders, electrodiagnostic studies are abnormal, although the abnormalities may be more apparent in some than in others.
1. For example, in patients with weakness secondary to upper motor neuron lesions:
   a. Conduction studies are normal.
   b. There may or may not be evidence of abnormal insertional activity on needle electromyography.
   c. Motor unit action potential (MUAP) recruitment is erratic and irregular.
2. In patients with defective neuromuscular transmission, repetitive stimulation or SFEMG studies are required to establish abnormality.

C. Sensory Evaluation.

1. Although the clinical examination may demonstrate marked involvement of the motor system without apparent sensory abnormality, an intact peripheral sensory system can be documented easily as the first step in the evaluation.
2. Mild, slowly progressive sensory loss may go unnoticed by the patient and the examining physician.
3. One of the most sensitive sensory tests for diffuse sensory involvement:
   a. Sural evoked responses.
   b. Reduced amplitude is the most sensitive indicator of axonal degeneration of sensory fibers.
4. A carefully performed sensory examination has a sensitivity approximately equal to that of the electrodiagnostic examination, differing only in its degree of quantification.

D. Motor Evaluation.

1. Should be performed on the most involved region, if possible.
2. Absent responses provide important information, but the information is not sufficiently specific to define the underlying pathophysiology.
3. Abnormalities on the screening motor examination should direct subsequent evaluation of specific problems.
   a. Neuromuscular junction abnormality.
   b. Myopathy.
4. Motor evoked response amplitudes are commonly reduced, and there may be a greater than 50% difference in amplitude between sides.
5. A simplified protocol for the initial evaluation of the weak patient is summarized in Table I.
6. In clinically involved muscles, there may be a decremental motor response to repetitive stimulation at low rates (2 Hz).
   a. Related to immature neuromuscular junctions following recent reinnervation from collateral sprouting of surviving axons.
   b. Related to terminal nerve twig conduction block.
   c. Decremental response implies poor prognosis (rapid denervation).

E. Concentric Needle Examination.

1. Progressive disorders of the motor neuron include evidence of acute and chronic denervation, characterized by:
a. Large, highly polyphasic MUAPs.
b. Frequent satellite potentials.
c. Large and small fibrillation potentials.
   (1) Chronically denervated fibers atrophy.
   (2) Surviving fibers hypertrophy prior to late denervation.

2. Denervation must be present in a distribution that cannot be explained by a single focal lesion.
a. i.e., in at least three extremities.
b. In this context, the head can be considered an extremity.

3. In any given extremity the needle examination should be sufficient to demonstrate that abnormalities are not confined to muscles innervated by a single nerve or root.
   a. Patient with chronic neurogenic changes in both lower extremities and a superimposed ulnar mononeuropathy should not be confused with a person with diffuse motor neuron involvement.

4. There may be evidence of ongoing denervation in paraspinal muscles.
   a. Commonly these muscles are involved to a lesser extent than extremity muscles.
   b. Paraspinal muscles may be normal.

5. Fasciculation potentials are frequently found but, by themselves, are not indicative of motor neuron disease.

F. The protocol for evaluation of suspected motor neuron disease is identical to the weakness protocol, although bilateral motor evoked responses may be performed to demonstrate the asymmetric involvement.

1. The protocol is summarized in Table II.
2. Of the listed criteria, the single most important one involves identification of multifocal disease over a widespread region of the neuroaxis that is not explained by other abnormalities.

III. Additional Comments Regarding EMG Evaluation in Suspected ALS

A. The disease is clinically characterized by subacute onset of progressive (occasional plateau), asymmetric weakness and wasting.

B. Additional signs of spasticity and hyperreflexia.

1. Perform screening neurologic examination prior to EMG.
2. Look for MUAP recruitment abnormalities suggestive of UMN involvement.

C. Fasciculations, commonly observed during examination, may or may not have been noticed by the patient.

D. The natural course of the disease is characterized by spreading to almost all muscles of the body (extra-ocular and sphincter muscles typically spared).

1. There may be periods of arrested progression or even improvement.
E. Average life expectancy after diagnosis is less than four years.
   1. Approximately 20% of patients demonstrate a "benign" form of motor neuron disease.
   2. Some patients live as long as 25 years after diagnosis.

F. Early involvement of bulbar muscles usually is associated with poor prognosis (not universal).

G. Electrodiagnostic studies are aimed at demonstrating widespread denervation (e.g. in three extremities or bulbar muscles and lower extremities).
   1. The most common pitfalls include:
      a. Failure to distinguish ALS from a focal spinal lesion such as cervical spondylosis with cervical polyradiculopathy (wasting of upper limbs) and myelopathy (hyperreflexia of lower limbs).
      b. Confusion with a diffuse polynovopathy. Like the clinical sensory examination, sensory conduction studies must be normal prior to making the diagnosis of motor neuron disease.
      c. Basing diagnosis upon fasciculations alone. Fasciculations can be seen in normal subjects and do not necessarily indicate pathology.

H. Ancillary electrodiagnostic procedures.
   1. Single fiber electromyography (SFEMG).
      a. This procedure permits quantitative evaluation of neuromuscular transmission and muscle fiber density.
      b. In motor neuron disorders, the ongoing denervation/reinnervation results in an increased muscle fiber density per individual motor unit.
      c. Immature, reinnervated fibers frequently demonstrate defective neuromuscular transmission.
      d. SFEMG studies are frequently abnormal in clinically normal extremities, providing evidence for a widespread, rather than focal, disorder.

I. Additional studies include:
   1. Muscle biopsy.
      a. Occasionally useful in demonstrating evidence of subclinical denervation in clinically normal muscle.
      b. Muscle biopsy may demonstrate chronic neurogenic changes in the lower extremity of a patient having only focal upper extremity findings.
      c. This procedure is of limited use in this context.
   2. The serum creatine phosphokinase (CK) and other muscle enzymes.
      a. Elevated in approximately 50% of patients.
      b. This may reflect the extent of ongoing muscle fiber degeneration.
   3. Myelography and CSF examination are normal with the exception of occasional elevation of CSF total protein.
IV. Specific Electrodiagnostic Findings in Adult Amyotrophic Lateral Sclerosis

The clinical and electrodiagnostic records of 35 consecutive patients having an established clinical diagnosis of ALS were reviewed (UM adult patients). The EMG findings are summarized below. An EMG protocol identical to that described above was used in all evaluations.

A. Conduction studies.

1. 73% of patients had at least one abnormally low motor evoked amplitude.
2. 88% of patients had asymmetric motor evoked amplitudes.
   a. Defined as 100% difference between sides.
   b. i.e., one side at least twice as large as the other.
3. When asymmetric motor evoked amplitudes were considered a significant abnormality, 82% of patients had abnormal studies.
4. 100% of patients had normal median or ulnar sensory conduction studies.
   a. 18% had mildly abnormal sural responses.
   b. Therefore, normal sensory studies not a "must", but need to qualify.
5. Frequency of abnormal motor studies (low amplitude or asymmetry):
   a. Median (67%).
   b. Ulnar (56%).
   c. Peroneal (48%).
   d. Tibial (33%).
6. 43% of patients had a decremental motor response to low rate (2Hz) stimulation. In all, the baseline response was of low amplitude and all of these patients had rapidly progressive disease.

B. Needle Electromyography.

1. All patients had studies that fulfilled the criteria of "3 extremity" involvement.
2. All patients had abnormal recruitment. "Giant" MUAPs were commonly noted.
3. MUAPs of increased polyphasia, representing collateral reinnervation, were common.
4. All patients had evidence of acute and chronic denervation.
   a. e.g., large, polyphasic MUAPs, with large and small fibrillation potentials.
   b. Complex repetitive discharges were recorded from 18% of patients.
5. Based upon subjective grading of fibrillation, if there was a single muscle "most" involved, it was most commonly the FDI in the hand (58%), followed by the anterior tibialis (25%).
   a. When multiple muscles were "most" involved, most commonly included were the FDI, anterior tibialis, APB, quadriceps, and gastrocnemius muscles.
6. Muscles most commonly spared or minimally involved were:
   a. Paraspinal muscles (81%).
   b. In only 13% of patients were there 3 to 4+ fibrillation potentials in paraspinal muscles (as opposed to the common occurrence in patients with polyradiculoneuropathy).
c. In a small patient sample, the rectal sphincter was found to be spared.

7. Prominant fasciculation potentials were recorded in most muscles in 68% of patients. In 13% of patients, no fasciculations were recorded.

8. In 22% of patients with moderately severe disease, there were muscles containing no voluntary MUAPs (most common muscle: FDI, 76%).

9. Four patients who initially did not fulfill the requirement for three extremity involvement, had only increased jitter and muscle fiber density on SFEMG in the asymptomatic, clinically normal limb. All four later developed diffuse disease.

V. Motor Neuron Disease In Infants and Children

A. The evaluation of children with suspected motor neuron disease is much more difficult than the evaluation of adults.

B. Although the general protocol is similar, technical difficulties in performing the evaluation are common.

1. Sensory evoked response amplitudes are normal, and it is usually possible to record sural or median sensory nerve action potentials even in the neonate.

2. The normal CMAP amplitude is highly variable in neonates and amplitude comparison between sides, while useful, often is difficult, particularly in the neonatal intensive care unit.

3. Repetitive motor nerve stimulation studies can be performed, and a decremental response is abnormal.
   a. The presence of a small decrement does not indicate neuromuscular junction disease, but may reflect ongoing reinnervation.
   b. Conduction studies most easily performed on the ulnar (hypothenar recording), median (thenar) or peroneal (EDB or anterior tibialis) nerves.

4. The needle EMG findings in Werdnig-Hoffman disease are similar to those described above for amyotrophic lateral sclerosis.
   a. The examination is more difficult in the infant because of the small amount of muscle tissue that can be sampled and because of limited cooperation.
   b. Fibrillation potentials away from the end-plate region are an abnormal finding after two to three days following birth in a term infant.
   c. The amount of abnormal spontaneous activity identified is directly related to the extent of the needle examination in a struggling child.
   d. Diligent evaluation of one or two muscles in an upper and lower extremity is preferable to limited study of many muscles.
   e. Recruitment abnormalities alone usually are meaningless.
      (1) Estimation of MUAP size is sometimes possible.
   f. Fasciculation potentials are relatively uncommon.
   g. Some of the slowly progressive forms of childhood motor neuron disease may mimic disorders such as myasthenia gravis when there is predominant bulbar involvement.
TABLE I
Weakness Protocol

A. Conduction Studies

1. Sural sensory (ankle); stimulate 14 cm proximal to recording electrode.

2. If sural equivocal or technically difficult:
   a. Opposite sural
   b. Median sensory

3. Ulnar motor (hypothenar); stimulate at wrist and elbow and record F-response latency. Repetitive supramaximal stimulation at wrist (2 Hz x 4 stimuli) before and immediately after 5 seconds of maximal voluntary exercise. (Fingers should be restrained or taped together).

4. If proximal weakness predominates: Musculocutaneous motor (biceps brachii); stimulate at axilla with repetitive supramaximal stimulation as in item 3.

5. If legs weaker: Peroneal nerve (EDB); stimulate at ankle. Record F-response latency and perform repetitive stimulation.

6. Abnormality in any of the above requires further evaluation of suspected disorder (e.g., polyradiculopathy, myopathy, neuromuscular transmission abnormality, etc).

B. Needle Examination.

1. Examine selected distal and proximal muscles, in upper and lower limbs, including paraspinal muscles.

2. For example, biceps brachii, first dorsal interoseous (hand); vastus lateralis; anterior tibialis; medial gastrocnemius; lumbar paraspinal muscles.
TABLE II

Motor Neuron Disease Protocol

(Supplement to Weakness Protocol)

A. Conduction Studies.

1. Conduction studies as indicated under Weakness Protocol.

2. When low or borderline-low evoked motor response amplitude is demonstrated:
   a. The contralateral side should be examined.
   b. Use repetitive supramaximal stimulation (2 Hz x 4 stimuli).

B. Needle Examination.

1. Needle electromyography should be based upon clinical findings with the following considerations:
   a. Two muscles innervated by different nerves and roots must have fibrillation potentials and MUAP changes in each of three extremities to confirm the diagnosis (head considered as extremity).
   b. Select muscles initially that are most likely abnormal, e.g., weak or atrophic.
   c. Do not attempt to localize abnormality to one nerve before looking for widespread changes.
   d. If clinically involved muscles show no definite abnormality, do not spend extensive time examining many normal muscles.
   e. Look for variation in MUAP amplitude suggesting defective neuromuscular transmission.