Chapter 12
Overview of Motor Neuron Diseases

Alice B. Schindler

Motor neuron disorders (MNDs) are a clinically and pathologically heterogeneous group of sporadic and hereditary neurologic diseases characterized by progressive degeneration of motor neurons. Either or both of the following two sets of motor neurons can be affected:

- Upper motor neurons (UMNs, also called corticospinal neurons), which originate from the primary motor cortex of the cerebrum (precentral gyrus) and possess long axons forming corticospinal and corticobulbar tracts
- Lower motor neurons (LMNs), which originate in the brainstem (cranial nerve [CN] motor nuclei) and spinal cord (anterior horn cells) and directly innervate skeletal muscles

MNDs can be classified into those affecting primarily the UMNs, those affecting primarily the LMNs, and those affecting both, and the nomenclature is used accordingly. The patient's symptoms vary by the set of motor neurons involved.

The motor neuron diseases are progressive neurological disorders that destroy motor neurons, the cells that control voluntary muscle activity such as speaking, walking, breathing, and swallowing. Normally, messages from nerve cells in the brain (UMNs) are transmitted to nerve cells in the brain stem and spinal cord (LMNs) and from there to particular muscles. Upper motor neurons direct the lower motor neurons to produce movements such as walking or chewing. Lower motor neurons control movement in the arms, legs, chest, face, throat, and tongue.

When signaling disruptions occur between the lower motor neurons and the muscle, the muscles do not work properly; the muscles gradually weaken, may begin wasting away (*atrophy*), and develop uncontrollable twitching (*fasciculations*). When signaling disruptions occur between the upper motor neurons and the

A.B. Schindler (✉)
Neurogenetics Branch/NINDS/NIH, 10 Center Drive, Building 10 Room 5S-219, Bethesda, MD 20892-1671, USA
e-mail: schindlerab@mail.nih.gov

J.S. Goldman (ed.), *Genetic Counseling for Adult Neurogenetic Disease*,
DOI 10.1007/978-1-4899-7482-2_12

lower motor neurons, the limb muscles develop stiffness (*spasticity*); movements become slow and effortful, and tendon reflexes such as knee and ankle jerks become overactive (hyperreflexive). Over time, the ability to control voluntary movement can be lost.

No specific tests can diagnose most MNDs definitively, although molecular genetic testing is available for some hereditary forms of MNDs such as spinal and bulbar muscular atrophy (SBMA)/Kennedy disease (KD), hereditary spastic paraplegia (HSP), spinal muscular atrophy (SMA), and some forms of amyotrophic lateral sclerosis (ALS)/Lou Gehrig Disease. Symptoms may vary among individuals and, in the early stages of the disease, may be similar to those of other diseases, making diagnosis difficult. A physical exam should be followed by a thorough neurological exam. The neurological exam will assess motor and sensory skills, nerve function, hearing, speech, vision, coordination and balance, mental status, and changes in mood or behavior. Diagnostic evaluations may include electromyography (EMG) with nerve conduction studies (NCV), brain and spine MRIs with and without contrast to evaluate for structural anomalies and changes in white matter, laboratory testing of blood and urine, and in some cases a nerve and/or muscle biopsy.

This chapter focuses on upper motor neuron diseases, such as HSP; lower motor neuron diseases, such as SBMA or Kennedy disease (KD); and those diseases affecting both systems, such as ALS or Lou Gehrig disease.

12.1 Genetic Counseling Issues for MNDs

Molecular genetic testing is often essential for diagnosis of MNDs. Due to clinical overlap of MNDs, genetic testing can be useful for confirming a clinical diagnosis or, in some instances, ruling out another disorder. Individuals with SBMA, for example, are often initially diagnosed with ALS. Molecular genetic diagnosis enables health providers to offer patients information regarding natural history, prognosis, inheritance pattern, and possible treatment and/or research trials.

Patients often report a lack of family history, and are therefore perplexed and in denial when molecularly diagnosed, as neither of the parents had overt symptoms. This is certainly the case with autosomal recessive forms of ALS and HSPs.

For family members interested in undergoing presymptomatic genetic testing to determine their mutation status, the familial mutation must be known. Once the familial mutation is known, most centers follow the protocol established for Huntington disease (HD) or have adopted a condensed protocol. At the very least, an individual should be offered face-to-face, pre- and post-test genetic counseling, a complete neurological examination performed by a neurologist familiar with the MND in question, and have a support person accompany them to each visit.

12.2 Family History Questions Pertinent to Motor Neuron Diseases

Targeted questions about family history can help determine if a condition is hereditary and assist with diagnosis. A three or more generation pedigree should always be taken that includes documentation of any neurological or psychiatric condition with ages of onset and ages of death.

When taking the pedigree, the patient and informant should be asked the following questions:

Upper Motor Neuron Diseases

- Does anyone in your family have spasticity?
- Does anyone in your family have balance or coordination problems?
- Does anyone in your family have stiffness in their legs (hamstrings or Achilles)?
- Does anyone in your family have exaggerated reflexes?
- Does anyone in your family have slurred speech or swallowing difficulties?

Lower Motor Neuron Diseases

- Does anyone in your family have muscle twitches?
- Does anyone in your family have muscle weakness?
- Does anyone in your family have muscle wasting/atrophy?
- Does anyone in your family have muscle cramping?
- Does anyone in your family have slurred speech or swallowing difficulties?