Clinical Neuromuscular Pathology
Core Curriculum and Core Content
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I. Core Curriculum

A. Definition of the Subspecialty

Clinical Neuromuscular Pathology is a subspecialty area of neurology defined by special competence in the interpretation of muscle and nerve pathology. It differs from neuropathology because it is highly integrated with the clinical management of neuromuscular disease. All United Council for Neurologic Subspecialties (UCNS) training programs in Clinical Neuromuscular Pathology must incorporate the evaluation of muscle and nerve biopsies in the context of clinical patient care.

B. Goals

The goal of the Clinical Neuromuscular Pathology training program is to train candidates to fully evaluate muscle and nerve pathology in the context of the unique clinical setting that each patient presents to the physician. The trainee should learn to stop at nothing short of exploring all means of relevant diagnosis. This does not mean performing tests without careful thought but rather to be inclusive to the extent that all avenues of specific diagnosis are explored on behalf of every patient. The trainee should not only be familiar with the appropriate histological methods for analysis but should be well-acquainted with the histological techniques through first hand exposure. This will require a laboratory rotation to become familiar with the methods. This is critical for the assessment of microscopic sections and stains in order to recognize artifacts of tissue handling (causes and cures). In addition, the training program should teach the principles and importance of research methods that can be applied to pathological material. For example, while it may be impractical to employ quantitative means of analysis (morphometrics) in the routine evaluation of all case material, trainees should learn the techniques used for this type of analysis. This will help prepare individuals for interpretation of the literature relevant to muscle and nerve pathology and expose individuals to research methodology. In addition, it will provide a basis for understanding when such methods might be important for the evaluation of cases submitted for diagnostic workup. With regard to research, the goal is not to train individuals in “bench” research but rather to familiarize trainees with the methods used for outcomes research that can be applied to clinical material. Such methods include data collection, organization, and storage appropriate to address specific questions. Trainees should also learn appropriate statistical methods applicable to outcomes research.

C. Objectives

1. Muscle
   a. Overall
      Upon completion of the training program, the fellow should have acquired the following fund of knowledge skills:
      1) Recognize the pathologic findings in muscle biopsy specimens.
      2) Correlate the pathological findings with clinical manifestations of muscle diseases.
      3) Accurately and concisely describe the pathologic findings in biopsy specimens, formulate an appropriate pathological diagnosis, and offer comments about diagnosis based on the biopsy findings in the context of the clinical history.
      4) Develop expertise in the relevant current and previous literature on neuromuscular diseases.

   b. Specific
      1) Understand the indications for obtaining a muscle biopsy and choose an appropriate biopsy site for it based on the clinical evaluation and electrophysiologic findings.
2) Be aware of potential untoward results of the muscle biopsy procedure: hemorrhage into the specimen, crushing of tissue, damage by inappropriate dissection, and insufficient amount of tissue.
3) Recognize artifacts due to improper flash-freezing, sectioning, staining, and storage of biopsy specimen.
4) Learn the use and application of the following:
   a) modified Gomori trichrome stain;
   b) histochemical reactions to display oxidative enzymes, histochemical fiber types, nonspecific esterase activity, lysosomal enzyme activity; and
   c) stains for lipid and glycogen deposits and for amyloid deposits.
5) Be familiar with the use and application of currently available immunostains for different types of muscular dystrophy, lymphocyte subsets in muscle, expression of Class I and II HLA antigens, and deposits of complement components C3 and C5b9.

2. Nerve
   a. Overall
      Upon completion of the training program, the fellow should have acquired the following fund of knowledge and skills:
      1) Recognize preparatory artifacts and pathologic abnormality in nerve tissue obtained at biopsy.
      2) Correlate the pathological findings with clinical manifestations of nerve disease.
      3) Enable the trainee to accurately and concisely describe the pathologic findings of biopsy specimens, formulate an appropriate pathologic diagnosis, and offer comments about diagnosis based on the biopsy findings in the context of the clinical history.
      4) Become familiar with the relevant current and previous literature on neuromuscular diseases.
   b. Specific
      1) Understand the indications for obtaining a nerve biopsy and choose an appropriate biopsy site for it based on the clinical evaluation and electrophysiologic findings.
      2) Be aware of potential untoward results of the nerve biopsy procedure; hemorrhage into the specimen, crushing of tissue, damage by inappropriate dissection, and insufficient amount of tissue.
      3) Recognize artifacts due to improper handling, flash-freezing, fixation, osmification, sectioning, staining, and storage of the biopsy specimen.
      4) Learn the use and application of the following:
         a) teased nerve fibers;
         b) H&E;
         c) trichrome stain;
         d) amyloid stains;
         e) semithin epoxy sections; and
         f) electron microscopy.
      5) Be familiar with the use and application of currently available immunostains, lymphocyte subsets in the nerve, Schwann cells, perineurial cells, amyloid subtypes, and other.

3. Research Methods
   a. Understand the principles of outcomes research
D. Methods of Training
The purpose of the clinical neuromuscular pathology fellowship is to train physicians expert in the care of neuromuscular patients and the interpretation of their nerve and muscle biopsies. The harvesting of nerve and muscle biopsies may be done by surgeons or by the neuromuscular physicians and fellows themselves depending on individual program's preference. Clinical neuromuscular fellows are not required to perform nerve or muscle biopsies during their training. While the taking of nerve and muscle biopsies is not an integral component of the fellowship training, the candidates must be familiar with these biopsy techniques and have witnessed the performing of both nerve and muscle biopsies in order to understand the artifacts that can occur during their harvesting.

The trainee will observe or perform the muscle or nerve biopsies, assist in histological preparations, staining procedures, and acquiring microscopic images of pathological feature and/or artifacts of all biopsies for presentation to the faculty. Each case will be reviewed by the trainee with faculty supervision. The appropriate method of reporting findings will be taught including the description of findings, diagnosis and comments related to interpretation of findings. Each trainee will evaluate and write up no less than 100 muscle and nerve biopsies of which no less than 30 should be either muscle or nerve.

Trainees must review and present all available clinical and laboratory findings of each patient undergoing muscle or nerve biopsy.

Trainees should also be taught the principles of data storage and organization, and outcomes research methodology using appropriate statistical measures.

E. Methods of Evaluation
The trainee will be working closely with the neuromuscular faculty on a frequent and regular basis completing muscle and nerve biopsy reports. This will provide the opportunity to evaluate progress as demonstrated by completion of reports and in case discussions. All reports will be edited, finalized and filed for longitudinal evaluation of the trainee’s progress.

At six month intervals the trainee will have a formal meeting with program director for feedback on progress. A written report will be generated with input from the entire neuromuscular faculty (each faculty member submitting a separate report and collated by the program director). At the six month meeting the trainee will also be provided the opportunity to discuss faculty performance and the trainee will be asked to submit a written report inclusive of the performance of each faculty member.

F. Methods of Feedback
Feedback will take place as described above. Following the six month meetings with the program director, a written report will summarize the performance of the trainee and include comments regarding expectations. The trainee will also provide a written evaluation that will include problems that have been encountered and comments regarding faculty training.
II. Core Content

A. Program Content

The Clinical Neuromuscular Pathology program is based upon the pathological studies of muscle and nerve and their clinico-pathological correlations. Muscle and nerve pathology is evaluated in the context of the clinical case history, physical findings, and laboratory assessment including electrophysiology, and all blood and urine tests, as well as any specific tests of other organ system functions. This material is collated and reviewed and serves to establish a plan of action for analyses of muscle and nerve biopsies. The differential diagnosis of the clinical problem is used to influence special stains used to assess the tissue. While a standard battery of stains follows a template for evaluation of all muscle and nerve biopsies, individual case analysis will dictate special stains that are required. These stains can include ones more clearly delineating a presumed autoimmune pathogenesis or a specific molecular-biochemical defect. In some instances recommendations for western blots or biochemical tissue analysis will be necessary.

1. Muscle
   a. Basic features and general reactions of muscle as a tissue:
      1) The histochemical properties of different muscle fiber types.
      2) The pattern and distribution of the histochemical fiber types in different muscles.
      3) Normal and abnormal distribution of muscle fiber diameters.
      4) Normal and abnormal frequency of internal fiber nuclei.
      5) Recognition and causes of type 2 or type 1 fiber atrophy.
      6) Features of necrotic and regenerating fibers.
      7) Evaluation of connective tissue elements and vasculature.
   b. Recognition of the pathologic features and knowledge of different categories of muscle diseases
      1) Congenital myopathies
         a) specific morphologic features of currently recognized congenital myopathies
         b) nonspecific morphologic features of currently recognized congenital myopathies
         c) currently recognized disease genes for congenital myopathies
      2) Metabolic myopathies and rhabdomyolysis
         a) specific and nonspecific features of glycogen storage myopathies
         b) available histochemical methods for the diagnosis of glycogen storage myopathies
         c) currently recognized etiologies of glycogen storage myopathies
         d) recognition and possible causes of polyglucosan deposits in muscle
         e) histologic features and causes of lipid storage myopathy
         f) histologic features indicating mitochondrial myopathies
         g) mitochondrial abnormalities secondary to aging
         h) histologic features and causes of rhabdomyolysis
      3) Channelopathies
         a) histologic features associated with Na⁺ and K⁺ channelopathies of skeletal muscle
      4) Inflammatory myopathies
         a) principal histologic features of major idiopathic inflammatory myopathies
            (polymyositis, dermATOMyositis, inclusion body myositis)
         b) methods to phenotype inflammatory cells and their usefulness
         c) methods to display the muscle microvasculature
d) distinguish features of necrotizing and other types of vasculitis in muscle
c) identification of parasites in muscle
f) pyomyositis

5) Systemic disorders
a) systemic sclerosis
b) sarcoidosis
c) identification of and knowledge of causes of amyloid deposits in muscle
d) hypokalemic myopathy
e) hyperthyroidism
f) hypothyroidism
g) uremic hyperparathyroidism
h) malnutrition
i) Critical illness myopathy

6) Muscular dystrophies
a) general histologic features of muscular dystrophies
b) histologic features suggesting specific types of muscular dystrophies
c) available monoclonal antibody tests for specific diagnosis
d) knowledge of gene-centered classification of muscular dystrophies

7) Toxic and exogenous trauma
a) emetine myopathy
b) colchicine myopathy
c) chloroquine myopathy
d) zidovudine therapy
e) HMG-CoA reductase inhibitors
f) fibric acid derivatives
g) hyper- and hypovitaminosis E
h) organophosphate poisoning
i) acute alcoholic myopathy
j) myopathy caused by intramuscular injections
k) focal muscle changes caused by EMG examination

8) Neurogenic disorders
a) patterns of recent denervation
b) patterns of chronic denervation associated with reinnervation

9) Neuromuscular junction
a) identification of neuromuscular junctions by the nonspecific esterase reaction
b) detection of immune deposits and risks of artifacts (C3-, C5b9-, and IgG localization with Protein A-reactivity)

2. Nerve
a. Basic Histological Alterations and Artifacts
1) Nerve fiber alterations
a) identification of nerve tissue – peripheral, ventral and dorsal root, spinal and autonomic, ganglia and nerve endings in the skin
b) fiber number – normal, decreased (slight, moderate, or severe), increased (slight, moderate, or severe), generalized, focal or multifocal, and other
c) size distribution of nerve fibers – abnormality of size classes, selectively of large MF, selectively of small myelinated fibers or selectively of unmyelinated fibers, or other

d) pathologic conditions of teased myelinated fibers – normal (A), myelin wrinkling (B), segmental demyelination (C), demyelination and remyelination (D), axonal degeneration (E), remyelination (F), myelin reduplication (G), axonal regeneration after degeneration (H), distal axonal degeneration (I), and other

e) axon alterations – axonal enlargement, axonal atrophy, dark axons with light cores suggestive of ischemic injury, axon spheroids, polyglucosan bodies, glycogen accumulation, adaxonal sequestration, and other

f) myelin and Schwann cell alterations – myelin irregularity, onion bulbs (generalized, focal, or multifocal), reduplication, increased spacing of myelin lamellae, and other

g) Schwann cell inclusion – Metachromatic Leukodystrophy (MLD), Krabbe, Fabry, and other

h) artifacts – crush, freezing, poor fixative, poor osmication from inadequate infiltration, inadequate control, and other

i) other

2) Interstitial alterations

a) endoneurium – size (normal, increased, or decreased), fluid (normal or increased), connective tissue (increased or decreased or abnormality), inflammatory cells (kind and frequency), neoplastic cells (kind and frequency), vessel alteration (microvessel, arteriole, or venule) and histologic change, tissues infiltrates, hemosiderin cellular infiltrates (CD45, CD68, and other), hemosiderin, and other

b) perineurium – number of lamellae (normal, decreased, or increased), increased perineurium (focal or generalized), cellular infiltration (kind and severity), vessel alteration (as in a)

c) epineurium – alteration of small arteries, large and small arterioles, venules and microvessels – degenerative alterations, e.g., atherosclerosis, medial arterial calcification, basement membrane reduplication, and infiltration of inflammatory cells or abnormal material (amyloid), inflammatory cell infiltration and histologic reaction, e.g., granuloma (as in a)

3) Hereditary and congenital (non-metabolic)

a) aplasia of normal nerve fiber population

b) maldevelopment of nerve fiber classes, e.g. Hereditary Sensory and Autonomic Neuropathy (HSAN) 2-5

c) Schwann cell and other nerve fiber or cellular inclusion in errors of metabolism, e.g., Metachromatic Leukodystrophy (MLD), Krabbe, Tay Sachs, Adrenal Leukodystrophy (ALD), Fabry, Tangiers disease, etc.

d) giant axonal polyneuropathy

e) neuroaxonal dystrophy

4) Metabolic

a) diabetic neuropathies – cranial, typical Diabetic Polyneuropathy (DPN) Diabetic Sensory Predominant Polyneuropathy (DSPN), atypical DPN, radiculoplexus neuropathies (RPN) – lumbosacral, thoracic or cervical, compression and entrapment neuropathies (median, ulnar, and peroneal nerves)

b) acromegaly neuropathy
c) hypothyroid neuropathy
d) hepatic neuropathy and xanthomatous neuropathy
e) Multiple Endocrine Neoplasia (MEN), 2b
f) Neuropathies associated with nutritional deficiency – after bariatric surgery, caused by nutritional deficiencies, copper deficiency neuropathy

5) Inflammatory and immune
   a) inflammatory and demyelinating
   b) acute – Acute Inflammatory Demyelinating Polyneuropathy (AIDP), AMAN
   c) chronic – Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), multifocal CIDP (MADSAM), sensory CIDP, Chronic Inflammatory Sensory Polyradiculopathy (CISP), Monoclonal Gammopathy of Undetermined Significance (MGUS) associated
d) multifocal motor neuropathy with conduction block
e) MGUS associated neuropathy
f) nerve large vessel vasculitis
g) nerve micro-vasculitis – Diabetic Lumbosacral Radiculoplexus Neuropathy (DLRPN), Lumbosacral Radiculoplexus Neuropathy (LRPN), inflammatory brachial plexopathy
h) sarcoid neuropathy

6) Infectious
   a) syphilis
   b) HIV
   c) leprosy – lepromatous, tuberculoid, and mixed
d) Lyme borreliosis
e) Chagas disease
f) herpes simplex
g) herpes zoster

7) Ischemic neuropathies
   a) assoc. with DM
   b) assoc. with nerve larger arteriole necrotizing vasculitis, nerve micro-vessel necrotizing vasculitis
c) atherosclerosis

8) Tumor
   a) sheath tumors – Schwannoma, neurofibroma
   b) perineurioma
   c) secondary tumors
d) lymphoma associated
e) paraneoplastic
f) amyloid neuropathy – inherited, monoclonal associated
g) POEMS syndrome

9) Toxic
   a) toxic neuropathy from industrial agents
   b) metal neuropathy – arsenic, mercury, thallium, gold, platinum
c) drug related neuropathies
10) Miscellaneous
   a) autonomic neuropathies
   b) entrapment neuropathies

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