36. Neuropathy

David Pleasure

Introduction:

peripheral nervous system anatomy;

clinical, electrophysiological, pathological classification of neuropathies;

special anatomic and molecular vulnerabilities of peripheral nerve.

Body of chapter *(each section to emphasize molecular mechanisms in so far as possible)*

toxic neuropathies: metals, organophosphates, medications, etc.

metabolic neuropathies: thiamine deficiency, diabetic.

genetic neuropathies: CMT, amyloids, mitochondrial.

infectious neuropathies: leprosy, HIV, Lyme, syphilis, etc.

immunologically mediated neuropathies:
Guillain-Barre, axonal Guillain-Barre, paraneoplastic, arteritic.

enteric neuropathies: Chagas, Hirschsprungís, etc.

Mechanisms of nerve regeneration and therapeutic approaches to neuropathy.

Summary

Bibliography

38. DISEASES INVOLVING MYELIN

Richard H. Quarles, Pierre Morell and Henry McFarland

(This outline is based on the 6th Edition. Items shown in [square brackets] below indicate subtopics that were covered, but not in the published outline. Changes planned for the new edition are shown in ***bolded blue italics***.)

I. GENERAL CLASSIFICATION

A. A deficiency of myelin can result either from failure to produce the normal amount of myelin during development [hypomyelination or dysmyelination] or from myelin breakdown after it is formed [demyelination].

B. Many of the biochemical changes associated with myelin deficiency are similar regardless of etiology.

II. ACQUIRED DISORDERS OF MYELIN HAVING AN ALLERGIC AND/OR INFECTIOUS BASIS

A. Nervous system damage in many acquired allergic and infectious demyelinating diseases is directed specifically against myelin or myelin-forming cells. ***(Because of the increased attention to axonal injury in many of these disorders including MS, this section needs to be changed with discussion of axonal pathology resulting either from inflammation or loss of the influence of myelin sheaths exerted by molecules such as PLP, MAG, CNPase, etc. Coordination with chapters #4 (myelin formation etc.) #8 (cytoskeleton) and the new #30 (axonal growth and regeneration) will be important here.)***

B. Experimental allergic encephalomyelitis (EAE) is an animal model of autoimmune demyelination [general aspects; acute and chronic forms; MBP, PLP and MOG as immunogens; pathogenic mechanisms; treatment]. ***(More discussion of MOG-induced relapsing/remitting EAE as a good model of MS).***

C. A number of disorders in animals caused by viruses involve primary demyelination and often are associated with inflammation. [Canine distemper virus; visna; mouse hepatitis virus; Theiler's virus].

D. Multiple sclerosis (MS) is the most common demyelinating disease of the CNS in humans. [General clinical and pathological aspects; imaging; biochemical analyses of lesions; genetics; epidemiology; evidence for viral and/or autoimmune etiology; therapy*]* ***(Increased discussion of MS subtypes with myelin or oligodendrocytes as the primary target; HHV6 and Chlamydia pneumoniae as new candidates for infectious agents; greater emphasis on axonal injury being responsible for irreversible neurological impairment and a target for therapy)***

Fig. 1. Coronal slice of brain from a patient who died of MS

Fig. 2. Polyacrylamide gel electrophoresis of proteins in MS and control tissue

E. Some human peripheral neuropathies involving myelin are thought to be immune-mediated. [Guillain-Barre Syndrome (GBS), chronic inflammatory demyelinating neuropathy (CIDP), multifocal motor neuropathy (MMN), and neuropathy in association with IgM gammopathy; glycolipids and MAG as potential target antigens; molecular mimicry between Campylobacter jejuni and gangliosides**]** ***(increased understanding of pathogenic mechanisms based on progress with animal models and in vitro systems)***

Fig. 3. Molecular mimicry in subsets of patients with Guillain-Barré syndrome.

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F. Other acquired disorders affecting myelin in humans may be secondary to viral infections, neoplasias or immunosuppressive therapy [postinfectious encephalitis; neuroAIDS; progressive multifocal leukoencephalopathy]

III. GENETICALLY DETERMINED DISORDERS OF MYELIN

A. Spontaneous mutations in experimental animals provide insights about the structure and assembly of myelin [Mutations in proteins of compact myelin- Shiverer, jimpy, trembler; Other mutations - quaking, taiep] ***(update with important progress on pathogenic mechanisms involved)***

B. The human leukodystrophies are inherited disorders affecting central nervous system white matter. ***(update with important progress on pathogenic mechanisms; add childhood ataxia with CNS hypomyelination (CACH)/vanishing white matter (VWM) disease; add occurrence of peripheral neuropathy with some PLP mutations)***

Table 1 - Genetically determined disorders affecting CNS myelin in humans [Krabbe's disease; metachromatic leukodystrophy; adrenoleukodystrophy; Canavan's disease; Pelizaeus-Merzbacher disease; phenylketonuria]

Table 2 - Human myelin composition in three diseases compared with controls ***(probably delete and mention important aspects in text)***

C. The deficiencies of peripheral nerve myelin in several inherited neuropathies are caused by genetic mutations of sheath proteins [PMP-22, P0 glycoprotein, connexin-32]. ***(update with important progress on pathogenic mechanisms; discuss axonal pathology; add new mutations such as periaxin gene)***

IV. TOXIC AND NUTRITIONAL DISORDERS OF MYELIN ***(Shorten with combining of subheadings A and B; also delete some items and refer to earlier editions or other references)***

A. Biological toxins can produce myelin loss. [diphtheria toxin, cytokines]

B. Many chemical toxins can impair myelin formation or cause its breakdown [organotin, hexachlorophene, lead, tellurium].

C. General undernourishment or dietary deficiencies of specific substances can lead to a preferential reduction in myelin formation. [underfeeding, deficiencies of protein, essential fatty acids, vitamins and copper]

V. DISORDERS PRIMARILY AFFECTING NEURONS WITH SECONDARY INVOLVEMENT OF MYELIN ***(shorten with elimination of subheadings A and B)***

A. The archetypical model for secondary demyelination is Wallerian degeneration.

B. Secondary demyelination occurs in subacute sclerosing panencephalits (SSPE) and other diseases of the central nervous system.

VI. REMYELINATION ***(change heading to "Repair in Demyelinating Diseases" and include subheading on potential importance of axonal survival and/or regeneration)***

A. The capacity for remyelination is much greater in the PNS than the CNS.

B. Remyelination in the CNS can be promoted by various treatments, and therapy of human myelin disorders by this approach may be feasible [growth factors, transplants of myelin-forming cells] ***(Add stem cells, overcoming Notch pathway inhibition of remyelination, and enhancement of remyelination with autoantibodies)***

REFERENCES

Chapter 39:

Genetics of Neurodegenerative Diseases

Lars Bertram, M.D. and Rudolph E. Tanzi, Ph.D.*

Genetics and Aging Research Unit,

Department of Neurology,

Massachusetts General Hospital

114 16th Street, Charlestown, MA, 02129,

(T) 1-617-726-6845, (F) 1-617-724-1949, (E-mail) tanzi@helix.mgh.harvard.edu

*To whom correspondence should be sent

39. Genetics of Neurodegenerative Diseases

Lars Bertram and Rudolph E. Tanzi
bertram@helix.mgh.harvard.edu tanzi@helix.mgh.harvard.edu

41. Inborn Errors of Metabolism and the CNS

Marc Yudkoff and Hugo Moser

1. Introduction
    A. History of the Inborn Errors of Metabolism
        i. Garrod: Concept of an Inborn Error of Metabolism
        ii. Concept of dynamic metabolic pathway, not a static system
        iii. Relationship to developments in genetics
        iv. Development of chromatographic approaches
        v. Advent of diet-therapy and newborn screening: spurs to the field

    B. Tabular Presentation of Inborn Errors of Intermediary Metabolism
        - Disorders of Carbohydrate Metabolism
        - Aminoacidurias
        - Organic acidurias
        - Mitochondropathies
        - Disorders of purine and pyrimidine metabolism
        - Disorders of lipid metabolism
        - Peroxisomal disease
        - Lysosomal disease
        - Disorders of membrane transport
        - Disorders of porphyrin metabolism
        - Disorders of metal metabolism

II. Phenylketonuria as Exemplar of Inborn Error of Metabolism Causing Brain Damage
    A. History of PKU
    B. Gene Defect in PKU
    C. Consequences of the defect: the clinical picture in PKU
        - Relationship to IQ
        - Relationship to behavior
        - Neurocognitive profile
        - Maternal PKU
    D. PKU and brain chemistry: the major theories to explain the encephalopathy
        - Possible tyrosine deficiency
        - Impaired transport into brain of neutral amino acids
        - Deficiency of dopamine and serotonin
        - Dysmyelination
        - Impairment of cholesterol synthesis
        - Relationship to energy metabolism
    E. Implications of Theory for Therapy
    F. Future research directions

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III. Peroxisomal Disease

1. Brief review of peroxisome structrure and function
2. Peroxisome import mechanisms
3. Disorders of peroxisome biogenesis that present woth the " Zellweger, neonatal adrenoleukodstrophy, infantile Refsem Disease contimuum phenotype' . a chart of the el;even gene defects that may lead to it and genotype-phenotype correlations. Pathogenesis of neuronal migtrtion defects
4. Pex 7 deficiency and rhizomelic chondrodysplasia punctata; pathpgenesis of skeletal defects
5 Single enzyme defects that involve peroxisomal fatty acid beta osidation
6. X-linked adrenioleukodystrophy
7. Refsum disease (Phytanoyl Co-A hydoxylase deficiency)
8 Future directions

IV. Lysosomal Disease

[to be added]

42. DISORDERS OF MUSCLE EXCITABILITY

Juan M. Pascual and Basil T. Darras
jmp53@columbia.edu basil.darras@TCH.Harvard.edu

ORGANIZATION OF THE NEUROMUSCULAR JUNCTION

Nerve and muscle communicate through neuromuscular junctions

Figure 42.1 The neuromuscular junction (photomicrograph)

Acetylcholine acts as a chemical relay between the electrical potentials of nerve and muscle

Figure 42.2 Molecular physiology of neuromuscular transmission (cartoon)

The fidelity of signal transmission relies on the orchestration of innumerable stochastic molecular events

EXCITATION AND CONTRACTION OF THE MUSCLE FIBER

The excitable apparatus of muscle is composed of membranous compartments

Figure 42.3 Organization of a skeletal myocyte (use 6th edition Figure 43.5, with modifications)

Myofibrils are designed and positioned to produce movement and force

Calcium couples muscle membrane excitation to filament contraction

Figure 42.4 Molecular physiology of muscle excitation-contraction coupling (schematic)

Table 42.1 Disorders of muscle excitability

GENETIC DISORDERS OF THE NEUROMUSCULAR JUNCTION

Congenital myasthenic syndromes impair the operation of the acetylcholine receptor

ChAT deficiency

AChR deficiency

Figure 42.5 Molecular pathology acetylcholine receptor (cartoon)

Rapsyn deficiency

Slow channel syndrome

Fast channel syndrome

Cholinesterase deficiency

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HEREDITARY DISEASES OF MUSCLE MEMBRANES

Figure 42.6 Molecular pathology of muscle voltage-gated ion channels and pumps (cartoon)

Mutations of the sodium channel cause hyperkalemic periodic paralysis

Hypokalemic periodic paralysis is due to calcium channel mutations

Abnormal potassium channels in Andersen syndrome cause more than periodic paralysis

Mutant chloride channels are responsible for myotonic dystrophy, a multisystemic disorder

Paramyotonia congenita and mutations in the sodium channel

Malignant hyperthermia caused by mutant RyR calcium release channels

Calcium channel mutations may also cause malignant hyperthermia

Brody disease is an unusual disorder of the sarcoplasmic reticulum calcium ATPase

IMMUNE DISEASES OF MUSCLE EXCITABILITY

Myastenia gravis is caused by antibodies that promote premature AChR degradation

Figure 42.7 Muscle action potentials during repetitive neural stimulation (use 6th edition Figure 43.7, unchanged)

Antibodies against MuSK mimic myasthenia gravis

Antibodies cause calcium channel dysfunction in Lambert-Eaton syndrome

Potassium channel antibodies in Isaacs syndrome cause neuromyotonia

TOXINS AND METABOLITES THAT ALTER MUSCULAR EXCITATION

Bacterial botulinum toxin blocks presynaptic ACh release

Dinoflagellates synthesize tetrodotoxin and saxitoxin to block the sodium channel

Scorpion, snail, spider and snake peptide venoms act on multiple molecular targets at the neuromuscular junction

Electrolyte imbalances alter the voltage sensitivity of muscle ion channels

REFERENCES

45. Disorders of Basal Ganglia

Mahlon DeLong ***medmrd@emory.edu***

Thomas Wichman ***twichma@emory.edu***

1. Anatomy and normal function of the basal ganglia

2. Parkinson's disease

3. Huntington's disease

4. Wilson's disease

4. Dystonia

5. Drug- and toxin-induced movement disorders

We will also emphasize neuroprotective and restorative strategies as appropriate in these subsections (particularly, of course, with regard to Parkinson's and Huntington's disease).

46. NEURODEGENERATIVE α-SYNUCLEINOPATHIES AND TAUOPATHIES.

Michel Goedert and *Maria Grazia Spillantini*
mg@mrc-lmb.cam.ac.uk *mgs11@cam.ac.uk*