The Neuropathology of Diseases of the White Matter

JUSTIN PARR, M.D.

Division of Neuropathology, Departments of Pathology and Medicine, Hahnemann Medical College, Philadelphia, PA 19102

ABSTRACT

The diseases of white matter compose essentially three nosological entities of a heterogeneous group. The clinical and neuropathological attention has been directed to the deficiency of myelin in more or less specific patterns and distribution as the primary characteristic, and the unique natural history and the respective cellular pathology as the modifiers which define each disease. Basically, 13 diseases are cited.

Current research investigations are concerned with theoretical hypotheses based on the pathology of the human diseases, etiologically proven naturally occurring animal diseases and experimentally produced animal demyelinative diseases of central and peripheral nervous system. Hypersensitivity mechanisms evoked by an immune response of the delayed type, circulating antibodies, and the possibility of viruses initiating an immune response as causative by direct or indirect effects are the key subjects today. The data are most exciting and the research efforts are challenging. Direct evidence is lacking for any of the hypotheses of etiology of the human disorders of white matter except perhaps for the leukodystrophies and progressive multifocal leukencephalopathy.

Introduction

All nerve fibers have a myelin sheath which consists of a lipid-protein covering of the axon. Even the so called unmyelinated fibers have a very thin sheath. In frozen tissue preparations stained by the Spielmeyer method, myelin may have a herring-bone pattern which results from the Schmidt-Lanterman incisures. This is the traditional diagramatic picture of myelin. However, myelin may appear as a loose vacuolated substance as well. In the more commonly studied sections of nervous tissue, the specimen is processed by use of alcohols and xylene prior to paraffin embedding. As a result, myelin appears as a reticulated substance in longitudinal sections and as a ring with a clear center in cross sections. The clear center is the site of the axon. Myelin is eosinophilic with hematoxylin and eosin, blue with luxol fast blue and magenta with phloxine fast green methods. The latter method stains axons green. It is a useful staining procedure for
differentiating the histological components of nervous system. Phosphatides, sphingosides and cholesterol are the chief lipids of myelin. Others have been isolated. Proteins are present mainly as proteolipids. The layers of lipid are radially arranged around the axis cylinder, and protein with water molecules is arranged longitudinally and concentrically.

Myelin is a cytoplasmic membrane product. In the central nervous system (CNS), evidence favors the origin of myelin from the oligodendrocyte. In the peripheral nervous system (PNS), myelin is the product of the Schwann cell. The Geren hypothesis states that the axis cylinder invaginates the cell cytoplasm (oligodendrocyte or Schwann cell) and then the cell rotates so that a concentric “jelly-roll” structure of myelin results. In Homo sapiens, relatively little myelin is present in the newborn. As shown by studies of Yakovlev and Lecours, myelin is actively formed and added to the nervous system into the fourth decade of life. Of the several anatomic sites studied, myelination of the intracortical association areas continues past the third decade, and myelination of the reticular formation continues into the last half of the second decade. Other sites are completed earlier in life.

**Phenomenon of Demyelination**

Alterations of myelin are encountered under a variety of circumstances. If a nerve is injured by physical trauma, the interrupted axon will degenerate distal to the site of injury and its myelin will also regress as a “secondary” degeneration. This occurs in peripheral as well as central nervous system and carries the eponym Wallerian degeneration. Again, a disease process which principally affects the neuron, mean-cell body, dendrites and axon will have myelin degeneration manifest as a secondary phenomenon. Such is secondary to the primary disease of the neuron. Examples of this are amyotrophic lateral sclerosis and the hereditary ataxias. The previous examples are not classified as primary demyelinating diseases.

Three nosological entities are described thus. The first consists of four disease patterns wherein perivenous lymphocytes and plasma cells are present at sites of myelin destruction and at multiple foci which are widespread or disseminated. The second nosological entity is the genetically determined enzyme deficiencies which affect myelin metabolism. The third and last nosological entity does not include perivascular infiltrates of lymphocytes, plasma cells or histiocytes as a criterion but does include focal or multifocal sites of demyelination.

**Demyelinating Diseases**

The demyelinating diseases are a heterogeneous group. The axon is histologically spared during the early stage of the illness even though its bioelectric function may be disturbed. The diseases chiefly affect the myelin sheath. Within the histological system of myelin structure and its cells of origin, present concepts about demyelination consider interfering with the oligodendrocyte, Schwann cells and myelin lipid or protein metabolism as possible causes which could result in destruction of myelin per se. As general characteristics, the demyelinating diseases are seen as loss of myelin in foci radiating from small veins. The foci are multiple and disseminated, some are large, and infiltrates of lymphocytes and plasma cells are present about the blood vessels as one of the criteria for diagnosis. The degree of phagocytosis varies from disease to disease and is best studied on frozen tissue section stained by the oil-red-O-hematoxylin method for neutral fat and cholesterol esters. The phagocytes containing ingested myelin particles will appear brilliant reddish orange as a result of the chemical conversion the phagocytes
have accomplished on the ingested particles of degenerated myelin. The luxol fast blue and phloxine fast green methods will demonstrate an absence of stainable myelin at such foci. Such foci will be faintly eosinophilic with hematoxylin and eosin. An axis cylinder stain, Bodian silver protargol method, will aid in identifying the intact axons at such foci of demyelination.

**Multiple Sclerosis**

Multiple sclerosis (disseminated sclerosis) is an acute or chronic relapsing disease. The greatest predilection is for the brain stem and the spinal cord. However, multiple asymmetrical foci of demyelination are seen in the white matter of the brain stem, spinal cord, cerebellum, optic nerves and cerebrum. Lymphocytes and plasma cells are found scattered around small veins. The loss of myelin is readily seen by the absence of magenta staining by phloxine on paraffin embedded sections. The fat containing macrophages are readily identified by oil-red-0 staining of their intracytoplasmic neutral lipids and cholesterol esters. The axons are relatively spared. Within and at the margins of the foci of demyelination, astrocytes with swollen nuclei and visible vitreous cytoplasm proliferate. They are commonly referred to as reactive Nissl plump astrocytes. After repeated attacks, axons are lost. The proliferation of astrocytes is more marked and dense astrocytic fibrils make up the gliotic or sclerotic plaque. Moderate numbers of macrophages are seen and perivascular mononuclear infiltrates may be prominent. In very old lesions, the macrophages are quite diminished but the fibrillary glial plaque remains. Nerve cell bodies remain relatively unaffected, but the axons are very few in old lesions. They have been destroyed by the final stage of the disease. Recall that axons are spared initially in acute lesions even though their bioelectric function may be altered.

The lesions vary from millimeters to several centimeters in size. Most are clearly located around small or medium sized veins, but notable subependymal (periventricular) sites of demyelination are common. The histographic survey will document widespread lesions throughout the CNS and they will be of different ages from acute lesions to chronic scars as interpreted from the reaction to injury on the part of the astrocytes and macrophages. These characteristics of "dissemination in time and space" distinguish this disease from the others to be mentioned.

The grey matter may contain lesions since grey matter contains myelin at some few sites. The lesions will be limited to the myelin component. A fairly rapidly developing variation which affects primarily the optic nerves and the spinal cord is neuromyelitis optica or Devic's disease. This syndrome is generally considered an example of acute multiple sclerosis.

**Acute Necrotizing Hemorrhagic Encephalomyelopathy**

The second disease pattern is that of acute necrotizing hemorrhagic encephalomyelopathy. The necrotizing characteristic is unique to this entity. It is a rapidly progressive disorder which often follows an infectious illness. It primarily affects the white matter of cerebrum by the formation of large asymmetrical foci of necrotizing myelitis wherein punctate hemorrhages are present at perivascular sites. It is most marked around small veins where fibrinoid necrosis is seen and polymorphonuclear leukocytes are numerous. Later, lymphocytes and plasma cells are seen. Axons are destroyed and reactive microglia (phagocytes) and astrocytes are present.

**Acute Disseminated Encephalomyelitis**

The third disease pattern is most interesting and is usually encountered as a dis-
ease of young children. When seen as a disease of children, it appears 5 to 18 days after the disappearance of the acute exanthemata of the childhood infectious diseases such as measles. Acute disseminated encephalomyelitis (ADEM) is the more common term and synonyms are post-vaccinal encephalomyelitis and post-infectious encephalomyelitis.30 The disease is an abrupt monophasic illness which consists of multiple lesions of simultaneous occurrence widespread throughout the CNS. Therefore, the lesions will be of the same age as a characteristic of this diagnosis. Again, perivenular mononuclear cells are seen in the center of demyelinative foci found in cerebrum, brain stem, spinal cord, cerebellum and occasionally optic nerves. They are small foci which vary from 0.1 mm to 1.0 mm. Notable is the subpial location of the lesions in brain stem and spinal cord.

The mortality rate is 10 to 30 percent in the acute phase. If the patient survives, recovery is usually fairly complete over a two to three month convalescence. Relapse does not occur. This disease resembles an experimental disease about which we will comment later. The cellular reaction to injury and bioelectric alterations of axons are similar to those previously described for acute demyelinative lesions.

**Acute Idiopathic Polyneuritis**

The fourth disease is an affliction of the PNS myelin. The principle characteristic is a segmental demyelination interrupted at the nodes of Ranvier. Lymphocytes and lipid-laden phagocytes are present within the perineurial sheaths and the substance of the nerve. Of interest is the increased protein in the cerebral spinal fluid without an increase of cells in the fluid. The neurohistopathology resembles the experimental disease “experimental allergic neuritis” (EAN).4,5,31

Two thirds of the patients with this disease reveal a history of respiratory or, less commonly, a gastrointestinal infection 5 to 12 days before the onset of the neuritis. Most recover completely; however, residual impairments such as postural hypotension may occur owing to autonomic nerve involvement.7 With respiratory paralysis and/or intercurrent infections the mortality is 15 to 60 percent. The disease is commonly termed “acute idiopathic polyneuritis” but also carries the eponym Landry-Guillain-Barre syndrome.

**Experimental Studies**

Similarities in the histopathology of these four diseases which compose the first nosological entity centers around the presence of lymphocytes and demyelination in unique temporal sequences. Consequently, current research endeavors are based on the possible theory of a hypersensitivity mechanism evoked by an immune response of the delayed type and mediated by lymphocytes. Viruses have never been established as a causative agent in the nervous system in any of these afore described human diseases. That a viral illness may antedate the onset of two of them is notable. Consequently, question has been raised about the possible role of viruses as initiators of the immune response and as causative by direct or indirect effects. Although this has not been determined for human diseases, the animal viral diseases canine distemper, Visna, and JHM (neurotropic strain of mouse hepatitis virus; RNA coronaviruses group) are examples of such.

Laboratory methods of diagnosis are principally limited to post-mortem studies. Unique laboratory models for investigation and premortem diagnosis exist at some research centers,—one of which maintains an *in vitro* system of organotypic mammalian nervous tissue cultures. They include spinal cord, cerebellum, cerebral neocortex or dorsal root ganglia. These cultures can be
studied by brightfield or phase microscopy. Meticulous microelectrode recordings of evoked or spontaneous bioelectrical activities can be made from the cultures, and they are readily studied by ultrastructural techniques of electron microscopy. With these models and methods, complement-dependent reactions of active serum factors in the gamma 2 globulin fraction from patients with multiple sclerosis have been studied. When such serum is added to the cultures, demyelination will occur in the first 24 to 96 hours after exposure to a “potent” serum. Even before this is observed, the bioelectrical activities of the cultures are diminished as a first affect. If the exposure to serum is interrupted, the demyelinating process is stopped and remyelination occurs. Prolonged exposure results in a glial “sclerosis.” Such effects were obtained from 75 percent of 37 patients with active multiple sclerosis in one report and also from sera of patients with motor system disease in another report. Current data on the IgG immunoglobulins in CSF and CNS has been summarized by Tourtellotte. The cerebrospinal fluid (CSF) IgG value is elevated in most cases of multiple sclerosis and it is compartmentalized to the CSF space and the CNS tissue. In general, it is not in the circulating blood. It has been found by Kabat that 80 percent of patients with multiple sclerosis had cerebrospinal fluid IgG elevated to amounts greater than 13 percent of normal. Studies have shown that 67 percent of multiple sclerosis patients and 73 percent of neurosyphilis patients had increased IgG values. Only 5.5 percent of 7,225 patients with neurological diseases other than demyelinating disorders had elevated cerebrospinal fluid IgG. These values are reported as fraction of IgG to total protein expressed as a percentage.

With these points in mind, Tourtellotte investigated the histological and analytical chemical localization of IgG in cerebral lesions in a post-mortem study of a patient with multiple sclerosis. High values of IgG (12 times normal) were found at the edge of plaques of demyelination, on the plaque side and just outside the plaque in what is called the “shadow plaque” of a typical lesion of multiple sclerosis. Lower but abnormally high values of IgG were found in the center of the plaque as well as in distant white and grey matter. The degree of perivascular mononuclear infiltrates correlated directly with the extent of elevation of IgG found in the above mentioned sites. Plasma cells were notable. In the experimental animal disease “experimental allergic encephalomyelitis” (EAE), Oldstone and Dixon found immunoglobulins about vessels in the CNS days before the perivascular lymphocytes were seen. The experimental animal models which histopathologically resemble acute disseminated encephalomyelitis and acute idiopathic polyneuritis are produced by injecting an oil emulsion of the animal’s homologous myelin and killed M. tuberculosis bacilli as adjuvant. If myelin from the peripheral nerve is used (EAN), demyelinating lesions occur in the nerve roots, dorsal root ganglia and peripheral nerves accompanied by the mononuclear response. When CNS myelin is used (EAE), the lesions resemble ADEM and, to a lesser degree, multiple sclerosis. In view of these findings, research investigations have been directed toward finding a sensitizing factor in the proteolipid extracts of myelin used in these experimental disorders. Published reports by Eylar identify an encephalitogenic A1 protein. Purification, evaluation and identity of bovine and human A1 protein are accomplished by polyacrylamide gel electrophoresis at pH 4.4. The bovine (m.w. 18,400) and human (m.w. 18,300) are similar in composition. The A1 protein is highly basic with approximately 25 moles percent of the basic residue composed of lysine, histidine and ar-
ginine. In addition, two methionine residues and a relatively high content of glycine, serine and proline are found. The tryptophan residue and high histidine content distinguish it from the histones. The A1 protein is an open chain molecule and not a glycoprotein or a phospholipid. In experimental animals, Eylar has been able to produce EAE with the selective use of the purified A1 protein with adjuvant instead of the homologous myelin. In addition, by suppression of the immune response with antigen in EAE using the A1 protein, Eylar has been able to reverse the disease state.13

The theory of an autoimmune etiology for the demyelinative diseases is reasonable and the hypothesis for viral etiology28 is attractive. However, direct evidence is lacking for either hypothesis. Although pathologic similarity is noted, a possible relationship of the experimental disorders to the human conditions requires much further investigation. A discussion of these subjects may be found elsewhere.15

**Metabolic Errors**

The second nosological entity is the leukodystrophies. As a group, they are genetically determined enzymatic disorders which effect myelin metabolism. They affect more than one member of a family and are manifest in infancy and childhood. The altered myelin lipid metabolism results in disintegration of myelin sheaths of the CNS and in some the PNS. The lesions are widespread and contain accumulations of myelin lipids and phagocytes. The axis cylinders eventually disintegrate.

**Metachromatic Leukodystrophy**

In metachromatic leukodystrophy, sulfatase activity is lacking and sulfatide accumulates.27 Metachromasia is the key to diagnosis and with acidified cresyl violet (acetic acid) the accumulated particles stain brown. They are weakly sudanophilic. The lesions are principally in CNS and small peripheral nerves even though increased levels of sulfatide are found in viscera (liver and kidneys).

**Krabbe’s Disease**

The deficiency of beta-galactosidase, lipid sulfatransferase results in the accumulation of cerebroside.6 Histologically, CNS multinucleated phagocytes, seen as “globoid” cells, contain the accumulated cerebroside. Proliferation of astrocytes is seen also. The cerebrosides are stained by the periodic acid Schiff method; they are not metachromatic.

**Sudanophilic Leukodystrophy**

Degeneration of white matter with perivascular myelin preservation characterizes the third disease. Axons are usually spared and the disease has a long course (one year). Consequently, abundant astrocytic proliferation is seen but accumulations of sudanophilic material are few however present. The disease is sudanophilic leukodystrophy.24

**Spongy Degeneration of CNS of Infancy**

The fourth disease is referred to as “spongy degeneration of central nervous system of infancy.”14 The white matter of the cerebral hemispheres and lower layers of cortex appear extremely vacuolated. The only reaction of cells is an increased size of protoplasmic astrocytes in the cortex. The nuclei are enlarged two-fold and commonly referred to as Alzheimer type II astrocytes.

**Alexander’s Disease**

When large numbers of condensed astrocytic cytoplasmic fibrils are found in myelin deficient white matter as well as at the subpial, perivascular and subependymal sites, the criteria for the diagnosis of leukodystrophy with Rosenthal fibers are met. The
condensed eosinophilic astrocytic fibrils are the Rosenthal fibers. Myelin breakdown products are not found. Consequently, the question is raised if the disease of these infants represents impaired formation of myelin. Peripheral nerves may be affected. The disease is transferred as an autosomal recessive trait.

Metachromatic leukodystrophy is transmitted as an autosomal recessive trait as are disordered galactocerebroside metabolism (Krabbe's) and spongy degeneration of central nervous system of infancy. Sudanophilic leukodystrophy is inherited as a sex-linked recessive trait.

Miscellaneous Disorders

The third nosological entity of the diseases of white matter is in contrast to the foregoing by an “absence” of mononuclear infiltrates at foci of myelin loss. The distribution of lesions is unique to each of the four diseases listed under this heading. The diseases are relatively uncommon.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a descriptive term for a disease which results in widespread foci of myelin loss which are asymmetrical and primarily in cerebral hemispheres. The brain stem and cerebellum may be involved; however the spinal cord rarely if ever. Axons are usually spared. Sudanophilic lipid-laden phagocytes are seen, and perivascular lymphocytes have been reported as components of some of the lesions (an exception in this group of diseases). The unique findings are enlarged nuclei of oligodendrocytes. On careful search, cosinophilic intranuclear inclusion bodies will be seen in these nuclei. With the aid of electron microscopy, viral particles have been found in these nuclei as well as in nuclei of neurons and in astrocytic cytoplasm. The astrocytic nuclei are frequently quite large, folded and multiple per cell.

The disease is usually a short terminal illness occurring in patients with chronic diseases associated with abnormalities of the immune system. The lymphomas have been the most frequently reported chronic diseases.

The etiology of PML has generated considerable excitement in viral research studies. JC and SV 40-PML types of papova viruses have been cultured from brain of humans dying with this disease. The possibility that these viruses are opportunistic invaders which cause diseases in organs not commonly associated with them is the general trend of thought in medical neurological theory today. The abnormalities of the immune system are a prerequisite, a posteriori. Verrucas vulgaris and other warts are the common integumentary lesions of these viruses (papova).

Central Pontine Myelinolysis

Central pontine myelinolysis is an established disease with loss of myelin in the center of the base of thepons. This occurs with an apparent loss of oligodendrocytes. Most of the reported cases occur in patients with severe malnutrition and diseases affecting the liver parenchyma. Many are alcoholics.

Marchiafava-Bignami Disease

The third disease of this group also occurs in nutritionally deficient people with or without chronic alcoholism. The myelin loss occurs in the central fibers of the corpus callosum. It is a rare disease and called Marchiafava-Bignami disease.

Vitamin B₁₂ Deficiency

The last of the “non-inflammatory” diseases of white matter occurs with vitamin B₁₂ deficiency. The early lesions consist of
References


22. Martenson, R. E. et al.: Microheterogeneity in species-related differences among myelin basic proteins. Immunological Disorders of the Nervous System. Association for Research in Nervous and Mental Diseases XLIX. Rowland,


