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LEUKODYSTROPHY AND MYELIN

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Introduction

There are many disorders that affect myelin in both children and adults. The increasingly widespread use of neuroimaging techniques – particularly magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI) – provides a powerful new resource for the study of myelin. Various abnormalities of myelin are reported frequently, even when they had not been suspected clinically, so that disorders of myelin need to be included in the differential diagnosis – more than had been true in the past. Their etiology, clinical significance, and therapeutic implications vary greatly, and precise definition of etiology is essential.

This applies particularly to the leukodystrophies, which are serious and progressive disorders that should be distinguished as quickly as possible from other conditions that involve myelin. Not so long ago, a period of clinical observation could be allowed, but this is no longer appropriate. Minimal delay in diagnosis is particularly important, so that therapies that have emerged in recent years can be applied when they are most effective, in the early stage of the illness and, when possible, presymptomatically. Prompt and accurate diagnosis is also essential for genetic counseling. These goals can be achieved by careful correlation of clinical features, analysis of radiological findings, and the targeted application of biochemical and molecular diagnostic techniques. The purpose of this book is to facilitate and speed the accomplishment of these goals.

Definition of leukodystrophies

The term leukodystrophy (*leuko* – white, *dystrophy* – defective nutrition) was introduced by Bielschowsky and Henneberg (1928). In this book we use the definition proposed by Powers (2004) who classified leukodystrophies as disorders that are known or presumed to have (1) a genetic causation, (2) a progressive clinical course, (3) a predominant and usually confluent involvement of the central nervous system (CNS) white matter, and (4) a primary lesion of myelin or myelinating cells. The latter may be manifested by either a loss or failed development of the CNS white matter due to a biochemical abnormality or a molecular abnormality of a myelinating cell.

The first three criteria are relatively clear-cut and separate the leukodystrophies from a large number of conditions that affect myelin and are not genetically determined, which include multiple sclerosis, infectious disorders, nutritional disorders, acquired toxic–metabolic disorders, and disturbances of blood flow (see Table 1.1).

TABLE 1.1
Disorders of myelin that are not mainly genetically determined

Demyelinating diseases

- Multiple sclerosis
- Acute disseminated encephalomyelitis

Infectious diseases

- HIV vacuolar myelopathy
- Progressive multifocal leukoencephalopathy
- Subacute sclerosing panencephalitis
- Postinfectious encephalomyelitis
- Postvaccinial encephalomyelitis

Nutritional diseases of myelin

- Vitamin B12 deficiency
- Marchiafava–Bignami disease
- Central pontine myelinolysis

Acquired toxic–metabolic disorders

- Hypoxic encephalopathy
- Carbon monoxide poisoning
- Hexachlorophene poisoning
- Triethyl tin poisoning
- Posterior leukoencephalopathy syndrome
- Blood flow disturbances
- Binswanger microangiopathic leukoencephalopathy
- Leukoararaiosis

Traumatic diseases of myelin

- Pressure release

Criterion 4 is the most difficult to apply precisely, is the cause of some controversy, and subject to change as the understanding of genetic disorders of myelin increases. The basic nature of the problem was stated well by Raymond D. Adams and Charles Kubic in their 1952 review (Adams and Kubic 1952), who wrote:

> It has long been the practice to set apart a group of diseases in which demyelination is a prominent feature. They are believed to possess characteristics that point to a unique etiology and pathogenesis as yet unknown. To state these characteristics in an exact definition is, however, difficult if not impossible. Neuropathologists pretend to know what a demyelinative disease is, yet have found it hard to describe in a few simple words. The actual difficulty is . . . that there is probably no disease in which myelin destruction is the primary or exclusive pathological change. The whole idea of a demyelinative disease is more or less of an abstraction which serves to focus attention on one of the more striking and distinctive features of a pathological process. . . . The commonly accepted criteria of a demyelinative disease are: (1) destruction of the myelin sheaths of the nerve fibers; (2) relative sparing of the other elements of nervous tissue, i.e., axis cylinders of the other elements of nervous tissue.

The science is now catching up with these prescient words. The interaction of the axon, and by extension the neuron, with the glia and myelin sheath is now well established, and it is becoming very apparent that the injury to myelin or the oligodendrocyte does not occur in isolation.

It has been argued that classification as leukodystrophy should be reserved for disorders in which the primary lesion affects myelin or myelination cells. Adherence to this criterion leads to the exclusion of certain genetically determined disorders that meet the first three criteria listed above and resemble the leukodystrophies in respect to clinical and radiological features. An example of this is CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy) in which the primary defect, a mutation of *Notch3*, affects the endothelium of small arteries, and the fundamental abnormality is ischemia. Other disorders that have been excluded from the leukodystrophy category are those which involve the neuron primarily, such as Tay–Sachs disease, or those such as Refsum disease and Charcot–Marie–Tooth disease, which affect peripheral nerves primarily. Disorders of amino acids, mucopolysaccharides, and gangliosides, which do not appear to affect myelin primarily, are also typically excluded, although myelin abnormalities have been clearly associated with many of them. Perhaps with less justification, mitochondrial disorders and the disorders of peroxisome biogenesis have been excluded because these disorders appear to affect many components of the nervous system and not myelin primarily.

However, in fairness, limits do need to be set, and so the main focus of this work is on disorders that affect CNS myelin or myelinating cells primarily, and for which the gene defect has been defined. These disorders are listed in Table 1.2.

Finally, with the use of new genetic tools, disorders are rapidly being identified, but more importantly, also rapidly being genetically clarified (Table 1.3). With this new information, previously undiagnosed leukodystrophies can now be diagnosed. The challenge remains to disseminate these developments clinically, and to further the care and treatment of this rapidly expanding group of patients. Clearly, important work still needs to be done.

TABLE 1.2
Examples of genetic disorders that affect myelin or myelinating cells mainly, and in which the gene defect has been defined

- X-linked adrenoleukodystrophy
- Metachromatic leukodystrophy
- Globoid leukodystrophy
- Pelizaeus–Merzbacher disease
- Canavan disease
- Alexander disease

TABLE 1.3
Recently identified genetic disorders affecting myelin

Disease	Gene where known	Reference
Leukoencephalopathy with brainstem involvement and high lactate	*DARS2*	Van der Knaap et al. 2003
Cystic leukoencephalopathy without megalencephaly	*RNASE 2*	Henneke et al. 2005
Hereditary leukoencephalopathy with spheroids		Van der Knaap et al. 2000
Progressive cavitating leukoencephalopathy		Naidu et al. 2005
Hereditary leukoencephalopathy and palmoplantar keratoderma		Lossos et al. 1995
Oculodentodigital dysplasia	*GJA1*	Norton et al. 1995
Hereditary adult-onset leukodystrophy	*Lamin B1*	Eldridge et al. 1984

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