Abnormalities of Developing White Matter in Lysosomal Storage Diseases

REBECCA D. FOLKERTH, MD

Abstract. Inborn metabolic errors causing lysosomal storage have well-recognized effects on neuronal function and morphology. In some classically "neuronal" storage diseases, however, neuroradiological observations of infants have suggested a delay in central nervous system myelination based on persistently "immature" signal intensities monitored over time. This review summarizes reported neuropathologic evaluations of central white matter in infantile and juvenile patients and in corresponding animal models with lysosomal storage disorders. The observed neuropathology is examined in light of published studies of the biochemistry and microscopic anatomy of normal myelination. Finally, arguments are advanced that at least part of the deficiency of white matter is attributable to direct effects of the metabolic state on oligodendrocyte maturation and function, in addition to secondary effects on neurons and their axons.

Key Words: Autopsy; Brain development; Dysmyelogenesis; Lysosomal storage disease; Myelination; Oligodendroglia.

INTRODUCTION

Neuronal storage disorders encompass a spectrum of inherited metabolic failure of lysosomal enzyme or cofactor synthesis, transport and localization, or function, and may become symptomatic from birth to adulthood. Many lysosomal storage diseases have their onset in infancy or early childhood and affect the central nervous system during the critical period in myelination, that is, from midgestation through the first 2 postnatal years (Table 1) (1–24). While neuropathologic evaluations historically have emphasized the accumulation of stored material in neurons as the cause of progressive brain dysfunction, primary effects of deficient lysosomal enzyme function on central white matter development are worthy of consideration. Based on observations of evolving white matter abnormalities on neuroimaging in patients (4–13, 25), and on neuroimaging, neuropathologic, and brain lipid studies of animal models with lysosomal storage diseases (LSDs) (25–27), direct metabolic effects on oligodendrocytes contributing to delayed or abnormal myelination (dysmyelogenesis) during the critical period have been hypothesized. This review considers the microanatomic, biochemical, and molecular evidence supporting this hypothesis. Because the subject of myelogenesis is most relevant in early life, only those LSDs with clinical onset in the neonatal period through late infancy will be considered. Adult- or late childhood-onset LSDs, the peroxisomal disorders, LSDs lacking CNS involvement, and those for which insufficient data exist will not be included (see exclusions listed in legend of Table 1). In the following review, first, the process of normal myelination in early human life will be outlined. Next, reported studies of white matter in LSDs of infantile or juvenile onset in human patients will be reviewed.

Animal models in which information has been gained experimentally regarding myelogenesis will be analyzed. Finally, based on these data, mechanisms of abnormal myelogenesis in pediatric LSDs will be considered. The reader is referred also to recent reviews for details of the molecular and cellular biology of myelination (28–31).

Normal Myelogenesis

Myelination in the normal immature nervous system can be thought of as a two-step process, 1) involving the pathway of proliferation and differentiation of the myelin-forming cells, beginning with the oligodendroglial progenitor cell and ending with the mature, myelin-producing postmitotic oligodendrocyte, followed by 2) the production of the myelin sheath by the mature oligodendrocyte (28) (Fig. 1). The first step of oligodendroglial proliferation and differentiation can be divided into 4 stages, distinguishable by morphologic changes seen in tissue culture, and by expression of characteristic cellular markers detectable by specialized immunohistochemical techniques (32, 33). Using these techniques, human oligodendrocyte (OL) progenitors (from the first stage in Fig. 1) are immunonegative only for marker A2B5, an antigen also present in immature neurons. Pre-OL cells (second stage) are marked by A2B5 and O4, an antibody recognizing surface glycolipids. Immature OLs in the next phase of development are immunostained with antibodies to O4 and O1, which recognize galactocerebroside (GalC). Mature oligodendrocytes further demonstrate immunoreactivity for myelin basic protein (MBP), and myelin-associated glycoprotein (MAG), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP). The timing of OL maturation varies with anatomic site. For example, in the parietal white matter at the level of the atrium, pre-OLs (O4+, O1−, MBP−) are noted after 18 weeks gestation (33), while the first immature OLs (O4+, O1+, MBP−) become identifiable beginning around 27 weeks, with the majority of OLs positive for these markers by 36 weeks. MBP-positive fibers

From the Departments of Pathology (Neuropathology), Brigham and Women's Hospital, and Children's Hospital, Harvard Medical School, Boston, Massachusetts.

Correspondence to: R. D. Folkert, MD, Brigham and Women's Hospital Department of Pathology, 75 Francis Street, Boston, MA 02115.
### Table 1: Early-onset Lysosomal Storage Diseases

<table>
<thead>
<tr>
<th>Lysosomal Storage Disease (subtype)</th>
<th>Age at onset</th>
<th>WM changes by MRa</th>
<th>Storage in</th>
<th>Pathology</th>
<th>Biochemistry</th>
<th>WM changes (unless noted)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early infantile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gα1 galactosialidosis (1)</td>
<td>3m</td>
<td>↑ T2 signal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>↓ proteolipid protein, myelin lipids; ↑ Gα1, Gα2, cholesterol, phospholipid (cortex)</td>
</tr>
<tr>
<td>Gα2 gangliosidosis (B, O, AB)</td>
<td>4m</td>
<td>atrophy</td>
<td>+</td>
<td>+</td>
<td>(ND)</td>
<td>↑ Gα1, ↑ Gα2 (in type B), ↓ cerebrosides, sulfatides; ↑ Gα1, Gα2 (cortex)</td>
</tr>
<tr>
<td>Gaucher (I)</td>
<td>&lt;6m</td>
<td>(ND)</td>
<td>+</td>
<td>-</td>
<td>(ND)</td>
<td>↑ glucocerebroside, glucosylphosphoinosine</td>
</tr>
<tr>
<td>Niemann-Pick (II A)</td>
<td>&lt;1y</td>
<td>+</td>
<td>(ND)</td>
<td>-</td>
<td>+</td>
<td>↑ sphingomyelin, cholesterol, Gα2, Gα3</td>
</tr>
<tr>
<td>Fabry</td>
<td>&lt;1y</td>
<td>(ND)</td>
<td>+</td>
<td>(ND)</td>
<td>(ND)</td>
<td>↑ ceramide, Gα2, glycolipids, mucopolysaccharides</td>
</tr>
<tr>
<td>Krabbe</td>
<td>4m</td>
<td>↑ T2, periventricular</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑ galactoside/cerebroside ratio, ↑ psychosine; ↓ myelin lipids</td>
</tr>
<tr>
<td>Schieller (IV)</td>
<td>8–15m</td>
<td>(ND)</td>
<td>+</td>
<td>+</td>
<td>(ND)</td>
<td>↑ glycosphingolipids, subunit c of mitochondrial ATP synthase</td>
</tr>
<tr>
<td>Pompe</td>
<td>1–4m</td>
<td>none</td>
<td>+</td>
<td>+</td>
<td>(ND)</td>
<td>↑ glycolipids</td>
</tr>
<tr>
<td>Wolman</td>
<td>1–2m</td>
<td>(ND)</td>
<td>-</td>
<td>+</td>
<td>(ND)</td>
<td>No consistent abnormalities of lipids</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis (CNL)</td>
<td>8m</td>
<td>↑ T2</td>
<td>+</td>
<td>+</td>
<td>(ND)</td>
<td>↑ glycosphingolipids, subunit c of mitochondrial ATP synthase</td>
</tr>
<tr>
<td>Sialidosis (II)</td>
<td>0–12m</td>
<td>atrophy on T1</td>
<td>+</td>
<td>(ND)</td>
<td>(ND)</td>
<td>↑ non-lipid sialic acid, Gα1; ↓ myelin lipids</td>
</tr>
<tr>
<td>Galactosialidosis a</td>
<td>&lt;1y</td>
<td>↓ volume; delayed</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>↑ glycolipids</td>
</tr>
<tr>
<td>Fucosidosis (I)</td>
<td>&lt;1y</td>
<td>↑ T2</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>↑ gangliosides</td>
</tr>
<tr>
<td>Mannosidosis (I)</td>
<td>3m–1y</td>
<td>↑ T2</td>
<td>+</td>
<td>(ND)</td>
<td>+</td>
<td>↑ gangliosides</td>
</tr>
<tr>
<td>Mucopolysaccharidosis IVa</td>
<td>&lt;1y</td>
<td>(ND)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>↑ gangliosides</td>
</tr>
<tr>
<td>Late infantile</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartylglucosaminuria b</td>
<td>&lt;1–2y</td>
<td>↑ T2; delayed</td>
<td>+</td>
<td>(ND)</td>
<td>+</td>
<td>↑ aspartylglucosamine</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>&lt;1–2y</td>
<td>↑ T2, anterior &gt;</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>↓ sulfatides, other myelin lipids</td>
</tr>
<tr>
<td>Multiple sulfatase deficiency</td>
<td>&lt;1y</td>
<td>↑ T2, anterior &gt;</td>
<td>+</td>
<td>(ND)</td>
<td>+</td>
<td>↑ sulfatides, mucopolysaccharides; abnormal ganglioside pattern (gray matter)</td>
</tr>
<tr>
<td>Mucopolysaccharidosis I</td>
<td>&lt;1–2y</td>
<td>↑ T1, perivascular; ↑ T2</td>
<td>+</td>
<td>(ND)</td>
<td>+</td>
<td>↑ dermatan sulfate, Gα1, Gα2, Gα3</td>
</tr>
<tr>
<td>Gaucher III</td>
<td>1–2y</td>
<td>+</td>
<td>(ND)</td>
<td>(ND)</td>
<td>+</td>
<td>↓ glucocerebroside</td>
</tr>
<tr>
<td>Niemann-Pick (II C, D)</td>
<td>1–2y</td>
<td>atrophy, hypoplasia</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑ glucosylceramide, lactosylceramide, Gα1, Gα2</td>
</tr>
<tr>
<td>Gα1 galactosidosis (2)</td>
<td>&lt;1y</td>
<td>(ND)</td>
<td>+</td>
<td>+</td>
<td>(ND)</td>
<td>(as in infantile form)</td>
</tr>
<tr>
<td>Gα2 galactosidosis</td>
<td>&gt;18m</td>
<td>(ND)</td>
<td>+</td>
<td>+</td>
<td>(ND)</td>
<td>↑ Gα2</td>
</tr>
<tr>
<td>Neuronal ceroid</td>
<td>18m</td>
<td>↑ T2, parieto-occipital</td>
<td>+</td>
<td>+</td>
<td>(ND)</td>
<td>(as in infantile form)</td>
</tr>
<tr>
<td>Mucopolysaccharidosis II, III</td>
<td>↑ T2</td>
<td>(ND)</td>
<td>+</td>
<td>(ND)</td>
<td>+</td>
<td>↑ dermatan sulfate (in III, also ↑ heparan sulfate and gangliosides)</td>
</tr>
</tbody>
</table>

Early-onset lysosomal storage diseases: Clinical, pathological, and biochemical features. Data obtained from Lake (1), Scriver (2), and Volk (3), unless otherwise noted by superscript. Abbreviations: WM = white matter; MR = magnetic resonance imaging; astro = astrocytes; oligo = oligodendrocytes; + = present; − = absent; ± = minimally present; ++ = present to a marked degree; (ND) = not described; (upward arrow) = increased; (downward arrow) = decreased; * = subcortical neurons only; ** = axonal storage leading to axonal dystrophy only; cc = corpus callosum. Excluded from this table (see text): Gaucher (I), mucopolysaccharidoses IV, VI, and VII, mucopolysaccharidoses II and III, Fabry’s disease, cystinosin, Salla disease, and all variants with onset after 2 years of age or for which insufficient data exist. Additional references: (4–13); (14); (15); (16); (17); (18); (19, 20); (21, 22); (13); (23, 24).
Fig. 1. Maturation of OL lineage cells is depicted in this representation of features of OL differentiation that are pertinent to human white matter development. Four principle stages of development are shown from the OL-progenitor to the mature OL, together with the corresponding morphologic features and potential for proliferation, migration, and myelination. The expression of antigenic markers, which in combination define each stage of OL maturation, are shown (modified from Back and Volpe [28]). POA=pro-oligodendroblast antigen; NG2=chondroitin sulfate proteoglycan; PDGFRα=platelet-derived growth factor receptor α; other abbreviations, see text.

are detectable at 30 weeks in the human optic radiation in the parietal lobe (33). In other sites in the cerebral hemispheres, myelination is detectable by MBP immunostaining at about 25 weeks gestation, at which time the myelin sheaths appear in the globus pallidus, pallido-thalamic fibers of the posterior limb, and ventrolateral nucleus of the thalamus (34). At 35 weeks, microscopic myelination, as detected by MBP and Luxol-fast blue (LFB) stain, is present in the striatum, precentral and postcentral gyri, and, at 37 weeks, in the anterior limb of the internal capsule and optic radiation. LFB-staining is visible to the unaided eye at 40 weeks (term) in the thalamus, posterior limb of the internal capsule, and post-central gyrus, whereas, with MBP immunostaining, larger areas of positivity are obvious in these regions. In the human brainstem, the medial lemniscus becomes MBP-positive at about 20 weeks, and is mature by 34 weeks (35). MBP identifies myelination by mature OLs as early as 12- to 13-weeks-gestation in the human spinal cord (36). These findings are built upon the foundation laid by Gilles and co-workers using population-based classical neuroanatomical observations of the human fetal brain (37).

The anatomic sequences of postnatal myelination, likely to be familiar to neuropathologists and neuroradiologists who see pediatric material, are the work of Brody et al (38) and Kinney et al (39), who determined at 62 white matter sites the degree of myelination as graded on an ordinal scale of 0-4 on Luxol-fast blue-stained standard sections. With this method, grading of sites was assigned relative to an internal standard of "mature myelin" (degree 3) present in the inferior cerebellar peduncle. Their findings established defined patterns of CNS myelination from late gestation through infancy, as functions of the time of appearance of microscopically visible myelin, the intervals over which maturation to degree 3 took place, and the median ages at which mature myelin was achieved in their study population. Single and composite fiber pathways therefore could be categorized as "early," "intermediate," "late," or "very late" myelinations, within each of 2 groups, divided according to whether myelination began before birth (group A) or after birth (group B) (Table 2). While the ranges of the values within each category are wide, suggesting variability among individuals in an autopsy population, the work is of great value in its documentation of the overall picture of normal myelogenesis as evaluable by routine light microscopy.
TABLE 2

Categorization of CNS White Matter Tracts According to Temporal Sequence of Myelination

<table>
<thead>
<tr>
<th>Group A (Prenatal onset of myelination)</th>
<th>Group B (Postnatal onset of myelination)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early</strong></td>
<td><strong>Intermediate</strong></td>
</tr>
<tr>
<td>Optic tract</td>
<td>Pyramid</td>
</tr>
<tr>
<td>Post. Limb IC</td>
<td>Hilum of dentate</td>
</tr>
<tr>
<td>MCP</td>
<td>Ansa lenticularis</td>
</tr>
<tr>
<td>Capsule red N</td>
<td>Lat. cerebellum</td>
</tr>
<tr>
<td>Hilum of olive</td>
<td></td>
</tr>
<tr>
<td>Perideminate</td>
<td></td>
</tr>
<tr>
<td>Optic radiation</td>
<td>Calcareous SA fibers</td>
</tr>
<tr>
<td>Body CC</td>
<td>Cingulum</td>
</tr>
<tr>
<td>Splenium CC</td>
<td>Heschl's gyrus</td>
</tr>
<tr>
<td>Ant. limb IC</td>
<td>Temporal pole</td>
</tr>
<tr>
<td>Post. frontal</td>
<td></td>
</tr>
<tr>
<td>Post. parietal</td>
<td></td>
</tr>
<tr>
<td>Occipital pole</td>
<td></td>
</tr>
</tbody>
</table>

Early = myelination is histologically mature (degree 3) by 6 postnatal months; Intermediate = myelination is mature between 7 and 15 postnatal months; Late = myelination is mature between 18 and 23 postnatal months; Very late = myelination is mature after 23 postnatal months. CST = corticospinal tract; IC = internal capsule; CC = corpus callosum; SA = subcortical association fibers; MCP = middle cerebellar peduncle; CTT = central tegmental tract; N = nucleus; Tr. = tractus or tract; Adapted from Kinney, et al. (39).

Concurrent with the maturation sequence of oligodendroglial cell lineage is the progressive appearance of key myelin-associated lipids and proteins in brain tissue, detectable by biochemical methods (sodium dodecyl sulfate—polyacrylamide gel electrophoresis and thin-layer chromatography) on white matter homogenates (40). Examining specific white matter sites (posterior limb of the internal capsule, body of the corpus callosum, and frontal pole) in human specimens from 20 to 91 postconceptional weeks of age, Kinney and co-workers established that phospholipids (phosphatidylethanolamine, phosphatidylcholine, phosphatidylserine, and phosphatidylinositol) developmentally precede spongomyelin at all sites. Likewise, spongomyelin precedes hydroxy- and non-hydroxycerebrosides and non-hydroxysulfatides, which are then followed by hydroxysulfatides. Neutral lipids (primarily cholesterol) are present in mid-gestation through early infancy, in a site-related sequence (posterior limb before corpus callosum before frontal pole). Furthermore, the appearance of the major myelin proteins MBP and PLP follow these anatomic sequences temporally and by site, tending to occur at the same time as the appearance of the cerebrosides and sulfatides. Thus, the major biochemical components of the myelin sheath are synthesized in a specific order, corresponding to the established light-microscopic sequences of myelination (38, 39).

Evidence for Abnormal Myelogenesis in Human Lysosomal Storage Diseases

With the normal cellular, regional, and biochemical sequences of human central myelogenesis in mind, evidence of dysmyelogenesis in pediatric LSDs can be examined. The neuroradiologic and neuropathologic features of early and late infantile LSDs affecting the CNS are summarized in Table 1. From this compilation, several critical observations can be made.

First, in both early and late infantile LSDs of varying types, magnetic resonance imaging of white matter reveals increased T2 signal in periventricular locations, interpreted as “delayed” myelination (i.e. corresponding to an expected pattern for a younger individual) in virtually all cases for which details are available. In a few reports, serial images of individual patients provide confirmation of this interpretation, showing an arrest in development of myelin as opposed to normal development followed by myelin loss (4–13, 25). In fact, the “early” myelinating tracts from groups A (initiated prenatally) and B (initiated postnatally) tend to be normal, while the “intermediate” or “late” myelinators from both groups are most affected.

Second, nearly all the listed LSDs are described as having white matter abnormalities, usually myelin pallor (Fig. 2), which is accompanied by few details of the light or electron microscopic appearance of oligodendrocytes or their numbers. The specific reason for decreased myelin staining (i.e. whether secondary to axonal loss or primary demyelination with axonal preservation) is rarely delineated. When included in descriptions or illustrations, the presence of axonal spheroids, with or without gliosis and macrophages, is taken as evidence for axonal degeneration-associated myelin pallor, and is judged by me in a detailed literature review supplemented by personal observation to be minimal or mild (∆) in G_{H1}, gangliosidosis, G_{A}, gangliosidosis, Niemann-Pick I, mucolipidosis

J Neuropathol Exp Neurol, Vol 58, September, 1999
DYSMYELINOGENESIS IN STORAGE DISEASES

IV, galactosialidosis, mannosidosis, aspartylglucosaminuria, Wolman disease, Pompe disease, neuronal ceroid lipofuscinoses, mucopolysaccharidoses II and III, and Morquio syndromes. Spheroids, gliosis, and macrophages suggesting a moderate (+) degree of secondary myelin loss are described in Schindler I disease, sialidosis, and fucosidosis. Of course, Krabbe's disease and metachromatic leukodystrophy demonstrate severe (+ +) white matter degeneration, and will be considered later insofar as elements of their pathogenesis, as currently understood, may have bearing on the other less severe storage disorders.

As for neuropathologic studies specifically addressing dysmyelino genesis in human LSDs, these are limited. Infantile G_{M2} gangliosidosis has been recognized from its earliest descriptions as having a disproportionate decrease in myelin as compared with axons, especially early in the course of the disease (3). Haberland and colleagues (15) are the first to report in the English literature a systematic study of the question of primary versus secondary myelin loss in G_{M2} gangliosidosis. Among their 4 infantile cases, the degree of white matter changes is variable: the 2 with the longest clinical course (45 and 31 months) have hemispheric white matter that is “entirely devoid of stainable myelin,” while a few thinly myelinated fibers are seen in the third case. In the fourth case, the volume of hemispheric white matter is reduced, but with a normal “staining intensity.” “Meager thin myelin fibers” are described in the anterior and posterior limbs of the internal capsule, cerebral peduncles, pallidal fibers, and ansa lenticularis in the 2 most severely affected infants. Transverse pontine fibers, middle and inferior cerebellar peduncles, and deep cerebellar white matter are also myelin-poor by light microscopy. Lesser such changes are found in the 2 other cases. Axons in the hemispheric white matter are “rarely, thinned, and occasionally fragmented,” and accompanied by lipid-laden macrophages, both dispersed and aggregated around blood vessels, in three fourths of the cases. Axons are preserved in brainstem tracts. All patients have intense white matter gliosis. Interestingly, all cases appear to have normal populations of oligodendroglial cells upon qualitative assessment.

From this study the authors conclude that failure of myelination is the dominant mechanism of myelin decrease in their most severe cases of infantile G_{M2} gangliosidosis, since myelin is lacking in the fiber tracts in which myelination usually begins postnatally (i.e. group B “late” myelinators; Table 2). Arrest of myelination is presumed in those brainstem and forebrain fiber systems which normally begin myelination before and continue after birth (i.e. group A “intermediate” myelinators; Table 2). Finally, only “early” myelinating pathways are fully myelinated, again suggesting interference with myelinogenesis only later (i.e. postnatally) in development. The investigators postulate that the accumulation of G_{M2} ganglioside in neurons could disrupt the normal axonal metabolism and function, occurring during the “vulnerable” period of myelination in late gestation and infancy. Differences in myelination among affected individuals could be thought, therefore, to be due to differences in onset and tempo of the neuronal storage process. Haberland and co-authors suggest, furthermore, that if neuronal degeneration were to take place “at a time when the myelin is chemically still immature, its degeneration could be facilitated.” The presence of decreased cerebrosides and sulfatides in white matter extracts of all their cases raises the question of a lack of precursor material as a cause of failure of myelin development. Given the apparent normal numbers of oligodendroglia, an effect of the metabolic disease on oligodendroglial function rather than on oligodendroglial proliferation (Fig. 1) seems tenable. In abortuses, neurons in the brainstem show ultrastructural storage by 12 weeks gestational age (41), before the earliest myelination sequences begin. The status of oligodendroglial cells is not described, however, at this early stage.

Infantile G_{M1} gangliosidosis also has been subject to specific evaluation of white matter abnormalities (14). Semiquantitative assessment of myelin maturation, performed according to the methods of Brody et al described above, was carried out in 215-month-old autopsied patients. As in the G_{M2} cases, “early” myelinating regions are preserved while “later” myelinating regions are delayed (Figs. 2–4). Since axonal degeneration, gliosis, and macrophage infiltration are only minimal, an arrest in myelination, rather than loss of myelin secondary to axon loss, is postulated. Oligodendrocyte numbers are qualitatively decreased in the hemispheric white matter; further suggesting a primary effect of the metabolic disorder occurring as early as the second trimester of gestation, that is, at the time of the proliferation of early differentiating OLs (i.e. O4+, O1–, MBP– and O4+, O1+, MBP–) (Fig. 1). The finding of storage in neurons of the brainstem in fetuses at 17–22 gestational weeks has been documented, although details of storage in or numbers of oligodendroglial cells are not mentioned (42). Therefore, the timing of the metabolic effect of G_{M1} gangliosidosis on OL cell development remains speculative.

In Niemann-Pick disease, type A, decreased oligodendrocyte numbers (17) correspond to a marked degree of myelin pallor in the cerebral hemispheric white matter, accompanied by only minimal evidence of axon loss. Further detailed studies are not available; however, fetal brain tissue also demonstrates neuronal storage (1).

A lesser degree of white matter pallor is also seen in mucolipidosis IV, along with ultrastructural evidence of storage in oligodendroglia (21) and decreased oligodendrocyte populations (22). Fetal neuronal storage has been found in this disorder as well (43).
Other early onset LSDs with ultrastructural evidence of storage in oligodendroglia, as listed in Table I, include Wolman disease, galactosialidosis, fucosidosis, and neuronal ceroid lipofuscinosis (CLN2); however, details of oligodendroglial populations or distribution of white matter changes by light microscopy are not available. Storage in fetal CNS tissues at the time of therapeutic abortion has been described in sialidosis (44), fucosidosis, Farber disease, and mucopolysaccharidoses II and III (1).

Krabbe's disease and early-onset metachromatic leukodystrophy are well recognized as leukodystrophies, and have been extensively characterized radiographically (5) and neuropathologically (1, 45). From the microscopic appearance of grossly reduced white matter volume, discoloration, and increased consistency, with relative preservation of cortical ribbon and deep nuclei, a primary white matter abnormality is easily deduced. Whereas axons are diminished in the centrum semiovale and cerebellar hemispheric white matter, they are relatively preserved in brainstem tracts (3). Interestingly, anterior and lateral spinal columns (structures that normally achieve mature myelin in later infancy) show moderate to severe demyelination, whereas dorsal columns (normally myelinated at birth) are only slightly affected. Loss of oligodendrocytes is marked, and thought to be due to a toxic response to psychosine (galactosylsphingosine) as one of the accumulated compounds (46). In fetal tissues at 21 weeks gestational age, the spinal cord has the highest level of psychosine, and is the only site of occurrence of globoid (inclusion) cells (47). In a 17–18 week fetus, dorsal and ventral columns have myelin tubule density, and density of "myelination glia," comparable to age-matched controls by light microscopy. In this younger fetus, rare inclusion-bearing cells also are seen in the spinal cord (48). Pollarinen and Brody reviewed all previously reported fetal cases, identifying an apparently increasing frequency of globoid cells in fetuses with increasing gestational ages, ranging in age from 18 to 23 weeks (48). Furthermore, the distribution of inclusion cells corresponds to sites of normal...
topographic progression of myelin development, such that sites with more myelin tubules have more inclusions. They speculate that the accumulation of storage material in globoid cells correlates with both the onset and progression of myelinogenesis in the human CNS, and that some of the inclusion-bearing cells may be “myelination glia,” i.e. immature cells of the oligodendrogial lineage.

Like Krabbe’s disease, the leukodystrophic character of metachromatic leukodystrophy (MLD) of infantile onset is remarkable upon inspection of the cut brain. By light microscopy, the “phylogenetically older areas” (e.g. optic radiation, paleocerebellar white matter) are less involved than the centrum semiovale, although the population of oligodendrogial cells in all white matter sites is severely decreased (3). The decreased myelin is considered to be due to primary dysmyelinogenesis. Metachromatic material is stored in macrophages, astrocytes, and remaining oligodendrocytes in the white matter. Axons may be reduced in severely affected areas (2).

Human case studies, in summary, indicate that LSDs with early onset can result in an arrest in myelination, beginning as early as the second trimester and interfering with oligodendrogial proliferation, differentiation, survival, or myelin production in the developmental period after “early” myelination begins (third trimester to first months of life), but before “late” myelination is complete (2 years postnatally).

Dysmyelinogenesis in Animal Models of Lysosomal Storage Diseases

Many models of human LSDs exist, both naturally occurring in domestic animals and from targeted gene disruption in laboratory species (please see reviews by Suzuki [49] and Jolly [50]). Of these, a subset has been investigated particularly with respect to developing white matter abnormalities. Despite the differences in patterns and timing of myelination among the various mammalian species, comparisons to human development are possible.
Fig. 4. Myelin basic protein immunostain (performed with monoclonal antibody [Biogenex, San Ramon, CA] according to standard protocols) in white matter from frontal pole. 18-month-old control (A; ×1,000); G3 long chain gangliosidosis, infantile type, at 15 months (B; ×1,000), with markedly decreased density of stained myelin sheaths.

Probably the best-known authentic animal model of a human LSD is the twitcher mouse, which, as in Krabbe’s disease, lacks galactocerebrosidase activity leading to leukodystrophy (45). Studies in twitcher have clarified many of the sequences and mechanisms of white matter loss. One interesting observation is the apparently early normal development of affected animals. Morphometric studies of glial cell numbers, myelinated axons, and myelin sheath thickness in dorsal columns and corticospinal tracts of cervical spinal cord demonstrate no differences between twitcher and control mice up to day 5 of postnatal life. Likewise, biochemical determinations of CNS galactolipids are normal at this age. However, by postnatal day 20, the ratio of myelin sheath to axon diameter in these sites is clearly decreased in affected animals relative to controls. Other than being thinner than normal, the myelin sheath is structurally well formed, with normal compaction, suggesting an arrest or delay in normal myelin wrapping. Evidence supporting this idea is the finding that the level of UDP-galactose:ceramide galactosyltransferase

*J Neuropathol Exp Neurol, Vol 58, September, 1999*
(CGT), the oligodendroglial-specific enzyme which catalyzes the final step of galactosylceramide synthesis, is normal until day 15, begins to fall at day 20, and precipitously drops thereafter (51). Similarly, MBP, MAG, PLP, and CGT mRNA levels are the same in twitcher and normal control mice until day 20, the point at which maximum levels occur in normal development. However, in twitcher animals these mRNA levels fall disproportionately between days 25 and 30, the period in which myelination should be progressing. An even greater decline in mRNA for myelin proteins occurs between days 35–45, corresponding morphologically to oligodendroglial cell loss. Interestingly, glial fibrillary acidic protein (GFAP) mRNA levels begin to rise before demyelination begins and therefore are not simply a response to demyelination.

After this point, failure of myelin synthesis in twitcher apparently gives way to breakdown of formed myelin, occurring in a defined pattern: demyelination begins in spinal, brainstem, and cerebellar white matter, followed...
by loss in the cerebral hemispheres. In particular, subpial
dorsal columns and dorsal root entry zones, and the pen-
tocerebellar junction in the brainstem are the earliest lo-
cations in which demyelination is detected. By electron
microscopy, macrophages in these sites appear to partic-
icipate in the demyelinating process by intercalating be-
tween axons and their sheaths, and phagocytizing degen-
erating sheaths.

In twitcher, oligodendroglial numbers are comparable
with those of littermate controls in the first days of life.
By about postnatal day 5, storage material is ultrastruc-
turally evident in oligodendrocytes. Later, enlarged so-
 mata, abnormal cytoplasmic processes, and “iron-rich”
cytoplasmic structures precede frank degenerative chang-
es by electron microscopy in oligodendroglia in the ear-
liest-demyelinating regions. In tissue culture, affected OL
cells develop poor cytoplasmic extensions, and eventu-
ally spontaneously degenerate, suggesting a primary met-
abolic abnormality intrinsic to the myelin-forming cells.
Surprisingly, despite this ready degeneration, prolifera-
tion indices of OL cells in twitcher spinal cord are in-
creased over normal (52). A post-proliferative defect,
therefore, must be responsible for the eventual marked
depletion of oligodendrocytes. As mentioned previously,
the mechanism of oligodendrocyte cell loss is thought to
be mediated by the toxic metabolite, psychosine (galac-
tosylsphingosine), possibly through its powerful inhibi-
tion of protein kinase C (45, 53), discussed in the next
section. By high-pressure liquid chromatography, psy-
chosine is indeed located at sites of greater demyelination
and globoid cell concentration (54).

A second early-onset human LSD for which an animal
model exists showing dysmyelinationogenesis is G₄₃, gaul-
gliosidosis. Two different naturally occurring canine mu-
nants have been studied by brain MR imaging, biochem-
istrY, and neuropathology (25). Relative to controls,
affected dogs have a lack of low-intensity signal on T₂-
weighted images in periventricular white matter, corre-
sponding macroscopically to reduced white matter vol-
ume, in the face of increased gray matter volume and
total brain weight. Topographically, earlier myelinating
regions (e.g. body of corpus callosum) in the dog, as in
the human, demonstrate more myelin than later myeli-
nators (e.g. lobar white matter). By light microscopy,
poor myelination is unaccompanied by evidence of axo-
nal loss or macrophage infiltration. Ultrastructurally,
axons are present in relatively normal numbers, but show
only focal ensheathment by normal myelin, as in the hu-
man infant with G₄₃, gaulngliosidosis (Fig. 3). These find-
ings are considered evidence of failure of myelination
rather than breakdown of previously formed myelin.

Biochemically, the canine feline models have excess
G₄₃ gaulnglioside and sialic acid, and decreased cerebro-
sides and sulfatides in the white matter relative to con-
trols, differences thought to be too great to ascribe to
axonal loss only, but instead suggesting a primary failure
of myelin development (25).

Another particularly well studied naturally occurring
mutant is the β-mannosidosis goat, corresponding to a
less severe, rare human phenotype (1). Regional variation
in the degree of myelin abnormality is seen, with the
greatest paucity of myelin observed in the corpus callo-
sum, anterior commissure, limbic structures, and medul-
lary pyramids. While myelination is generally complete
at birth in the goat, the order of myelination is similar to
that of other mammals, so that the deficiency of myelin
corresponds to the latest-myelinating regions (55). Re-
duced oligodendroglial cell numbers and vacuolation of
individual oligodendroglia, presumably representing oli-
gosaccharide storage, are widespread (55). While spher-
oids are identified occasionally, most axons are preserved
even in regions of severe myelin deficit. The finding of
normally myelinated internodes alternating with unmy-
elinated internodes further suggests a primary oligo-
dendroglial, rather than axonal, defect (56). Morphometry
of fetal optic nerve from affected goats confirms the im-
pression of preserved (and even slightly increased) axon
diameter; where present, myelin sheath thickness is nor-
mal. The normal axon size speaks against a problem with
axon growth as the mechanism of decreased myelination.
Quantitatively, decreased populations of oligodendro-
cyes and increased proportions of astrocytes relative to
controls are established (57). Most important is the im-
plcation by this investigation that the prenatal myelina-
tion abnormalities are “the beginning of a permanent my-
elin deficiency” rather than a mere delay in myelination
(37). Specifically, the authors postulate a change in the
dynamics of oligodendroglial cell proliferation, or pos-
sibly cell death, prior to gestational day 124/150 in the
optic nerve of β-mannosidosis goats. Similar though ul-
timately more severe changes in the corpus callosum in
animals ranging from fetal day 115/150 to 4 postnatal
weeks are also documented (58). A progression of ab-
normality of glial cells, from vacuolation in earlier-ges-
tation fetuses, to decreased numbers of glia, is found in
the corpus callosum, suggesting that the cellular defects
occur before the onset of myelin sheath formation.

Further evidence of primary oligodendroglial abnor-
mality in caprine β-mannosidosis has been obtained in tis-
ue culture studies by Boyer and Lovell (59). They
showed increased numbers of galactocerebroside-nega-
tive bipolar (i.e. immature) cells from white matter of
affected animals, consistent with persistence of undiffer-
entiated glia in a later-than-expected developmental stage,
supporting the hypothesis of defective maturation of OL
precursors. One might speculate that the levels of oligo-
saccharide storage would correlate with the degree of ab-
normal myelination in affected CNS regions. However,
such is not the case. The pattern of regional myelin abnormality in caprine β-mannosidosis is apparently not related to the distribution of stored oligosaccharides (60). In fact, metabolite accumulation is greatest in spinal cord, a site of early myelination in the goat, whereas dysmyelination is of increasing severity in more rostral (i.e., later myelinating) sites. A correlation does exist, however, between the pattern and tempo of myelin loss with respect to the regional expression of major myelin proteins in caprine β-mannosidosis (61). Myelin yields are progressively decreased from spinal cord (38% of normal expression) to brainstem (2.2% of normal) and cerebral hemispheres (7% of normal) in newborn animals. Levels of PLP and MBP are successively diminished in the same pattern, in both newborn and 2–4-week-old animals. These results confirm biochemically the morphological observations of regionally variable myelin deficiency, corresponding to developmental sequences of myelination. Again, the apparently progressive disruption of the process of myelination as development proceeds is a recurring theme.

Feline models of Gm2 gangliosidosis have MR abnormalities and neuropathology resembling the human disease (Sandhoff variant) (62). By MR, affected animals have white matter signal hypointensity on T1- and hyperintensity on T2-weighted sequences, which progress on serial imaging, as compared with littermate controls. Areas affected include the subcortical periventricular zones and internal capsule. Upon neuropathologic examination, diminished white matter volume and pallor on I.FB stain are found in these regions. Vacularation and macrophage infiltrates are seen in the white matter of some animals, as are smaller axons. Decreased numbers of gangliosidroglia, with storage in remaining cells by electron microscopy, are described in another feline Gm2 gangliosidosis model (27). In this model, a qualitatively normal population of axons, many of large diameter, have proportionately few normal myelin sheaths.

In “knock-out” mouse models of Gm2 gangliosidosis, phenotypic variations exist among the mice depending upon whether they are missing the α-chain (minimally affected neurologically), or β-chain or Gm2 activator protein (severely affected) (63), unlike the human disease, in which the affected infants are indistinguishable phenotypically from one another. Hexa −/− mice (lacking the α subunit of hexosaminidase A), equivalent to human Tay-Sachs disease, are thought to retain the ability to partially catabolize accumulated Gm2 to Gm3 gangliosides via sialidase and β-hexosaminidase pathways, unlike the hexb −/− mice, models of Sandhoff’s disease. Unexpectedly, “double knock-out” mice, lacking expression of both genes encoding the α and β subunits, and therefore deficient in all hexosaminidases, not only accumulate Gm2 ganglioside but also glycosaminoglycans reminiscent of the human mucopolysaccharidoses (64, 65). Apparently, glycosaminoglycans are also substrates for β-hexosaminidase, but in humans must be catabolized in a redundant pathway. Despite these species differences between murine and human ganglioside metabolism (66), both murine and human Gm2 gangliosidoses likely have deranged intercellular signalling and interaction due to the disorders in glycosphingolipid turnover, to be discussed in greater detail in the next section.

In the NTCR-Balb/C mouse, a model of spongomyelin lipidosis (Niemann-Pick C), dysmyelination is inferred from a lack of LFB staining of the corpus callosum, mammillothalamic tract, medial lemniscus, and internal capsule in affected versus control animals. Electron microscopy reveals “naked axons,” without significant gliosis, macrophages, or myelin debris to indicate a secondary myelin breakdown (67). Scarcity of oligodendrocytes is obvious in the corpus callosum of affected postnatal 12-day-old mice (68). Biochemical lipid composition is altered in affected animals, with accumulated gangliosides and glycosphingolipids, and markedly decreased cerebrosides and sulfatides in white matter, suggesting myelination failure, possibly resulting from a block in the esterification of exogenously derived cholesterol (67).

Recently generated “knock-out” mice lacking acid sphingomyelinase resemble Niemann-Pick A (69). Progressive accumulation of vacuoles and, later, lamellated membrane structures in neurons, glia, and vascular cells is documented from 18–225 postnatal days. Neuronal loss is not observed, although axonal storage in single fibers is described. Central myelination is complete by 80 postnatal days, but ultrastructural thinning of myelin sheaths and storage in oligodendrocytes is present. Axonal swellings are prominent only in the oldest animals.

White matter changes in a dog with neurovisceral glucocerebrosidase storage, similar to Gaucher’s disease, include vacuolation and breakdown of myelin sheaths accompanied by a few macrophages. Axonal spheroids are rare. Affected sites include central hemispheric white matter, corpus callosum, optic tracts, cerebellar peduncles, trapezoid body, deep cerebellar white matter, and spinocerebellar and corticospinal tracts in the spinal cord (70). Specific details regarding oligodendrocyte numbers and intracellular storage are not available.

In mice with targeted disruption of aspartylglucosaminidase gene expression, lysosomal storage vacuoles in brain are detectable as early as 19 days gestation (71). Postnatal MR imaging of pups in vivo showed signal intensity alterations in white matter similar to those seen in affected infants, diagnosed with delayed myelination (13).

Possible Mechanisms of Abnormal Myelination in Human LSDs

Given the foregoing evidence that humans and animals with diverse early-onset lysosomal storage disorders have
at least some degree of primary myelin abnormality, the question of pathogenesis arises. In this section, consideration of possible mechanisms of dysmyelination will focus on the relationship of defective lysosomal metabolism to OL development, OL function, and neuronal influences on myelination. The multiplicity of factors involved in the cellular biology of myelination, and the incompleteness of current understanding of many of these factors, must be emphasized.

Factors Influencing OL Development

Dysmyelination may result from perturbation at one or more points in the process of OL cell development outlined above, from generation of OL precursors, to migration and proliferation of OL precursors, to maturation of oligodendrocytes capable of synthesizing and transporting components of myelin. Since oligodendrocytes are present histologically in the diseases under discussion, a defect in initial gliogenesis is not likely, and shall not be considered further.

Growth factors have an important role in oligodendroglial precursor migration and proliferation (reviewed in Back and Volpe [28], Barres et al [31], and McMorris and McKinnon [72]). It is known that immature OLs migrating from subventricular zones move toward platelet-derived growth factor (PDGF) derived from neurons and astrocytes (73, 74). In synergy with neurotrophin (NT)-3, PDGF acts on OL progenitors and pre-OLs to induce proliferation, while NT-3 alone supports survival of the differentiated daughter cells (75, 31). Nerve growth factor (NGF) and its high-affinity receptor, trkA, also are expressed in OL lineage cells. Along with basic fibroblast growth factor (bFGF), NGF has mitogenic effects on oligodendrocyte precursors as well as survival (i.e. anti-apoptotic) effects on mature oligodendrocytes, perhaps in an autocrine manner (75). NGF and NT-3 have receptors on neurons, astrocytes, and microglia, as well as on oligodendroglia, possibly indicating additional sources of modulation of these effects. Differentiation of pre-OLs (O4+, O1−, MBP−) to immature OLs (O4+, O1+, MBP−) and mature OLs (O4+, O1+, MBP+), and survival of these mature forms, therefore, appear to require continuous, coordinated signalling by multiple factors (31).

Since many growth factor receptors and intercellular adhesion molecules are glycosylated membrane proteins, and since the expression of cytoplasmic and cell-surface sugar moieties is known to be widely altered in a variety of LSDs (76), impairment of the normal interrelated action of these elements could lead to deranged OL migration, proliferation, or differentiation. Altered glycosylation of cell surface sphingolipids, for example, is known to induce premature cellular differentiation (77).

Glycolipids, another group of integral membrane molecules, are central to a developmentally important apoptotic pathway of particular relevance to primary dysmyelogenesis in lysosomal storage diseases. As in many immature tissues, regulation of cell numbers in the developing white matter is determined by the delicate balance between growth factor-mediated proliferation (discussed above) and physiologic apoptosis (see reviews by Back and Volpe [28], Kolesnick and Golde [78]). In the sphingomyelin pathway, sphingomyelin is hydrolyzed to ceramide, which acts as a lipid second messenger mediating the apoptotic effects of tumor necrosis factor-α (TNF-α) (79), acting via ceramide-activated protein kinase (78). Application of exogenous cell-permeable ceramides to primary cultures of human oligodendrocytes and precursor cells results in dose-dependent apoptotic cell death (80). Importantly, neurons, bipotential progenitor cells committed to an astrocytic phenotype, and mature astrocytes are unaffected by the exogenous ceramides, suggesting cell type-specific vulnerability to this apoptotic pathway.

Pathologic apoptosis occurs via the stress-activated protein kinase/c-jun N-terminal kinase (SAPK/JNK) pathway, which also can be induced by ceramide (81). In addition to its proliferation-promoting functions described above, nerve growth factor (NGF) can lead to apoptosis by stimulating the low-affinity receptor p75 (82, 83); in oligodendroglia, this action is mediated via caspases-1, -2, and -3, but not -8 (84). Whether catabolite accumulation in LSDs might contribute to initiation of these stress/inflammatory responses is an intriguing possibility. The effects of sphingolipids and gangliosides on the immune system (77), in particular the regulation of cytokine production by mononuclear cells (78), are of possible significance in this regard, but are beyond the scope of this review.

Since the discovery that lysosphingolipids inhibit protein kinase C (PKC), a ubiquitous calcium-dependent enzyme involved in a wide range of cellular activity, a link between the metabolic defect and the pathogenesis of cell dysfunction and death in the sphingolipidoses (e.g. gangliosidoses, Niemann-Pick, Krabbe's, and Gaucher diseases [Table 1]) has been hypothesized (53). PKC is particularly abundant in the central nervous system, and is involved in the transduction of neurotransmitter signals, regulation of receptor expression, and cell differentiation, including cytoplasmic process outgrowth in maturing OLs (85). Ceramide-related apoptosis, discussed above, is prevented by the action of PKC (53). Therefore, the accumulation of brain lipids in the sphingolipidoses, leading to inhibition of PKC-mediated OL differentiation and to promotion of ceramide-related OL apoptosis, is implicated directly in arrested white matter development.

Ceramide also mediates TNF-α-induced down-regulation of c-myc, possibly stopping proliferation as terminal
differentiation takes place (78). Ceramide also inhibits thymidine incorporation, accompanied by dephosphorylation of the retinoblastoma gene product, signifying growth suppression/cell cycle arrest in certain cell lines (86). Such mechanisms, that is, premature arrest of differentiation, could be operative in those LSDs (e.g. G\textsubscript{\textalpha} gangliosidosis) without decreased numbers of oligodendroglial nuclei, but with decreased myelin sheath production.

The coexistence of abundant gliosis with hypomyelination in many of the infantile LSDs has been presumed to represent a response to axon loss or injury. Alternatively, the astrocytes are reactive to primary dysmyelino genesis by OLs. An interesting additional possibility is a reflection of glial cell plasticity, as has been demonstrated in a murine model of phenylketonuria, a nonlysosomal storage inborn error of metabolism (87). In this experimental setting, exposure of cultured oligodendrocytes to high levels of phenylalanine resulted in expression of glial fibrillary acidic protein (GFAP) and failure of membrane sheet (myelin sheath) formation in 50% of the cells. In addition, double-labelled tissue sections showed significantly increased numbers of GFAP+/MBP+ cells in the white matter, again suggesting adoption of a nonmeylinating phenotype by cells from the oligodendroglial lineage. The decreased proportion of oligodendroglia and increased proportion of astrocytes determined morphometrically by Lovell and Boyer (57) in caprine \beta-mannosidosis may also reflect such a process.

Factors Influencing Mature OL Function and Myelin Stability

Mature OL function includes myelin sheath assembly and long-term turnover and maintenance. While storage of undigested and possibly toxic catabolites is the hallmark of the LSDs, the other major consequence of an enzymatic block is the eventual lack of substrates needed for anabolic activities. In the white matter, therefore, the decreased synthesis of myelin proteins and lipids (e.g. in G\textsubscript{\textalpha} and G\textbeta, gangliosidosis, Krabbe’s disease, galactosialidosis, and metachromatic leukodystrophy; see Table 1) means an ongoing shortage of the components of the myelin sheath. The fairly consistent pattern of delayed, but not absent, myelination in LSDs bespeaks a critical point in early development at which this substrate shortage becomes manifest.

The timing of substrate shortage may be related to cell membrane turnover dynamics, in which membrane sphingolipids appear to play a significant role (77, 88, 89). Glycosphingolipids may be either synthesized de novo or recycled in a salvage pathway, in which they are degraded in the cell membrane, transferred to the Golgi, and reglycosylated for reincorporation into membranes. The salvage pathway predominates in nonproliferating/differentiated cells, including oligodendrocytes (77). Theoretically, the disrupted degradation of compounds, particularly in the sphingolipidoses, could increase susceptibility of mature oligodendroglial cells to failure of normal membrane turnover. In addition, the altered galactocerebroside (GaIC) and sulfatide availability could affect vesicle sorting and transport, leading to faulty trafficking of other myelin components, such as proteins which are otherwise normally produced (88). Myelin assembly and maintenance would then be jeopardized.

Experimental evidence of the consequences of disruption of normal sphingolipid metabolism is seen in the “knock-out” mouse lacking UDP-galactose:ceramide galactosyltransferase (CGT) (90). CGT is necessary for synthesis of GaIC and its sulfated derivative, which are principle components of the myelin sheath. Affected mice have normal OL differentiation, normal expression of MBP and PLP mRNA and protein, and, surprisingly, form myelin sheaths, which, however, contain glucocerebroside instead of GaIC. The myelin sheaths are subtly abnormal ultrastructurally, being thinner than normal, with increased numbers of heminodes and astrocytic processes intercalated between the axon and myelin sheath, as well as vacuolation of myelin with intraperitoneal splitting suggestive of defective cell-cell interactions causing myelin instability (88, 91). In vivo conduction defects by electrophysiology correspond to progressive neurologic disease. Thus, in the “knock-out,” myelin can be formed using alternative components, but has significant abnormalities in function and stability. Whether similar aberrances in myelin sheaths exist in some of the human LSDs is distinctly possible, but unknown at present. Interestingly, twitcher mice exhibit down-regulation of CGT mRNA as development proceeds, suggesting an effect of the galactocerebroside deficiency on CGT production, with possible influence on myelin stability (51).

Other galactolipid perturbation studies pointing to the importance of GaIC and sulfatide in myelin formation and myelin stability include the work of Dyer and Benjamins (reviewed in Dyer [92]). In their investigations of cultured human OLs, antibodies to GaIC cause antigen: antibody complex formation, calcium influx, reorganization of membrane surface GaIC, and loss of intracellular microtubules, with resulting changes in cytoskeletal morphology, later shown to be mediated by MBP (93). The inference is that the cytoskeletal integrity of oligodendrocytes is crucial to their ability to enwrap axons. It follows that abnormal metabolism due to enzyme deficiency and progressive accumulation of catabolites in LSDs could perturb membrane GaIC homeostasis, resulting in defective myelin wrapping and myelin stability as development proceeds.
Factors Influencing Neuronal Stimulation of Myelination

These factors will be mentioned briefly (reviewed in Colello and Pott [30]). Lysosomal storage disorders have deranged neurite outgrowth and synaptogenesis (94), microtubule-associated protein (MAP2) expression (95), calcium transport across membranes (96), and neurotransmitter chemistry (97), as well as frank neuron loss, all of which may contribute to myelin deficiency. In Batten disease (CLN2), a role for excitotoxicity to neurons due to abnormal metabolism of subunit c of mitochondrial ATPase has been postulated (98). As mentioned above, altered glycosylation of cell-surface molecules in axonal membranes could interfere with normal axon/oligodendrocyte contact, necessary for the initiation of myelination (30). Interestingly, the electrical state of the axon also is critical to myelination, as it is required for proliferation of OL progenitors, possibly by way of astrocyte-generated PDGF (99). Whether the electrical function of the axon is affected specifically in LSDs is unknown, although the seizure disorder common to many of the LSDs begs the question.

In summary, lysosomal storage disorders with onset in infancy have dysmyelination resulting from a multiplicity of factors, likely reflecting both a primary effect of the metabolic disease on normal oligodendroglial growth and function, as well as a secondary influence of aberrant neuroaxonal development on myelination. Investigations of animal models of lysosomal storage diseases have contributed a great deal toward the understanding of possible mechanisms of dysmyelogenesis. Current and future research on human white matter development in normal and pathological states, such as the white matter injury of prematurity, may provide valuable insights into the pathogenesis of dysmyelination in LSDs and other inborn metabolic disorders.

ACKNOWLEDGMENTS

The help and support of Drs. Hannah C. Kinney and Joseph Alroy have been indispensable and are greatly acknowledged. I also thank Drs. Stephen Back and Wiley-Liss (Brooklyn), and Springer-Verlag (New York) for use of previously published figures. Ms. Linda Palscey provided expert secretarial support.

REFERENCES

35. Takino S, Mito T, Takashima S. Progress of myelination in the human fetal spinal nerve roots, spinal cord and brainstem with myelin basic protein immunohistochemistry. Early Hum Dev 1995;41:49–59
41. Adachi M, Schneek L, Volk BW. Ultrastuctural studies of eight cases of fetal Tay-Sachs disease. Lab Invest 1974;30:102–12
82. Dobrowsky RT, Werner MH, Castellino AM, Chao MV, Hanun YA. Activation of the sphingomyelin cycle through the low-affinity neurotrophin receptor. Science 1994;265:1596–99