

# Cerebral White Matter

## Neuroanatomy, Clinical Neurology, and Neurobehavioral Correlates

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Lesions of the cerebral white matter (WM) result in focal neurobehavioral syndromes, neuropsychiatric phenomena, and dementia. The cerebral WM contains fiber pathways that convey axons linking cerebral cortical areas with each other and with subcortical structures, facilitating the distributed neural circuits that subserve sensorimotor function, intellect, and emotion. Recent neuroanatomical investigations reveal that these neural circuits are topographically linked by five groupings of fiber tracts emanating from every neocortical area: (1) cortico-cortical association fibers; (2) corticostriatal fibers; (3) commissural fibers; and cortico-subcortical pathways to (4) thalamus and (5) pontocerebellar system, brain stem, and/or spinal cord. Lesions of association fibers prevent communication between cortical areas engaged in different domains of behavior. Lesions of subcortical structures or projection/striatal fibers disrupt the contribution of subcortical nodes to behavior. Disconnection syndromes thus result from lesions of the cerebral cortex, subcortical structures, and WM tracts that link the nodes that make up the distributed circuits. The nature and the severity of the clinical manifestations of WM lesions are determined, in large part, by the location of the pathology: discrete neurological and neuropsychiatric symptoms result from focal WM lesions, whereas cognitive impairment across multiple domains—WM dementia—occurs in the setting of diffuse WM disease. We present a detailed review of the conditions affecting WM that produce these neurobehavioral syndromes, and consider the pathophysiology, clinical effects, and broad significance of the effects of aging and vascular compromise on cerebral WM, in an attempt to help further the understanding, diagnosis, and treatment of these disorders.

**Key words:** fiber tracts; neuropsychiatry; cognition; demyelination; vascular dementia

The cerebral white matter (WM) was considered in antiquity to be the seat of all sensa-

tions, movements, and intellect. It was relegated to relative obscurity as the cerebral cortex ascended to prominence, and cerebral cortical association areas, in particular, came to be regarded as the substrates for cognition.<sup>1–3</sup> These notions have required revision. Neurobehavioral disconnection syndromes occur

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after lesions of selected fiber bundles<sup>4,5</sup>; dementia can result from lesions confined to the cerebral WM<sup>6</sup>; and it has become apparent that all neurological function is subserved by distributed neural circuits, in which geographically distant regions in cortical and subcortical nodes are linked together by axonal connections conveyed in the fiber pathways that constitute the cerebral WM.<sup>4,5,7–14</sup>

Knowledge of the anatomical, functional, and clinical relevance of the WM is thus integral to the understanding of neurological and neuropsychiatric disease. This development is further emphasized by the rapid evolution in magnetic resonance imaging (MRI) techniques that makes it possible to visualize fiber pathways in humans in health and disease.<sup>15–19</sup> Here we present an overview of essential anatomy of the cerebral WM; survey several diseases in which the pathology is principally or commonly confined to it; and discuss the clinical manifestations of WM disorders, with an emphasis on neurobehavioral impairments.

## Neuroanatomy of WM Pathways

### Historical Background

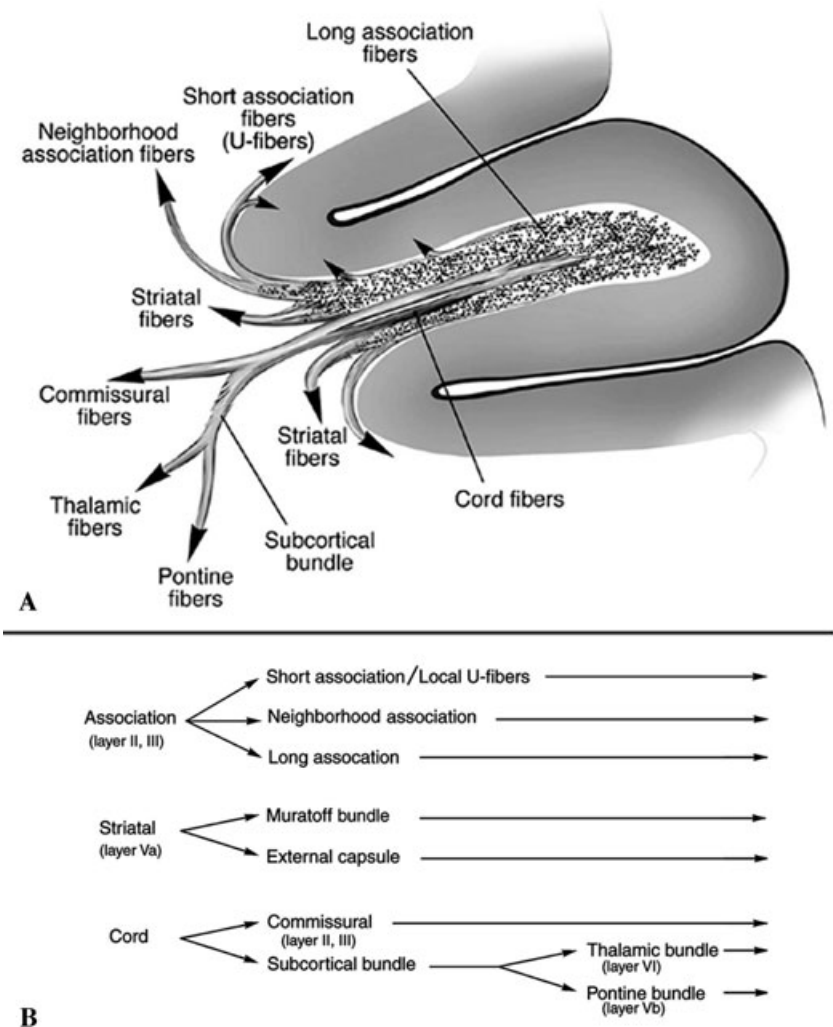
Galen's (AD 129–130 to 200–201) identification of the corpus callosum<sup>20</sup> was perhaps the first recognition of a major fiber bundle, but it was not until the scientific renaissance of the 17th century that it became apparent that the WM was not an amorphous mass but rather consisted of distinct fibers.<sup>2,3,21</sup> The gross dissection methodology of investigators in the 19th century led to the identification of distinct fiber fascicles<sup>22,23</sup> and the recognition that these bundles could be considered association, projection, or commissural in nature.<sup>2,3,24–26</sup> The clinical relevance of association pathways was introduced by Carl Wernicke's (1848–1900) description of conduction aphasia from what he believed to be the arcuate fasciculus,<sup>27</sup> and Joseph Jules Dejerine's (1849–1917) account of alexia without

agraphia from lesions that involved the left occipital pole in addition to the splenium of the corpus callosum.<sup>28</sup> Disconnection syndromes were first emphasized in the modern era by Norman Geschwind (1926–1984)<sup>4,5</sup> and provided clinical and neuroanatomical impetus to the emergence of behavioral neurology as a discipline. The distributed neural circuitry notion has become fundamental to the understanding of the nervous system in health and disease. It provides a conceptual underpinning to the observation of neurobehavioral deficits that arise not only from cortical lesions but also from lesions of basal ganglia, thalamus, and cerebellum, as well as from the fiber tracts that link cortical areas with each other and with the subcortical nodes.<sup>2,29</sup>

### Organizational Principles

To understand the effects of WM lesions on neurological function, including cognitive and neuropsychiatric impairments, it is essential to know the anatomy of the fiber tracts that it contains. These tracts are aggregations of axons running in close apposition to each other, sharing common cortical and/or subcortical origins and destinations. The great complexity of connections and pathways arising from the cerebral cortex can be reduced to a relatively simple schema (Fig. 1). There is a general principle of brain organization<sup>2</sup> that every area of the neocortex is linked with other cortical and subcortical areas by pathways grouped into five fiber bundles, identified as follows.

1. Association fibers travel to other ipsilateral cortical areas.
2. Striatal fibers course to the basal ganglia. There is a confluence of fibers (termed the cord) that divides into:
3. Commissural fibers that pass to the contralateral hemisphere, and another contingent of the cord, the subcortical bundle of projection fibers, that segregates into
4. Thalamic fibers, and

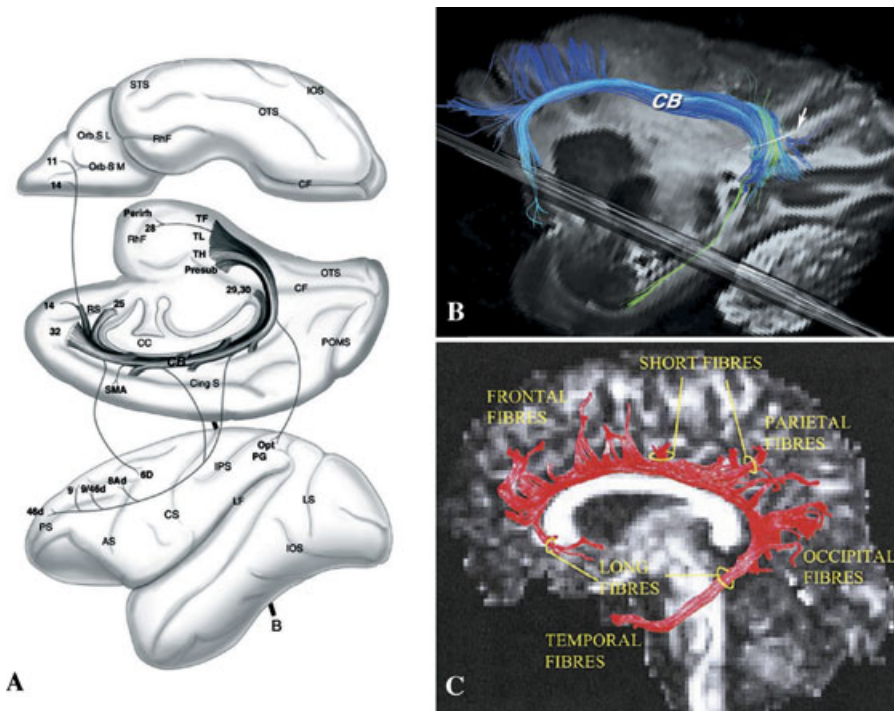


**Figure 1.** Diagram (A) and schema (B) of the principles of organization of white matter fiber pathways emanating from the cerebral cortex. Long association fibers are seen end-on as the stippled area within the white matter of the gyrus. In their course, these fibers either remain confined to the white matter of the gyrus or travel deeper in the white matter of the hemisphere. Short association fibers, or U-fibers, link adjacent gyri. Neighborhood association fibers link nearby regions, usually within the same lobe. Striatal fibers intermingle with the association fibers early in their course, before coursing in the subcallosal fascicle of Muratoff or in the external capsule. Cord fibers segregate into commissural fibers that arise in cortical layers II and III, and the subcortical bundle, which further divides into fibers destined for thalamus arising from cortical layer VI, and those to brain stem and spinal cord in the pontine bundle arising from cortical layer V.<sup>2</sup>

5. Pontine fiber fibers that descend to the diencephalon, pons, other brain stem structures, and/or the spinal cord.

We now elaborate on these five classes of fiber tracts and their putative functional prop-

erties, because this knowledge is useful when considering the clinical consequence of WM diseases. Many of these tract tracing observations<sup>2</sup> are supported by MRI findings in monkey by using diffusion spectrum imaging<sup>30</sup> and in human subjects by using diffusion tensor



**Figure 2.** Course of the cingulum bundle (CB). **(A)** Surface views of the ventral (top), medial (middle), and lateral (lower) convexities of the cerebral hemisphere of a rhesus monkey show the trajectory of the CB reflected onto the cortical surface, and the cortical areas that it links, as determined by autoradiographic tract tracing.<sup>2</sup> **(B)** CB fibers in the monkey are shown in this sagittal dimension by using diffusion spectrum magnetic resonance imaging (DSI). CB fibers that intersect a disc (shown by the arrow) course between rostral and caudal cingulate regions and link the cingulate gyrus with the prefrontal and parietal areas. Fibers in the ventral limb of the CB course to the parahippocampal region.<sup>30</sup> **(C)** The course of the CB in human brain is demonstrated using diffusion tensor imaging (DTI), remarkably similar to the findings in monkey.<sup>19</sup>

imaging (DTI<sup>19,31,32</sup>), probabilistic tractography,<sup>33,34</sup> and functional connectivity mapping.<sup>35,36</sup> It is likely, therefore, that the observations in monkey will be in general agreement with the anatomical organization of these pathways in humans. See Figure 2.

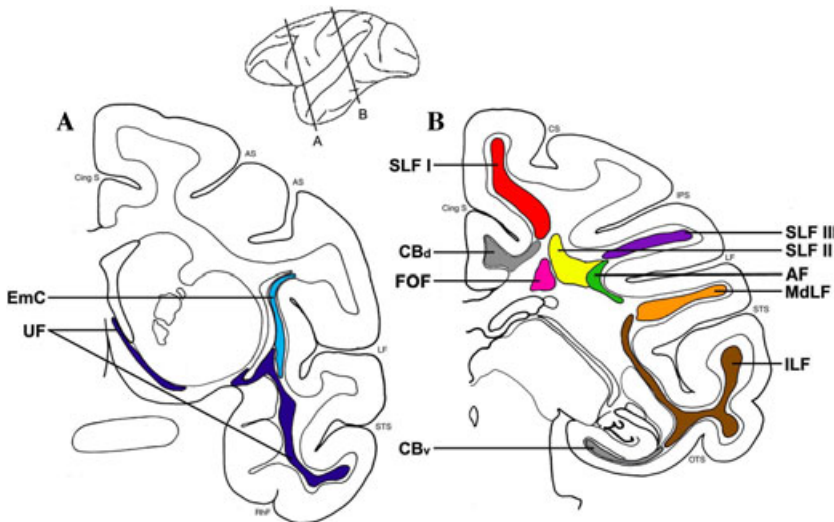
### Association Fiber Tracts

Association fibers travel to other cortical areas in the same hemisphere. *Local association fibers*, or U-fibers, travel to adjacent gyri, running immediately beneath the sixth layer. *Neighborhood association fibers* are directed to nearby regions and are distinguishable from U-fibers

by their location. *Long association fibers* travel in discrete fascicles leading to distant cortical areas in the same hemisphere. These named fiber tracts are the essential anatomic substrates for the interdomain communication between cortical areas that subserve different behaviors, and these deserve particular emphasis (Fig. 3).

**The superior longitudinal fasciculus** (SLF) has three subcomponents.

**SLF I** lies medially situated in the WM of the superior parietal lobule and the superior frontal gyrus. It links the superior parietal region and adjacent medial parietal cortex in a reciprocal manner with the frontal lobe supplementary and premotor areas. It is thought to play a role in the regulation of higher aspects of



**Figure 3.** Location of long association fiber pathways in the monkey. The coronal sections in (A) and (B) are taken at the corresponding levels shown on the figure of the lateral hemisphere (top). The fiber bundles are colored for ease of identification. Fiber pathways: AF, arcuate fasciculus; CBd, cingulum bundle dorsal component; CBv, cingulum bundle ventral component; EmC, extreme capsule; FOF, fronto-occipital fascicle; ILF, inferior longitudinal fascicle; MdLF, middle longitudinal fascicle; SLF (I, II, III), superior longitudinal fascicle, sub-components I, II, and III; UF, uncinate fasciculus. Cerebral sulci: AS, arcuate sulcus; CS, central sulcus; Cing S, cingulate sulcus; IPS, intraparietal sulcus; LF, lateral fissure; PS, principal sulcus; OTS, occipitotemporal sulcus; STS, superior temporal sulcus.<sup>2</sup>

motor behavior that require information about body part location, and it may contribute to the initiation of motor activity.

**SLF II** is more laterally situated and occupies a position in the central core of the hemisphere WM, lateral to the corona radiata and above the Sylvian fissure. It links the caudal inferior parietal lobule (equivalent in human to the angular gyrus) and the parieto-occipital areas, with the posterior part of the dorsolateral and mid-dorsolateral prefrontal cortex. It is thought to serve as the conduit for the neural system subserving visual awareness, the maintenance of attention, and engagement in the environment. It provides a means whereby the prefrontal cortex can regulate the focusing of attention within different parts of space.

**SLF III** is farther lateral and ventral and is located in the WM of the parietal and frontal operculum. It provides the ventral premotor region and pars opercularis with higher-order somatosensory input, may be crucial for mon-

itoring orofacial and hand actions, and in the human it may be engaged in phonemic and articulatory aspects of language.

The **arcuate fasciculus** (AF) runs in the WM of the superior temporal gyrus and deep to the upper shoulder of the Sylvian fissure. By linking the caudal temporal lobe with the dorsolateral prefrontal cortex it may be viewed as an auditory spatial bundle, important for the spatial attributes of acoustic stimuli and auditory-related processing. The AF has historically been regarded as linking the posterior (Wernicke) and anterior (Broca) language areas in the human brain and to be involved in conduction aphasia. Our anatomical studies in monkey raise doubts about these anatomical and functional conclusions. This issue is not yet definitively resolved.

The **extreme capsule** is situated between the claustrum and the insular cortex caudally and between the claustrum and the orbital frontal cortex rostrally. In monkey, the extreme

capsule is the principal association pathway linking the middle superior temporal region with the caudal parts of the orbital cortex and the ventral-lateral prefrontal cortex, including area 45. These areas are homologous to the Wernicke and Broca language cortices in human, and thus the extreme capsule (rather than the AF) may have an important role in language.

The **middle longitudinal fasciculus** (MdLF) is situated within the WM of the caudal inferior parietal lobule and extends into the WM of the superior temporal gyrus. It links several high-level association and paralimbic cortical areas, including the inferior parietal lobule, caudal cingulate gyrus, parahippocampal gyrus, and prefrontal cortex. In the human the MdLF may play a role in language, possibly imbuing linguistic processing with information dealing with spatial organization, memory, and motivational valence.

The **uncinate fasciculus** occupies the WM of the rostral part of the temporal lobe, the limen insula, and the WM of the orbital and medial frontal cortex. By connecting these temporal and prefrontal areas, the uncinate fasciculus may be a crucial component of the system that regulates emotional responses to auditory stimuli. It may also be involved in attaching emotional valence to visual information, is likely to be an important component of the circuit underlying recognition memory, and is implicated in cognitive tasks that are inextricably linked with emotional associations.<sup>37</sup>

The **inferior longitudinal fasciculus** (ILF) is in the WM between the sagittal stratum medially and the parieto-occipital and temporal cortices laterally. It has a vertical limb in the parietal and occipital lobes and a horizontal component contained within the temporal lobe. The ILF is the long association system of the ventral visual pathways in the occipitotemporal cortices. Visual agnosia and prosopagnosia are two clinical situations that may arise from ILF damage.

The **fronto-occipital fasciculus** (FOF) travels above the body and head of the caudate

nucleus and the subcallosal fasciculus of Muratoff (Muratoff bundle [MB]), lateral to the corpus callosum and medial to the corona radiata. It links the parieto-occipital region with dorsal premotor and prefrontal cortices. The FOF is the long association system of the dorsomedial aspects of the dorsal visual stream, and it appears to be an important component of the anatomical substrates involved in peripheral vision and the processing of visual spatial information.

The **cingulum bundle** (CB) nestles in the WM of the cingulate gyrus. It links the rostral and caudal sectors of the cingulate gyrus with each other, as well as with the dorsolateral, orbital, and medial prefrontal cortices, and the parietal, retrosplenial and ventral temporal cortices (including the parahippocampal gyrus and entorhinal cortex). By virtue of these connections, the CB may facilitate the emotional valence inherent in somatic sensation, nociception, attention, motivation, and memory.<sup>2</sup> Cingulectomy, and subsequently bilateral stereotaxic cingulotomy, has achieved the status of established management for certain forms of neuropsychiatric illness, such as obsessive-compulsive disorder, and for intractable pain.<sup>38–44</sup>

## Striatal Fibers

Corticostriatal fibers to the caudate nucleus, putamen, and claustrum are conveyed mainly by the subcallosal fasciculus of Muratoff and the external capsule.

### Muratoff Bundle (Subcallosal Fasciculus of Muratoff)

The MB is a semilunar condensed fiber system situated immediately above the head and body of the caudate nucleus. It conveys axons to the striatum principally from association and limbic areas, with some fibers also from the dorsal part of the motor cortex. (There has been confusion about the nature and location of the

MB and the FOF. This issue has recently been clarified.<sup>2,45)</sup>

### External Capsule

The external capsule lies between the putamen medially and the claustrum laterally. It conveys fibers from the ventral and medial prefrontal cortex, ventral premotor cortex, precentral gyrus, the rostral superior temporal region, and the inferotemporal and preoccipital regions. Projections from primary sensorimotor cortices are directed to the putamen; those from the supplementary motor area and association cortices terminate also in the caudate nucleus.

The MB and external capsule thus convey fibers from sensorimotor, cognitive, and limbic regions of the cerebral cortex to areas within the striatum in a topographically arranged manner. These corticostriatal pathways provide the critical links that enable different regions with the basal ganglia to contribute to motor control, cognition, and emotion.

### Cord Fiber System

In addition to association and corticostriatal systems, every cortical region gives rise to a dense aggregation of fibers, termed the cord, which occupies the central core of the WM of the gyrus. The fibers in the cord separate into two distinct segments: a commissural system and projection fibers in the subcortical bundle.

### Commissural Fibers

#### Anterior Commissure

The anterior commissure (AC) traverses the midline in front of the anterior columns of the fornix, above the basal forebrain and beneath the medial and ventral aspect of the anterior limb of the internal capsule. Its fibers link the caudal part of the orbital frontal cortex, the temporal pole, the rostral superior temporal

region, the major part of the inferotemporal area, and the parahippocampal gyrus with their counterparts in the opposite hemisphere. In the nonhuman primate the AC is concerned with functional coordination across the hemispheres of highly processed information in the auditory and visual domains, particularly when imbued with mnemonic and limbic valence.

### Corpus Callosum

We divide the corpus callosum (CC) into five equal sectors conveying fibers across the hemispheres from the following locations: (1) (rostrum and genu)—fibers from the prefrontal cortex, rostral cingulate region, and supplementary motor area; (2) premotor cortex; (3) ventral premotor region and the motor cortex (face representation most rostral, followed by the hand and the leg), and postcentral gyrus fibers behind the motor fibers; (4) posterior parietal cortex; (5) (splenium)—superior temporal fibers rostrally, inferotemporal and preoccipital fibers caudally. These comments regarding CC topography apply to the midsagittal plane.

Studies of the CC have led to novel understanding of the anatomic underpinnings of perception, attention, memory, language, and reasoning and provided insights into consciousness, self-awareness, and creativity.<sup>46–50</sup> Knowledge of CC topography is relevant in the clinical context of callosal section for control of seizures.

### Hippocampal Commissures

Three fiber systems link the ventral limbic and paralimbic regions across the hemispheres.

Anterior (uncal and genual) hippocampal fibers are conveyed in the ventral hippocampal commissure—those from the presubiculum, entorhinal cortex, and posterior parahippocampal gyrus in the dorsal hippocampal commissure. The hippocampal decussation conveys fibers from the body of the hippocampal formation to the contralateral septum.<sup>51</sup>

## Projection Fibers

Projection (cortico-subcortical) fibers in the subcortical bundle are conveyed to their destinations via the internal capsule (anterior and posterior limbs) and the sagittal stratum. Each fiber system differentiates further as it progresses in the WM into two principal systems: one destined for thalamus, the other for brain stem and/or spinal cord.

### Internal Capsule

The *anterior limb* of the internal capsule (ICa) conveys fibers from the prefrontal cortex, rostral cingulate region, and supplementary motor area (coursing through the genu of the capsule), principally to the thalamus, hypothalamus, and basis pontis.

The *posterior limb* of the internal capsule (ICp) conveys descending fibers from the premotor and motor cortices. Face, hand, arm, and leg fibers are arranged in a progressively caudal position. The ICp also conveys descending fibers from the parietal, temporal, and occipital lobes, and the caudal cingulate gyrus. These are topographically arranged within the capsule, in the rostral–caudal and superior–inferior dimensions.

Focal motor and sensory deficits follow infarction of the ICp, and complex behavioral syndromes result from lesions of the genu of the ICa and genu.<sup>52–54</sup> Deficits include fluctuating alertness, inattention, memory loss, apathy, abulia, and psychomotor retardation, with neglect of contralateral space and visual–spatial impairment from lesions of the genu in the right hemisphere, and severe verbal memory loss after genu lesions on the left. Deep brain stimulation has been successfully applied to the ICa in some patients with obsessive–compulsive disorder<sup>55</sup> and intractable pain.<sup>56</sup>

### Sagittal Stratum

The sagittal stratum (SS) is a major cortico-subcortical WM bundle that conveys fibers

from the parietal, occipital, cingulate, and temporal regions to thalamus, basis pontis, and other brain stem structures. It also conveys afferents principally from thalamus to cortex. The SS comprises an internal segment conveying corticofugal fibers efferent from the cortex and an external segment that contains incoming corticopetal fibers. The rostral sector of the SS corresponds to the anteriorly reflected fibers of the Flechsig–Meyer loop, whereas the ventral parts of the midsection of the SS contain the optic radiations and thalamic fibers of the caudal inferior temporal and occipitotemporal areas.

The SS is the equivalent of the internal capsule of the posterior part of the hemispheres. The functional implications are also analogous to those of the ICa and ICp. Whereas damage to the optic radiations in the ventral sector of the SS lead to hemianopsia, damage to the dorsal part of the SS may result in distortion of high-level visual information.

### Thalamic Peduncles

Cortico-subcortical fibers enter the thalamus in locations determined by their site of origin. The afferent and efferent fibers between thalamus and cerebral cortex are arrayed around the thalamus and are collectively termed the thalamic peduncles.<sup>2</sup>

### Intrinsic and Extrinsic Cerebellar WM Tracts

There are surprisingly few published details regarding the anatomical organization of cerebellar WM at the systems level, that is, which parts of the cerebellar WM convey afferent and efferent fibers to which specific cerebellar lobules. Further, it has long been suspected that nuclei in the rostral part of the basis pontis project via the middle cerebellar peduncle (MCP) to the posterior lobe of the cerebellum, and those in the caudal basis pontis project to the anterior cerebellum,<sup>57</sup> but more precise information concerning MCP organization remains to



be elucidated. Similarly, the degree to which there is anatomical and functional differentiation within the superior cerebellar peduncle efferents to thalamus is not presently known. There appears to be topographical organization of function within motor, cognitive, and affective domains in cerebellum,<sup>58,59</sup> and therefore defining the WM arrangement of the cerebellar connections with extracerebellar structures is of great interest.

Having completed this overview of cerebral WM anatomy, we now proceed to a consideration of diseases that afflict the cerebral WM either in isolation or as the principal site of pathology.

Diseases of the Cerebral WM

Disorders of cerebral WM are common at any age and in many clinical settings. The history in a particular patient, the results of the clinical examination, and specifically targeted laboratory investigations will often lead to the correct diagnosis. MRI has proven invaluable in the study of these disorders because it discloses structural aspects of WM systems *in vivo* with great clarity. The most useful means of classifying WM disorders is by careful analysis of the specific neuropathology, which reveals an impressive range of diseases, injuries, and intoxications to which the WM is vulnerable (Table 1). Few disorders damage only the WM, and there is usually some combination of gray matter (GM) and WM neuropathology. However, all the entities we discuss here feature prominent or exclusive WM involvement, and we highlight the contribution of these changes while not dismissing the importance of GM pathology. Neuropathology is central for understanding etiology and improving treatment, but the location of the WM damage is more directly pertinent than its etiology for studying brain–behavior relationships. The categories of WM disorder and selected examples of each are discussed, along with an account of their salient neurobehavioral manifestations,

TABLE 1. Cerebral White Matter Disorders

Genetic	Leukodystrophies (e.g., adrenoleukodystrophy, metachromatic leukodystrophy, globoid cell leukodystrophy) Vanishing white matter disease Alexander’s disease Adult-onset leukodystrophy with neuroaxonal spheroids Mitochondrial encephalopathy with lactic acid and stroke (MELAS) Fragile X tremor-ataxia syndrome Aminoacidurias (e.g., phenylketonuria) Phakomatoses (e.g., neurofibromatosis) Mucopolysaccharidoses Myotonic dystrophy Callosal agenesis
Demyelinative	Multiple sclerosis Acute disseminated encephalomyelitis Acute hemorrhagic encephalomyelitis Schilder’s disease Marburg’s disease Balo’s concentric sclerosis
Infectious	HIV and AIDS dementia complex Progressive multifocal leukoencephalopathy Subacute sclerosing panencephalitis Progressive rubella panencephalitis Varicella zoster encephalitis Cytomegalovirus encephalitis Lyme encephalopathy
Inflammatory	Systemic lupus erythematosus Behcet’s disease Sjögren’s syndrome Wegener’s granulomatosis Temporal arteritis Polyarteritis nodosa Scleroderma Isolated angiitis of the central nervous system Sarcoidosis
Toxic	Cranial irradiation Therapeutic drugs (e.g., methotrexate, BCNU, cyclophosphamide) Drugs of abuse (e.g., toluene, heroin) Alcohol (Marchiafava–Bignami disease) Environmental toxins (e.g., carbon monoxide)
Metabolic	Cobalamin deficiency Folate deficiency Central pontine myelinolysis

Continued

**TABLE 1. Continued**

Vascular	Hypoxic–ischemic injury
	Posterior reversible encephalopathy syndrome
	Hypertensive encephalopathy/eclampsia
	High-altitude cerebral edema
	Binswanger’s disease
	CADASIL
	Leukoaraiosis
	Cerebral amyloid angiopathy
	Intravascular lymphoma
	White matter disease of prematurity
Traumatic	Migraine
	Traumatic brain injury (diffuse axonal injury)
	Shaken baby syndrome
	Corpus callosotomy
	Focal lesions of WM tracts (e.g., fornix transection, splenium of CC tumor)
Neoplastic	Gliomatosis cerebri
	Diffusely infiltrative gliomas
	Lymphomatosis cerebri
	Langerhans cell histiocytosis
	Focal white matter tumors
Hydrocephalic	Early hydrocephalus
	Normal pressure hydrocephalus
Degenerative	White matter changes in Alzheimer disease
	Effects of aging on myelin

followed by consideration of the effects of aging and vascular disease on cerebral WM.

**Genetic Diseases**

The leukodystrophies are a heterogeneous group of genetic diseases involving dysmyelination as a result of substrate accumulation due to enzymatic defects. This group includes adrenoleukodystrophy, inherited in an X-linked recessive manner, and metachromatic leukodystrophy, globoid cell leukodystrophy, and vanishing WM disease, which are autosomal recessive (Table 2). These disorders are more common than previously recognized, in large part because of the improved detection with advances in MRI techniques and appropriate genetic analyses. Collectively, their incidence rivals that of multiple sclerosis. The

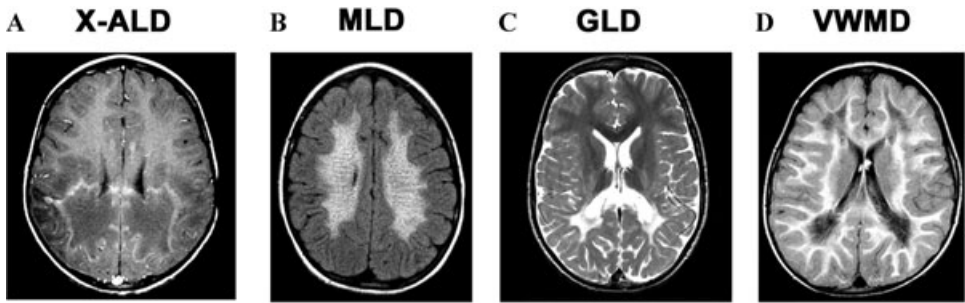
prevalence of adrenoleukodystrophy alone is 1 in 17,000, about 20,000 patients in the United States.<sup>60</sup> Other inherited disorders we consider here are adult-onset leukodystrophy with neuroaxonal spheroids, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, and fragile X–associated tremor ataxia syndrome.

*X-linked adrenoleukodystrophy* (X-ALD) is characterized by impaired ability to degrade very long-chain fatty acids (VLCFAs) that causes malfunction of the adrenal cortex and nervous system myelin.<sup>61</sup> It presents in childhood in approximately 35% of patients. Affected boys develop normally until 4–8 years of age and then suffer dementia and progressive neurologic decline that leads to a vegetative state and death. More than 90% have adrenal insufficiency. The disorder presents as adrenomyeloneuropathy in young adulthood in 35%–40% of patients, characterized by progressive paraparesis and sphincter disturbances due to involvement of the long tracts in the spinal cord. Rapidly progressive inflammatory demyelination develops in 20% of these patients, leading to death in 1–2 years,<sup>62,63</sup> a pattern that is similar to that encountered in the childhood form of cerebral X-ALD. This presentation of cerebral X-ALD in adulthood may manifest with impaired psychomotor speed, spatial cognition, memory, and executive functions, whereas those with MRI evidence of severe cerebral disease have global and language impairment as well.<sup>64</sup> These deficits are highly correlated with degree of brain MRI involvement. We have seen this disease (Schmahmann, Eichler unpublished) produce a relentlessly progressive dementia in a man in his sixth decade, with inattention, amnesia, impaired cognitive flexibility and problem-solving skills, and visual spatial disorganization, progressing to stereotyped nonmeaningful but complex behaviors, relentless wandering, perseveration, apraxia and posterior aphasia with fluent jargon, impaired comprehension, and poor repetition. In this case there was relative sparing of elementary motor features, normal reflexes,

**TABLE 2.** Biochemistry and Genetics of X-linked Adrenoleukodystrophy (X-ALD), Metachromatic Leukodystrophy (MLD), Globoid Cell Leukodystrophy (GLD), and Vanishing White Matter Disease (VWMD)

Variable	X-ALD	MLD	GLD	VWMD
Affected gene	ABCD1	ASA gene	GALC gene	Any of 1–5 subunits of eIF2B
Gene locus	Xq28	22q13	14q31	Several
Enzyme/protein	ALDP	Aryl-sulfatase A*	GALC	eIF2B
Substrate	VLCEA	Sulfatide	Galactosylceramide	Heat shock and other proteins

\*Rare cases due to saposin B deficiency.



**Figure 4.** MRI appearance of (A) X-linked adrenoleukodystrophy (X-ALD), T1-weighted image post-gadolinium; (B) metachromatic leukodystrophy (MLD), FLAIR image; (C) globoid cell leukodystrophy (GLD), T2-weighted image; and (D) vanishing white matter disease (VWMD), T1-weighted image.

and plantar responses, but striking release phenomena (palmar grasp, snout, root, suck) were present.

Presymptomatic cerebral involvement in X-ALD can be detected on neuroimaging.<sup>65</sup> Eighty percent of patients show symmetric, posterior parietal, and occipital periventricular WM lesions,<sup>66</sup> with a characteristic garland of gadolinium contrast enhancement<sup>67</sup> (Fig. 4A), and increased choline (Ch) and decreased *N*-acetyl aspartate (NAA) on MRI spectroscopy (MRS) in WM that appears normal on conventional MRI or DTI.<sup>68,69</sup> Inflammatory demyelination of the brain is prominent, commencing in the center of the CC where the fiber bundles are most tightly packed, and spreading into the periventricular WM<sup>70</sup> in a parieto-occipital (about 80%) or frontoparietal (20%) distribution. The inflammation lies behind the leading edge of demyelination and therefore is probably a response to the primary dysmyelinative process. Recent evidence suggests that microglial apoptosis may precede the demyelination.<sup>71</sup>

*Metachromatic leukodystrophy* (MLD) is a lysosomal storage disorder resulting from a deficiency of aryl sulfatase A leading to a defect in the desulfation of 3-O-sulfogalactosyl lipids and intracellular accumulation of sulfatides.<sup>72</sup> It occurs in about one per 40,000 live births.<sup>73</sup> Late infantile MLD is most common, usually appearing between 18 and 24 months.<sup>74</sup> The juvenile form emerges between 4 and 16 years.<sup>75</sup> The adult form begins after 16 years of age.<sup>76</sup> Symptoms vary by age of onset (Mahmood and Eichler, unpublished). Children usually present with gait disturbance and develop ataxia, spastic quadriplegia, and optic atrophy as they progress to a decerebrate state. Progression in adults is slower, and psychosis, behavioral disturbances, and dementia are the major presenting features.<sup>77,78</sup> MRI reveals involvement of the periventricular WM, centrum semiovale, genu and splenium of the CC, ICp, descending pyramidal tracts, claustrum, and occasionally cerebellar WM (Fig. 4B). Subcortical U-fibers are usually spared.<sup>79</sup> Active lesions do not enhance, although areas that

have previously undergone massive dysmyelination can show punctuate striated (tigroid) enhancement,<sup>79</sup> corresponding to patchy areas of preserved myelin.<sup>80</sup>

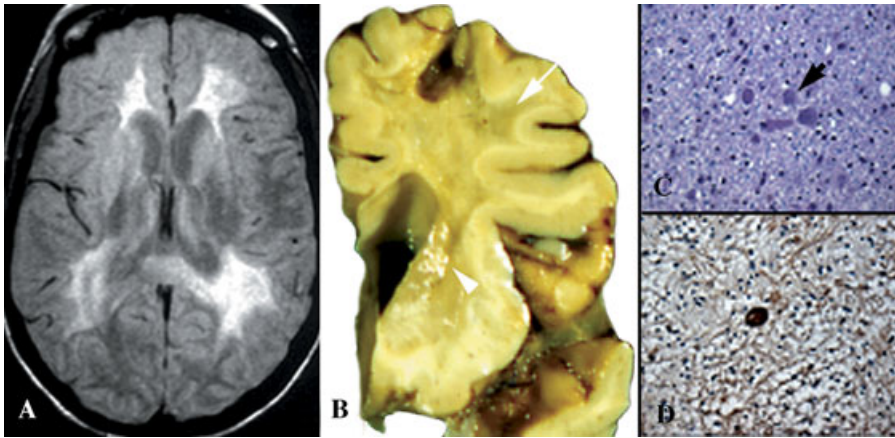
*Globoid cell leukodystrophy* (GLD), also known as Krabbe's Disease, is caused by deficiency of the enzyme galactosyl ceramidase (GALC) that is responsible for converting galactosylceramide into galactose and ceramide. The absence of GALC leads to the accumulation of galactosylceramide as well as psychosine, a cytotoxic by-product of galactosylceramide. Galactosylceramide accumulation prompts a macrophagocytic response.<sup>81</sup> Psychosine accumulation is thought to poison cells and lead to oligodendrocyte cell death.<sup>82</sup> Incidence is estimated at one per 100,000 births.<sup>83</sup> Infantile GLD presents in the first 6 months of life with hyperirritability, increased muscular tone, fever, and developmental arrest, leading to further cognitive decline, myoclonus, opisthotonus, nystagmus, and optic atrophy. Patients rarely survive beyond 2 years. In an estimated 10% of cases<sup>83</sup> symptoms begin after the patient has begun to walk; these are considered late onset.<sup>84,85</sup> Reports of adult-onset cases have increased in recent years, presenting with slowly evolving hemiparesis, intellectual impairment, cerebellar ataxia, and visual failure, and, in a few instances, with spastic paraplegia and increased T2 MRI signal along the corticospinal tracts.<sup>86</sup> Early imaging reveals symmetrical involvement of the basal ganglia, thalami, and posterior aspect of the centrum semiovale<sup>87</sup> (Fig. 4C). The later stages of the disease are characterized by dramatic cerebral and cerebellar atrophy. In the cerebellum, the dentate nuclei and WM are usually involved. Contrast enhancement has been reported in the lumbosacral nerve roots, but not elsewhere, setting this entity apart from X-ALD.<sup>88</sup>

In the neuropathology of both MLD and GLD, central WM is reduced to the point of cavitation, replaced by marked gliosis.<sup>75,89–91</sup> Both disorders show dysmyelination of peripheral nervous system with histiocytic infiltration. In MLD the cerebellar WM is also affected, together with loss of granule and Pur-

kinje cells.<sup>91</sup> MLD acquires its name from the abundant sulfatide granules in macrophages that take on their characteristic metachromatic hue after treatment with acidified cresyl violet. In GLD, the pathognomonic multinucleated globoid cells are actually dysmorphic macrophages, engorged with undigested galactosylceramide.

*Vanishing white matter disease* (VWMD) can be caused by a defect in any one of the five subunits of eukaryotic initiation factor 2B (eIF2B),<sup>92,93</sup> a highly conserved, ubiquitously expressed protein that plays an essential role in the initiation of protein synthesis. Clinical symptoms begin in the first few years, after normal or mildly delayed early development. Symptoms include ataxia and seizures, often occurring after fever or minor head trauma. The course is chronic and progressive, with episodic declines after stressors such as fever, head trauma, or periods of fright. Patients usually survive only a few years past the clinical onset, although survival into adulthood has been described.<sup>94,95</sup> MRI shows vanishing of WM over time, best recognized on proton density and fluid-attenuated inversion recovery (FLAIR) images (Fig. 4D). Contrast enhancement has not been reported. The cerebellar WM and brain stem show varying degrees of involvement. Imaging abnormalities are found even in presymptomatic individuals.<sup>96</sup> Autopsy confirms WM rarefaction and cystic degeneration. The cerebral WM is diffusely affected with a consistency that ranges from gelatinous to cavitory.<sup>97</sup> The frontoparietal regions are most severely affected, with myelin pallor, thinning, and cystic changes. Axonal loss varies with the degree of cavitation. GM is largely unaffected. An inflammatory response is notably absent—a failure of astrogliosis may be responsible for the cavitated appearance.

*Adult-onset leukodystrophy with neuroaxonal spheroids* (AOLNS) is a familial or sporadic disorder characterized radiographically by symmetric, bilateral, T2-hyperintense, and T1-hypointense MRI signal involving frontal lobe WM (Fig. 5A). Neuropathologic examination



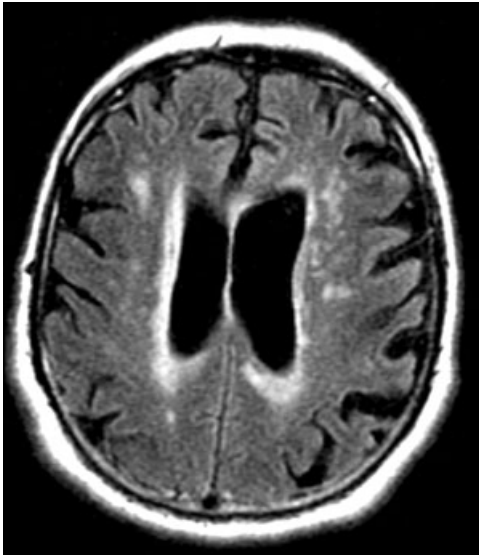
**Figure 5.** Imaging and pathology in a patient with adult-onset leukodystrophy with neuroaxonal spheroids. **(A)** FLAIR MRI in the axial plane showing confluent high signal in the periventricular, deep, and subcortical white matter of the frontal and parietal lobes extending through the splenium of the corpus callosum. **(B)** Gross pathology of a coronal section of the cerebral hemisphere, showing gliosis in the centrum semiovale (arrow) and internal capsule (arrowhead). **(C)** Several neuroaxonal spheroids on microscopic analysis of frontal white matter (original magnification,  $\times 20$ ; Luxol fast blue hematoxylin and eosin stain). **(D)** Neurofilament immunostain of white matter reveals mild loss of axons and an axonal spheroid (original magnification,  $\times 20$ ).<sup>99</sup>

demonstrates a severe leukodystrophy with myelin and axonal loss, gliosis, macrophages, and axonal spheroids, with early and severe frontal WM involvement, and complete sparing of cerebral cortical neurons<sup>98,99</sup> (Fig. 5B–D). The etiology is unknown, although in our series we detected abnormalities in some mitochondrial enzymes, and in one patient, electron transport chain analysis revealed equivocal complex I deficiency, suggesting mitochondrial dysfunction.

The disorder usually presents with executive system dysfunction and other neurobehavioral deficits, progressing to dementia. The extent and degree of change outside the frontal lobe correlates with disease duration. The WM containing long association tracts interconnecting parietal, temporal, and occipital lobes with the frontal lobe are affected early and most severely. In contrast, projection pathways are spared until late in the illness, as exemplified in a patient whose cortical blindness corresponded to the late pathological changes in the SS that contains the optic radiations.<sup>99</sup> This dichotomy of early dementia, but late failure of gait, strength,

dexterity and sensation, provides an interesting glimpse into the clinicopathological distinction between association and projection fiber tract involvement in AOLNS, and the functional contributions of these different WM tracts.

*Mitochondrial encephalopathy with lactic acidosis and strokelike episodes (MELAS)* was initially described in patients with normal early development and short stature, who developed seizures, hemiparesis, and hemianopia or cortical blindness, and in whom ragged red fibers were evident on muscle biopsy.<sup>100</sup> Criteria for diagnosis<sup>101</sup> are strokelike episodes before age 40 (not confined to vascular territories); encephalopathy characterized by seizures, dementia, or both; with lactic acidosis and/or ragged-red fibers. Recurrent headache or vomiting may be present. The disease is most commonly maternally inherited through the mitochondrial DNA, and in 70%–80% of MELAS patients the enzymatic defect is a complex I deficiency and, to a lesser degree, a complex IV deficiency, associated with a point mutation at 3243 in the tRNA Leu (UUR) region. Periventricular and diffuse WM hyperintensities, as well as areas of



**Figure 6.** FLAIR MRI in a patient with mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS).<sup>2</sup>

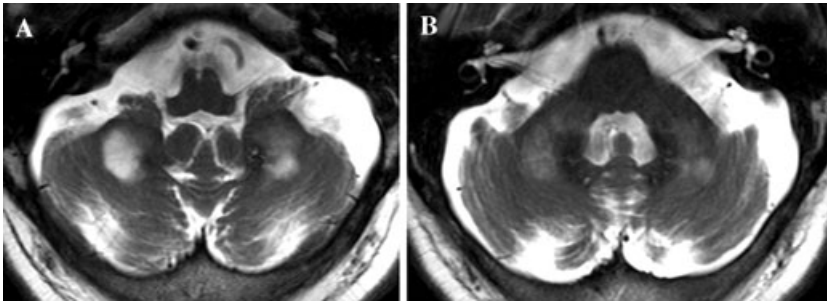
cortical infarction and cerebral edema, are seen on MRI<sup>102</sup> (Fig. 6), consistent with the pathology showing diffuse gliosis of cerebral and cerebellar WM, and diffuse atrophy of the cerebral and cerebellar cortices.<sup>103</sup> Dementia and psychosis may be the initial clinical manifestation of MELAS. In one published case<sup>104</sup> a young woman presented with headaches, confusion, aphasia, and apraxia, followed some years later by temper tantrums, aggressive and paranoid behavior, disinhibition, and ideas of reference. In our patient,<sup>105</sup> a man in his 40s presented with memory loss, social withdrawal, hallucinations, paranoia, impaired planning and strategy formation, and a right homonymous hemianopsia. Over the ensuing decade, his frontal lobe syndrome remained problematic and the dementia progressed, but only mild motor slowing appeared. MRI currently shows volume loss with multiple scattered WM T2 and FLAIR hyperintensities.

*Fragile X-associated tremor ataxia syndrome (FXTAS)* is an adult-onset neurodegenerative disorder that affects carriers, principally males, of premutation alleles (55–200 CGG repeats) of the fragile X mental retardation 1 (FMR1)

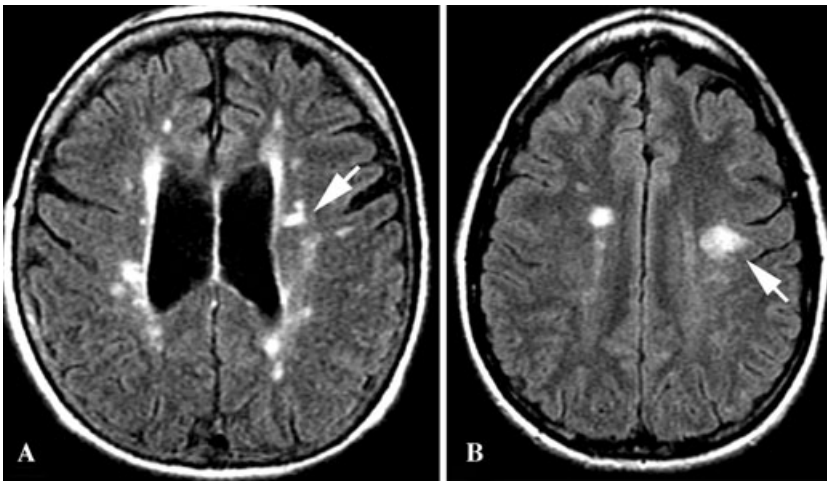
gene, with a powerful predictive relationship between the length of the CGG repeat and the neurological and neuropathological involvement.<sup>106–108</sup> Patients present in older adulthood primarily with gait ataxia and intention tremor. Progressive cognitive decline is characterized by impaired executive function, working memory, intelligence, declarative learning and memory, information processing speed, temporal sequencing, and visuospatial functioning, but language is spared.<sup>109</sup> The MRI pattern of WM pathology in FXTAS is distinctive (Fig. 7): increased T2 signal in the MCP is typical, and cerebellar and cerebral WM changes are also consistently observed.<sup>107</sup> Neuropathology reveals marked abnormalities in cerebral and cerebellar WM, dramatically enlarged inclusion-bearing astrocytes in cerebral WM, and widespread intranuclear and astroglial inclusions in brain, cranial nerve nuclei, and autonomic neurons of the spinal cord. Spongiosis is present in the MCPs. Cerebral WM can be severely affected both grossly and microscopically, with parenchymal pallor and spongiosis. Periventricular WM is generally spared.<sup>108</sup> Greco *et al.*<sup>108</sup> postulate that in the setting of normal cortical thickness and neuronal counts, neuronal and/or glial dysfunction causes or contributes to the clinical presentation. Involvement of the MCP is interesting in light of the fact that the MCP conveys essentially all cerebral cortical input (including associative and paralimbic) to the cerebellum,<sup>110</sup> and the cerebellum contributes not only to motor control but also to the modulation of cognition and emotion.<sup>58,59</sup> When the deaf-ferentation of cerebellum by the MCP lesions is added to the massive disruption of cerebral long association fiber tracts evident in pathological studies of FXTAS, the cognitive decline becomes readily understandable.

## Demyelinative Diseases

*Multiple sclerosis (MS)* is an inflammatory disease of myelin, but it may also damage axons, conferring a worse prognosis.<sup>111</sup> In terms of



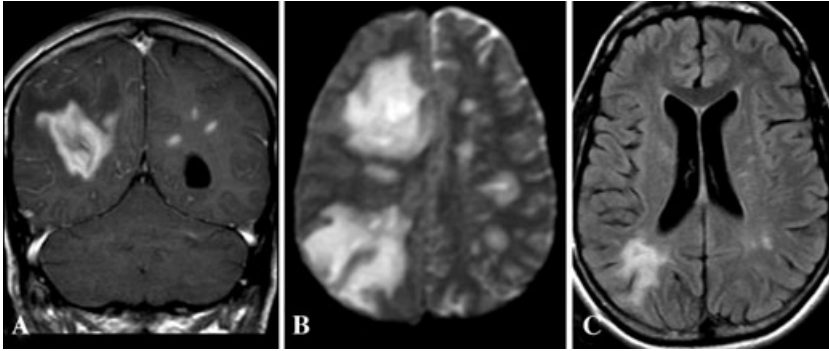
**Figure 7.** MRI features of fragile X-associated tremor ataxia syndrome (FXTAS). White matter pallor is seen in the cerebellar parenchyma (**A**), as well as in the middle cerebellar peduncles (**B**).



**Figure 8.** FLAIR MRI in multiple sclerosis. (**A**) White matter hyperintensity perpendicular to the lateral ventricle (Dawson's finger), shown by the arrow. (**B**) In a second case, the focal area of hyperintensity (arrow) corresponded to the initial clinical presentation.<sup>2</sup>

higher function, MS has recently been better appreciated as a source of cognitive and emotional impairment, recalling the initial insights of Jean-Martin Charcot (1825–1893).<sup>112</sup> As recently as 1970, cognitive impairment of any degree in MS was thought to occur in about 5% of patients,<sup>113</sup> but community-based neuropsychological studies place this figure in the 40%–50% range.<sup>114</sup> Dementia may occur, with an estimated prevalence as high as 23%.<sup>115</sup> Cognitive impairments in MS also include a wide range of focal neurobehavioral syndromes and neuropsychiatric disturbances.<sup>116</sup> The source of cognitive impairment appears to be related primarily to WM involvement (Fig. 8), because many studies find at least modest cor-

relations between extent of MRI WM damage and the degree of cognitive loss.<sup>116</sup> Subtle WM pathology may not be detected by conventional MRI, but more sophisticated MRI techniques (diffusion-weighted imaging [DWI], FLAIR sequences, ultrahigh field strength, magnetization transfer, and magnetic resonance spectroscopy [MRS]<sup>117,118</sup>) have documented abnormalities in the normal-appearing WM. Cerebral cortical demyelination is also present in MS,<sup>119</sup> raising the possibility that cognitive impairment may result from this aspect of the disease. Whereas a contribution of cortical demyelination is plausible, this remains uncertain because the cortical lesion load in MS may be limited and therefore have minimal effect on



**Figure 9.** MRI features of acute disseminated encephalomyelitis (ADEM). **(A)** Coronal T1-weighted postgadolinium image showing enhancing lesions in the right more than left hemispheres. **(B)** Axial zero-B MRI demonstration of the multiple lesions. **(C)** FLAIR MRI 6 months after marked clinical recovery shows much improved areas of hyperintensity.

cognition.<sup>120</sup> Given that demyelination in large fiber tracts probably exerts a far greater effect on the distributed neural networks subserving higher functions,<sup>121</sup> the main determinant of cognitive dysfunction in MS appears to be WM demyelination.

*Acute disseminated encephalomyelitis* (ADEM) is another inflammatory demyelinating disease, probably postinfectious and autoimmune in origin. It is generally monophasic, but repeated episodes have been described. Diagnostic criteria do not reliably distinguish ADEM from first presentations of relapsing diseases such as MS and neuromyelitis optica,<sup>122,123</sup> but ADEM can be aggressive, massively disseminated, and life threatening.<sup>124</sup> Four patterns of cerebral involvement in ADEM have been described based on MRI findings: (1) lesions of less than 5 mm; (2) large, confluent, or tumefactive lesions, with perilesional edema and mass effect; (3) additional bithalamic involvement; and (4) acute hemorrhagic encephalomyelitis (AHEM) with hemorrhage identified in the large demyelinating lesion.<sup>125</sup> ADEM can be treated, sometimes with dramatic success, using immune-modulating agents such as intravenous immunoglobulin (IVIG). The presentation depends on the location of the pathology. One of our recent patients presented with inability to find her shoe with the left foot, the beginning of a hemineglect syndrome from a right parieto-occipital WM lesion that heralded

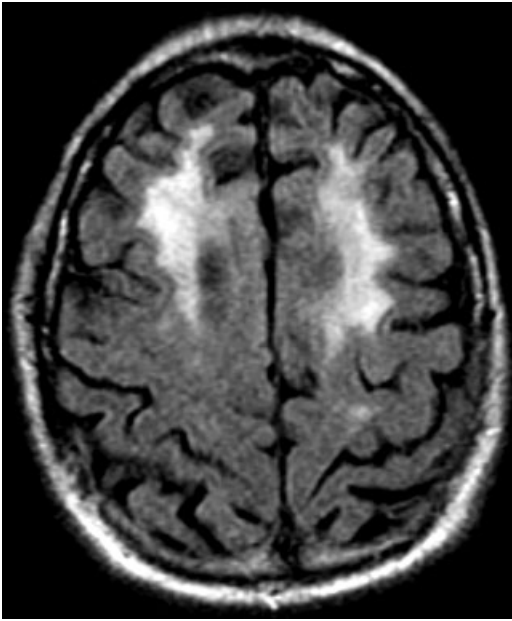
disseminated, asymmetric, bihemispheric demyelination; her deficits responded immediately to IVIG (Fig. 9). A second young woman with AHEM presented with hemianopsia related to the posterior location of the initial pathology. She evolved to hemispheric edema requiring craniotomy for herniation before she came to our attention and recovered with IVIG treatment.

### Infectious Diseases

Some nervous system infections have a predilection for the cerebral WM and include prominent neurobehavioral sequelae.

*AIDS dementia complex* (ADC) commonly has WM abnormalities on MRI, and WM pallor is an early neuropathological finding.<sup>126</sup> Rarely, fatal and fulminant leukoencephalopathy can be seen as the only manifestation of human immunodeficiency virus (HIV) infection.<sup>127</sup> Involvement of the basal ganglia is also evident in ADC, and the initial reports of dementia in AIDS stressed the subcortical profile of the dementia syndrome,<sup>128</sup> analogous to that in patients with subcortical dementias such as Huntington's and Parkinson's diseases. The role of WM dysfunction is not easily dismissed, however, in light of evidence that MRI WM changes (Fig. 10) improve in parallel with cognitive decline in patients with successful treatment of dementia.<sup>129–131</sup> Advanced





**Figure 10.** FLAIR MRI showing hyperintensities in prefrontal white matter in a patient with HIV and cognitive impairment.<sup>2</sup>

neuroimaging illuminates this issue. Tensor-based morphometry in HIV/AIDS patients showed that, whereas atrophy was widespread in the brain, only WM tissue loss correlated with cognitive impairment.<sup>132</sup> The neuropathology of ADC is still being elucidated, but evidence supports the role of WM dysfunction in neurobehavioral dysfunction. This issue highlights a more general need for studies that delineate the relative contributions of subcortical GM and WM dysfunction to the pathogenesis of dementia.

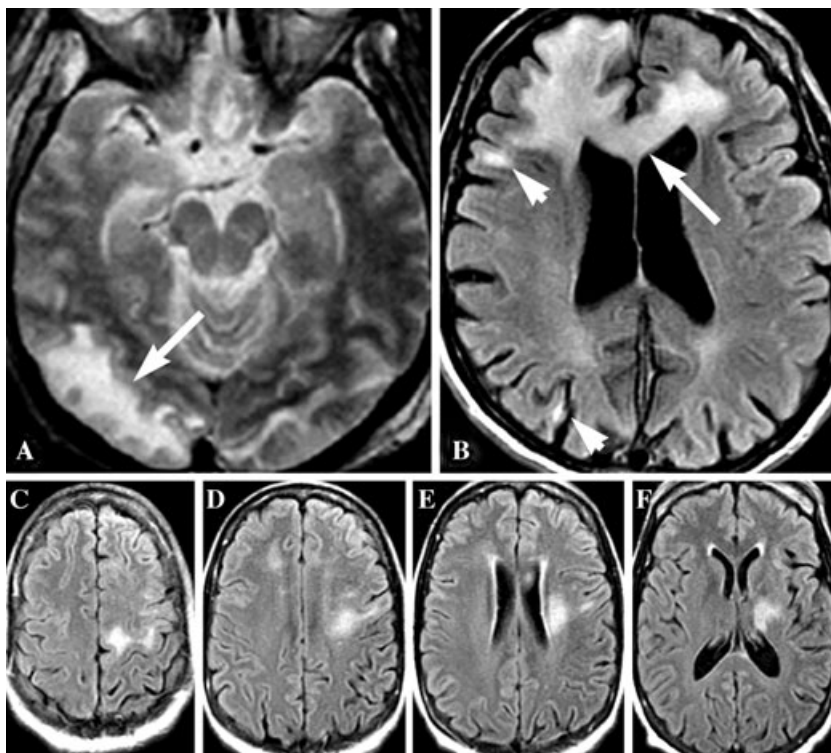
*Progressive multifocal leukoencephalopathy* (PML) is an opportunistic demyelinating infection of immunocompromised patients, caused by a human polyomavirus, JC virus, that attacks the myelin-producing oligodendrocyte.<sup>133,134</sup> PML was previously recognized in the setting of immune compromise after organ transplantation, bone marrow-derived tumors, and chemotherapy, until the worldwide HIV/AIDS pandemic produced an explosion of cases. Interest in the relevance of this disorder for a new patient demographic has emerged with the report that PML occurred in some MS patients

treated with the adhesion-molecule  $\alpha$ -integrin inhibitor natalizumab.<sup>135</sup> The clinical manifestations vary greatly, depending on the location of the demyelination. Focal elementary findings include hemianopsia, cortical blindness, hemiparesis, and cerebellar motor symptoms of ataxia and dysarthria. Cognitive presentations include frontal lobe syndromes and aphasia, progressing to quadriplegia, mutism, and unresponsiveness. The virus has a predilection for subcortical U-fibers, but cortical demyelination appears to be integral to the process, together with macrophage and microglial activation.<sup>136</sup> MRI findings of widespread, asymmetric, nonenhancing infiltrative lesions without mass effect<sup>137</sup> (Fig. 11) may also be located in subcortical gray nuclei, because the axons conveyed in WM tracts course to, and terminate in, these GM destinations, and because there is probably intrinsic pathology of axons and neurites in the GM. Cerebellar WM may be involved early,<sup>138</sup> and brain stem disease is also described.<sup>139</sup> Multiple locations of abnormal findings on MRI and pathological observation are expected, and the disease has a relentlessly progressive course, although limited advances have been made in AIDS patients by using highly active antiretroviral therapeutic regimens.<sup>140</sup>

### Autoimmune Inflammatory Diseases

These central nervous system diseases are similar to infectious diseases in that their pathology cannot be assigned only to the cerebral WM. Nevertheless, growing evidence implicates a role for WM involvement in neurobehavioral dysfunction.

*Systemic lupus erythematosus* (SLE) is the best-studied example and proves illustrative. Neuropsychiatric lupus refers to a diverse group of syndromes in SLE patients that includes cognitive dysfunction,<sup>141</sup> and milder cognitive impairment can be noted even in SLE patients without overt neurologic disease.<sup>142</sup> MRI WM hyperintensities are common, related to vasculopathy and presumably autoimmune factors,



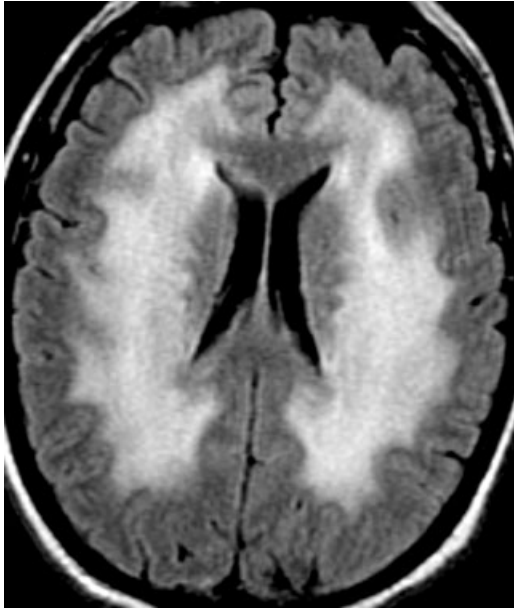
**Figure 11.** MRI features of progressive multifocal leukoencephalopathy (PML). (A) T2-weighted image shows involvement of white matter of the right occipital region (arrow), accounting for the hemianopsia in this HIV-positive patient. (B) FLAIR MRI in a patient with systemic lymphoma and PML, demonstrating confluent prefrontal white matter lesion spreading across the genu of the corpus callosum (arrow), and additional lesions affecting local association fibers of the right prefrontal and parieto-occipital cortices (arrowheads). (C, D) Axial FLAIR images in an HIV-positive patient showing confluent subcortical and deep white matter involvement by PML. (Panels A and B are from reference 2.)

and a relationship between dementia and leukoencephalopathy in SLE has been suggested.<sup>143</sup> Data from studies with MRS have shown that, even in SLE patients with normal WM on conventional MRI and no neuropsychiatric features, subtle cognitive impairment correlates with increased WM Ch, but not with the neuronal marker NAA or hippocampal atrophy.<sup>144</sup> Support is thus accumulating for a contribution of cerebral myelin damage to cognitive impairment in SLE. Other proposed pathogenic factors in SLE, such as autoimmune mediators including antiphospholipid antibodies, proinflammatory cytokines, and anti-*N*-methyl-D-aspartate receptor antibodies, also merit study.

### Toxic Leukoencephalopathy

Many toxic brain disorders preferentially affect the cerebral WM.<sup>145</sup> A spectrum of severity has been described, ranging from mild, reversible confusion, to coma and death, with concomitant MRI and neuropathological WM changes.<sup>145</sup> Cranial irradiation and cancer chemotherapeutic drugs, most notably methotrexate<sup>146,147</sup> (Fig. 12), are leukotoxic, an effect that complicates the treatment of many malignancies.

*Toluene leukoencephalopathy* (TL) is an intriguing disorder that convincingly illustrates the ability of pure WM damage to produce dementia.<sup>148–152</sup> Toluene (methylbenzene) is a



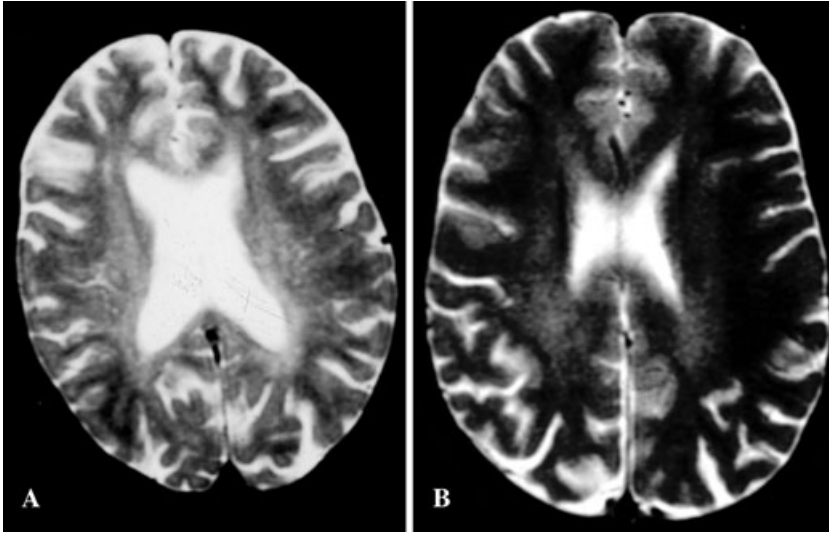
**Figure 12.** FLAIR MRI in the axial plane of a patient with cognitive decline after receiving methotrexate.<sup>2</sup>

common household and industrial solvent and is the major solvent in spray paint. It is abused by millions of people worldwide for its euphoric effect, an abuse that has a lifetime prevalence in the United States estimated at 18%.<sup>152</sup> The intentional inhalation of toluene, often for years without respite, results in a dramatic syndrome of dementia, ataxia, and other neurologic signs.<sup>149,150</sup> The effects are readily detectable on MRI and include diffuse cerebral and cerebellar WM hyperintensity (Fig. 13). The degree of cerebral involvement strongly correlates with the severity of dementia, which is the most prominent manifestation of the syndrome.<sup>148,150</sup> Autopsy studies of TL reveal selective myelin loss that spares the cerebral cortex, neuronal cell bodies, and even axons in all but the most severe cases.<sup>151,152</sup> TL thus exemplifies the toxic WM disorders and stands out as a convincing example of WM dementia (WMD).<sup>6,116,153</sup>

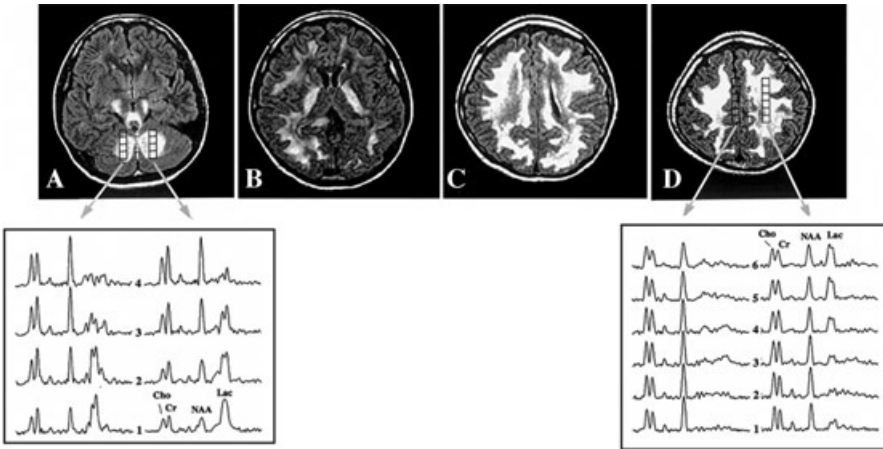
*Inhalation of heated heroin vapor* (colloquially termed “chasing the dragon”) produces a devastating, progressive spongiform leukoencephalopathy. The MRI appearance<sup>154–156</sup>

is highly suggestive, if not pathognomonic (Fig. 14). Cocaine use may produce similar findings, including symmetric and widespread involvement of the posterior cerebral hemispheric WM, cerebellar WM, splenium of the CC, and brain stem (medial lemniscus and lateral brain stem), with sparing of the deep cerebellar nuclei. MRS in areas of parenchymal damage demonstrates elevated lactate and myoinositol, reduced NAA and creatine, normal to slightly decreased Ch, and normal lipid peak. Neuropathologically this is WM spongiform degeneration with relative sparing of U-fibers, whereas electron microscopy reveals intramyelinic vacuolation with splitting of intraperiod lines. Preservation of axons with no evidence of Wallerian degeneration, inflammatory cellular reaction, or demyelination is taken to indicate that axons may be relatively spared, consistent with the degree of recovery in some cases.<sup>154</sup> Clinical manifestations include cerebellar motor findings of ataxia, dysmetria and dysarthria, bradykinesia, rigidity, and hypophonia, and the syndrome may progress over weeks to pseudobulbar palsy, akinetic mutism, decorticate posturing, and spastic quadriparesis. Death occurs in approximately 20% of cases. Clinical and MRI findings can progress after cessation of drug use, indicating that the toxic exposure precipitates an evolving injury. The lack of concordance between MRI perfusion and spectroscopy may reflect impaired energy metabolism at the cellular level. The lactate peak on MRS; mitochondrial swelling and distended endoplasmic reticulum in oligodendrocytes on autopsy; and apparent response to antioxidants and mitochondrial cofactors such as vitamin E, vitamin C, and coenzyme Q suggest mitochondrial dysfunction as a basis for this entity.<sup>154,155,157</sup>

Other toxin-induced spongiform leukoencephalopathies with fluid accumulation restricted to myelin sheaths include those precipitated by cuprizone, ethidium bromide, actinomycin D, triethyl tin, hexachlorophene, isonicotinic acid, hydrazine, and cycloleucine.<sup>154,158</sup>



**Figure 13.** T2-weighted MRI appearance in the axial plane of toluene encephalopathy in two patients (**A**, **B**).

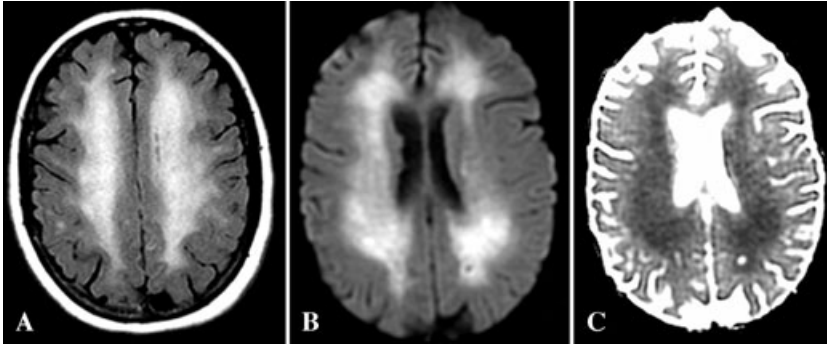


**Figure 14.** MRI scans after heroin inhalation, known colloquially as “chasing the dragon.” FLAIR images in the axial plane (**A–D**). Corresponding 1H MRS imaging spectra in two of the images show characteristic lactate peak and decreased NAA.<sup>154</sup>

### Metabolic Disorders

A diverse group of metabolic disturbances features WM neuropathology and a variety of neurobehavioral syndromes. In some patients, metabolic disturbances coexist with toxic disorders (including methotrexate) to produce a clinical and MRI picture known as posterior reversible leukoencephalopathy syndrome<sup>159</sup> that also occurs in patients with hypertension, including those with preeclampsia.

*Deficiency of cobalamin* (vitamin B<sub>12</sub>) can lead to dementia with a prominent WM component radiologically and pathologically. Cobalamin is important in the maintenance of normal myelin, and its deficiency results in subacute combined degeneration (SCD) of the spinal cord. Cobalamin deficiency may also cause perivascular degeneration of myelinated fibers in the cerebrum that is identical to the WM pathology in SCD, and these brain lesions probably account for dementia.<sup>160</sup>



**Figure 15.** Axial MRI in delayed leukoencephalopathy after hypoxic–ischemic insult. **(A)** FLAIR image shows extensive, symmetric white matter hyperintensities with relative sparing of subcortical white matter. **(B)** Diffusion-weighted imaging shows restricted diffusion of the white matter abnormalities, confirmed on **(C)**, apparent diffusion coefficient mapping.<sup>165</sup>

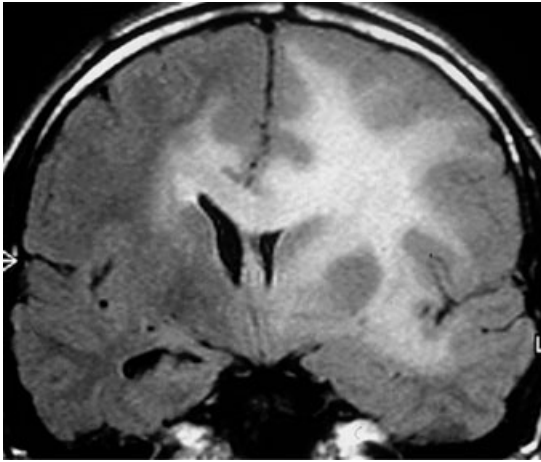
Because cobalamin deficiency may produce dementia that is easily correctable with treatment, vitamin B<sub>12</sub> screening is routine in the evaluation of dementia. Well-documented cases of WM lesions and dementia have improved after parenteral treatment with vitamin B<sub>12</sub>.<sup>161,162</sup>

*Hypoxic ischemic encephalopathy* itself may produce a delayed, diffuse leukoencephalopathy.<sup>163,164</sup> We described a woman who suffered presumed cardiac arrest, was reportedly comatose for 2 days, and then recovered well, only to develop confusion, gait difficulty, and incontinence over the ensuing 2 weeks. She was mute and unable to follow commands and had right hemianopsia, arms held in a flexion, although she could move her legs, with spasticity and hyperreflexia in all extremities. MRI showed extensive, symmetric WM T2 and FLAIR hyperintensities, and DWI and apparent diffusion coefficient mapping revealed restricted diffusion of the WM<sup>165</sup> (Fig. 15). Demyelination has been proposed as a pathophysiological mechanism in these cases, accounting for both latency to onset and variable prognosis. A proposed mechanism is that the demyelination might be triggered by selective vulnerability of the WM to hypoxic injury, resulting from its widely spaced arterioles and lack of anastomoses.<sup>165</sup> Delayed leukoencephalopathy in the setting of hypoxic encephalopathy has also been associated with carbon monoxide poi-

soning,<sup>166,167</sup> but exposure to the toxin is not a prerequisite.

### Trauma

Traumatic brain injury (TBI) is a major source of neurobehavioral disability estimated to affect 1.4 million Americans per year.<sup>168</sup> Of all the major neuropathological complications of TBI (cortical contusion, intracerebral hemorrhage, subdural hematoma, epidural hematoma, penetrating injury, hypoxic–ischemic damage), arguably the most important is the WM lesion known as diffuse axonal injury (DAI),<sup>169,170</sup> or WM shearing injury. DAI involves primarily the brain stem, cerebral hemispheres, and CC and is likely to be ubiquitous in TBI.<sup>116,171</sup> Both myelin and axons are highly vulnerable to DAI, and this injury disrupts distributed neural networks by disconnecting widespread cortical and subcortical regions. DAI has been linked with acute effects such as loss of consciousness, as well as chronic sequelae including persistent attentional, executive, comportment, and memory disturbances. These deficits may occur with DAI in all degrees of TBI severity, from concussion to the vegetative state.<sup>172,173</sup> Damage to the frontal lobe WM appears to be particularly detrimental to long-term outcome, interfering with comportment, occupational function, and community reintegration.<sup>116</sup>



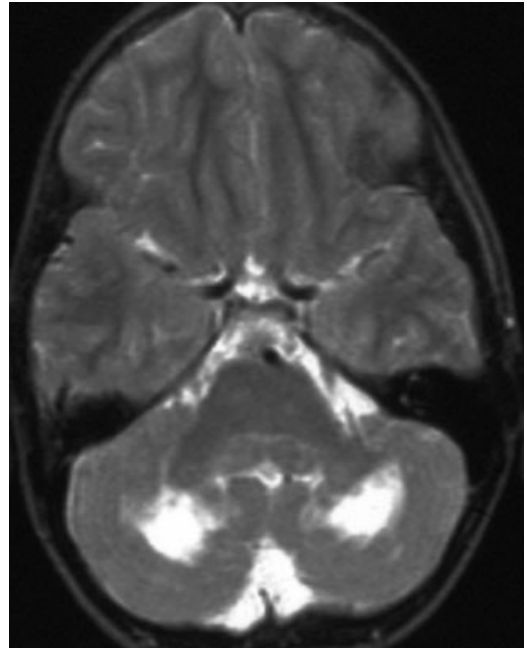
**Figure 16.** Coronal T1-weighted image in a patient with gliomatosis cerebri. Note the spread of tumor along white matter planes.

### Neoplasms

Central nervous system tumors have been considered problematic for investigating brain–behavior relationships because their often wide extent, mass effect, and associated edema can complicate precise localization of the neuropathology. However, with improved neuroimaging, neurobehavioral effects of many cerebral tumors can be studied using detailed clinical–neuropathological correlations.<sup>174</sup>

*Gliomas* can be particularly illustrative in terms of their effects on WM tracts because they originate primarily in WM and spread via WM tracts to other regions.<sup>175,176</sup> Gliomatosis cerebri (GC), a diffusely infiltrative astrocytic malignancy with a clear predilection for cerebral WM, can be seen by MRI to spread via inter- and interhemispheric WM pathways<sup>177</sup> (Fig. 16). Neurobehavioral features leading to progressive dementia are the most common presenting, and persistent, clinical manifestations of this tumor. This scenario underscores the conclusion that selective WM dysfunction is sufficient to produce clinically significant cognitive and emotional disturbances.

*Cerebral lymphoma* may demonstrate a clinical propensity similar to GC when it takes the diffusely infiltrative form of lymphomatosis cere-



**Figure 17.** T2-weighted axial MRI in a patient with Langerhans cell histiocytosis, showing hyperintense signal abnormality in the white matter of the cerebellum.<sup>182</sup>

bri.<sup>178</sup> Study of brain tumors producing neurobehavioral changes related to WM dysfunction deserves more attention, particularly as more powerful neuroimaging modalities make it possible to identify the location and spread of these tumors throughout their course.

*Langerhans' cell histiocytosis* (LCH) is a disorder of unknown cause characterized by proliferation of the Langerhans' cell—a bone marrow–derived, antigen-presenting dendritic cell. It may affect the nervous system, notably the hypothalamic–pituitary region, leading to diabetes insipidus and other endocrinopathies. It may also be located in the pons, cerebellum, basal ganglia, and cerebral WM<sup>179,180</sup> (Fig. 17). The cerebellar lesions are characterized as neurodegenerative and exhibit a profound inflammatory process dominated by CD8-reactive lymphocytes, associated with tissue degeneration, microglial activation, and gliosis.<sup>181</sup> We have seen two patients with LCH (unpublished; and case 8b in reference 182), in whom, on MRI, the disorder appears isolated within

cerebellar WM. The cerebellar motor syndrome is troublesome but is overshadowed by cognitive and neuropsychiatric dysfunction. In one patient, high T2 signal on MRI was isolated to the cerebellar WM during childhood; images during the teenage years demonstrated pancerebellar atrophy and attenuated cerebellar WM. The patient had been placed in special-education classes because of cognitive impairment, and his behaviors were perseverative, impulsive, self-absorbed, immature, and unreliable. He demonstrated poor judgment, took unnecessary risks, engaged in inappropriate interactions, and was “his own worst enemy.” He was alternately agitated, tearful, and sarcastic, and he had a cerebellar motor syndrome of moderate severity. An earlier report of a patient with LCH involving cerebellar WM also reported significant deficits in global cognitive scores, memory, attention and concentration, and perceptual–organizational capabilities, along with substantial emotional and behavioral problems.<sup>183</sup> These behaviors fall within the domain of the cerebellar cognitive affective syndrome and its neuropsychiatric manifestations,<sup>182,184,185</sup> and they probably reflect involvement of the nonmotor region of cerebellum in the posterior lobe.

### Hydrocephalus

Whether originating early or late in life, hydrocephalus exerts its most prominent neuropathological effects on cerebral WM.<sup>186,187</sup> Cortical damage is uncommon, occurring only late in the course. Injury to the deep GM is also less prominent than WM injury, indicating that the cognitive effects of hydrocephalus are related primarily to tract damage, at least at the time when diagnostic and treatment issues are most crucial. Periventricular WM is compromised by the excess volume of ventricular cerebrospinal fluid. In patients with normal pressure hydrocephalus (NPH)<sup>188</sup> characterized by the clinical triad of dementia, urinary incontinence, and gait impairment, treatment with ventriculoperitoneal shunt can be most

effective.<sup>189,190</sup> Improvement is not universal, particularly in older patients with coexistent ischemic damage in the WM<sup>191</sup> or concomitant Alzheimer’s disease (AD).<sup>192</sup> The reversibility of NPH, at least early in the course before widespread GM damage has occurred, likely results from the significant ability of compromised WM to recover.

### Aging, Vascular Disease, and WM Lesions

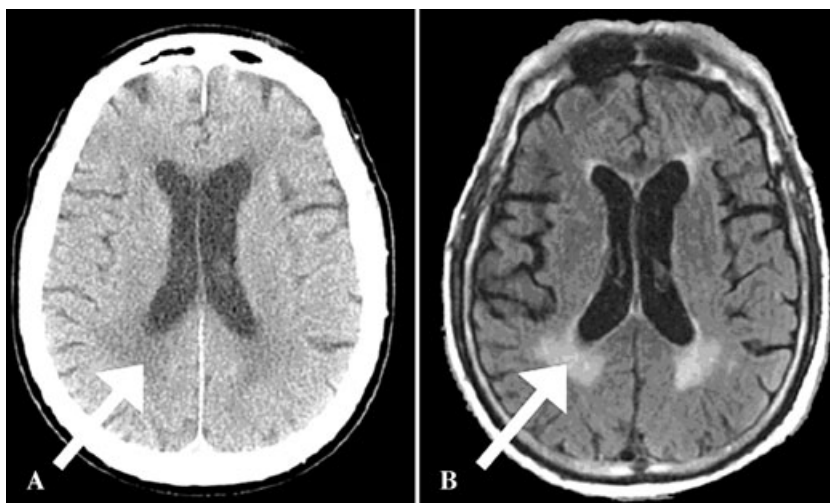
Aged monkeys lose WM within the cerebral cortex and subcortical regions<sup>193,194</sup> and display memory impairment on tasks of spatial and visual recognition that correlates with the extent of degeneration of myelinated fibers in cortex and WM.<sup>195</sup> There is now a vigorous field of investigation into the WM changes that characterize the aging process, as well as the relevance of these findings for speed of information processing, cognition, and dementia in humans.

### WM Hyperintensities in the Elderly: MRI Observations

Computed tomography (CT) and MRI have led to an increased recognition of the prevalence of WM lesions in the elderly. Termed leukoaraiosis (WM rarefaction) by Hachinski *et al.*<sup>196,197</sup> (Fig. 18), these findings were initially thought to be a radiographic manifestation of Binswanger’s disease (Fig. 19). It is now appreciated that these lesions are extremely prevalent both in successful aging and in aging associated with cognitive decline.

### Definition of WM Hyperintensities

WM lesions can be visualized on CT as areas of hypoattenuation (Fig. 18). MRI has greater sensitivity and reveals WM lesions that may not be identified on CT and appear as hyperintensity (WMH) on T2-weighted and FLAIR images. These WMHs are distinguished from

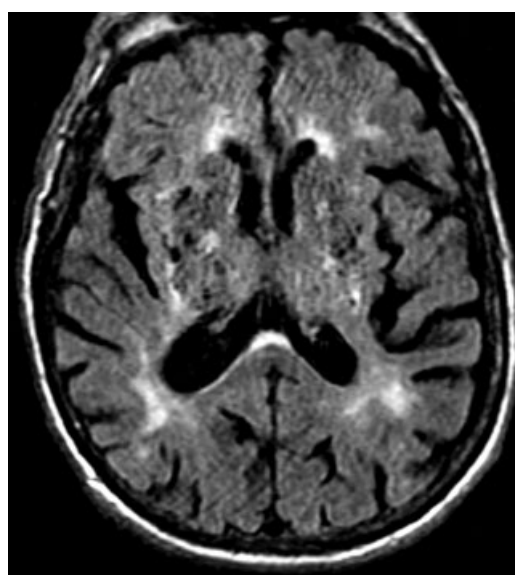


**Figure 18.** Leukoaraiosis is visible as (A) white matter hypodensity on CT and (B) white matter hyperintensity on FLAIR MRI in the same patient.

infarction by the absence of well-defined hypointensity on T1-weighted images. Periventricular regions are most commonly affected, particularly around the frontal and occipital horns. In severe cases there is a halo of WMH surrounding the lateral ventricles<sup>198</sup> (Fig. 19), and a variable extent of discrete ovoid subcortical WMH. MRI measurements of water proton diffusion taken using apparent diffusion coefficient mapping show increased diffusivity within the lesions.<sup>199</sup> These features are not disease specific, however, because they reflect an increased concentration of water within the affected tissue. The most common cerebral small-vessel pathologies associated with WMH are related to hypertension, diabetes, atherosclerosis, and cerebral amyloid angiopathy. Rare vascular diseases associated with WMH include Fabry's disease and hereditary mutations of the COL4A1 gene.

### WMHs in the Elderly: Pathophysiology and Clinical Features

Multiple lines of evidence suggest that vascular pathology is the main cause of most of the age-related WMHs, once other neurological diseases are excluded. Histopathology shows demyelination with various degrees of axonal



**Figure 19.** FLAIR MRI of a patient with Binswanger's encephalopathy. Hyperintense signal abnormality is seen at periventricular zones, white matter immediately beneath cortex, splenium of the CC, and internal and external/extreme capsule regions. Multiple hypodensities consistent with lacunar infarcts are also seen in the basal ganglia and thalamus.<sup>2</sup>

loss and gliosis, consistent with injury to the myelin or oligodendrocyte, but this has not helped determine the underlying causes.<sup>200</sup> CT and MRI findings are visually more dramatic



than gross or routine microscopic pathology, but there is good correlation between imaging and pathology when using myelin stains that reveal relative myelin loss.<sup>200</sup> Arteriosclerosis or microinfarction may be present, but careful studies of the vascular system with serial sections are rarely performed.

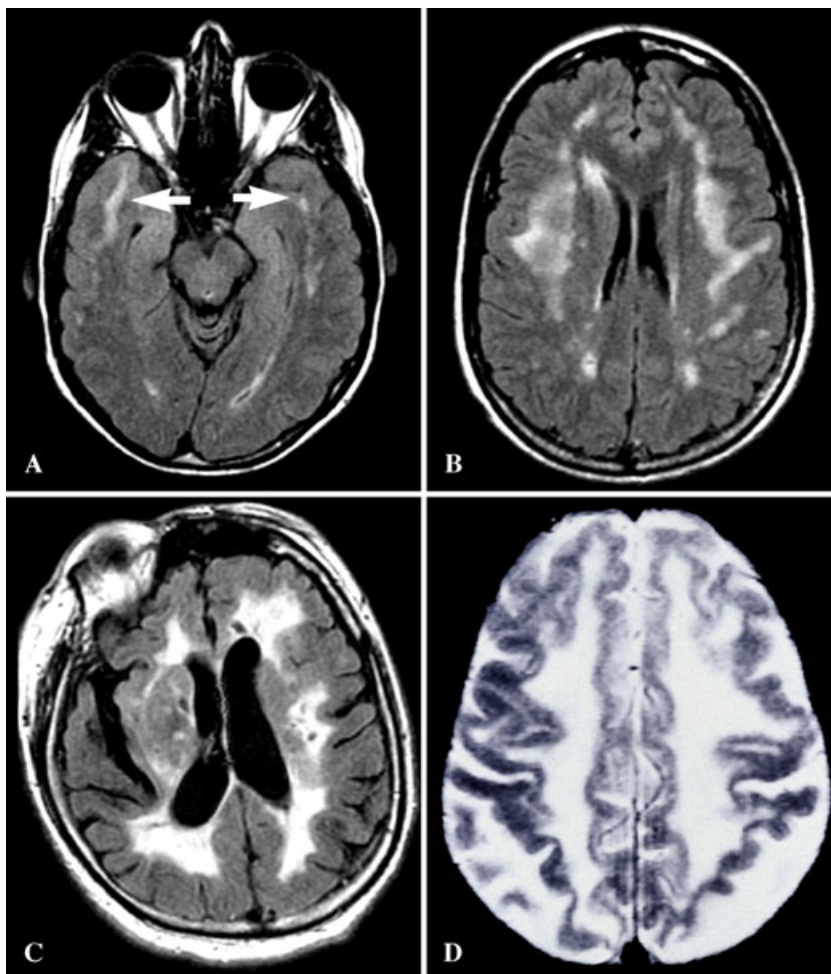
### Epidemiology of WMH

Prospective, population-based cohort studies (Framingham Study,<sup>201</sup> Rotterdam Study,<sup>202,203</sup> Cardiovascular Health Study<sup>204</sup>) have elucidated the epidemiology of WMH. One study using a sensitive ordinal scale for grading WMH severity<sup>205</sup> found that more than 95% of persons older than 70 years have detectable WMH on MRI. Consequently, studies of WMH in older persons are focused on determining variability in extent of WM lesions rather than their presence or absence. The strongest risk factors for greater extent of WMH are age, hypertension, diabetes, and smoking,<sup>203,204</sup> whereas systemic measures of atherosclerosis, such as internal carotid artery plaques, are weakly associated. Retinal vascular changes<sup>206</sup> and indices of renal function<sup>207</sup> are closely associated with WMH, possibly reflecting the presence of shared risk factors for small vessel disease. Serum studies show associations between WMH, or their progression, and markers of endothelial dysfunction (serum homocysteine and intercellular adhesion molecule 1),<sup>208</sup> thrombogenesis (thrombomodulin and fibrinogen),<sup>209,210</sup> inflammation (C-reactive protein),<sup>208</sup> and antioxidant levels.<sup>210</sup> A link with  $\beta$ -amyloid metabolism is shown by associations with either increased serum A- $\beta$ <sup>211,212</sup> or decreased cerebrospinal fluid A- $\beta$ .<sup>213</sup> The basis for these findings is unknown but might be related to the presence of cerebral amyloid angiopathy (CAA).<sup>211</sup> Despite these known risk factors, much of the variance in age-related WMH remains unexplained and may be accounted for by genetic factors.<sup>214</sup>

### Pathophysiology of WMH: Small-vessel Disease

A strong relationship with cerebrovascular disease is shown by robust associations between WMH burden and history of ischemic<sup>215</sup> or hemorrhagic stroke,<sup>216</sup> ischemic stroke evolution,<sup>217</sup> incidence of new ischemic<sup>215,218</sup> or hemorrhagic stroke,<sup>219–221</sup> and presence and incidence of silent brain infarcts.<sup>222</sup> These relationships with stroke and infarction are not accounted for by shared vascular risk factors. Treatment of hypertension, the strongest modifiable risk factor for cerebrovascular disease, with an angiotensin-converting enzyme inhibitor and thiazide diuretic, was associated with reduced WMH progression,<sup>223</sup> whereas treatment with a 3-hydroxy-3-methyl-glutaryl (HMG) CoA reductase inhibitor (statin) had no effect.<sup>224</sup>

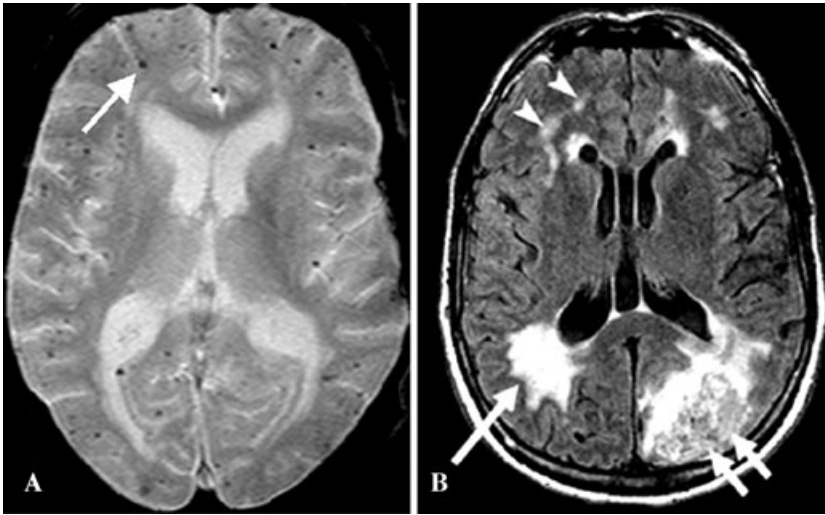
Cerebral small-vessel disease is thought to cause ischemia through vascular stenosis, occlusion, or impaired reactivity producing the WM changes. Tissue pathology consists only of nonspecific injury without evidence of frank infarction, although lesions show immunoreactivity for hypoxia-inducible factor 1, which is expressed in the presence of ischemia.<sup>225</sup> Hemispheric WM blood supply is derived predominantly from penetrating branches of the middle cerebral artery stem or from penetrating branches of circumferential arteries coursing over the hemispheric surface.<sup>226</sup> The few millimeters of WM adjacent to the wall of the lateral ventricle represent a distal endzone territory of blood supply from the choroidal arteries. Blood flow studies show this to be a low-perfusion region, and the fact that it is the most frequent site of WMH involvement possibly reflects a vulnerability to blood flow reduction.<sup>227</sup> Brain regions with higher burden of WMH in demented subjects show decreased blood flow and metabolism, as well as increased oxygen extraction indicative of hypoperfusion.<sup>228–232</sup> Blood flow disturbances are less severe in the nondemented.<sup>233</sup>



**Figure 20.** MRI appearance of white matter changes in axial sections of patients with CADASIL. **(A, B)** FLAIR MRI in an asymptomatic 39-year-old, notch 3 gene positive with family history of early stroke, whose imaging findings were incidentally noted. Characteristic temporal lobe white matter involvement is highlighted (arrows). **(C)** FLAIR MRI in a patient with clinically established CADASIL. **(D)** T2-weighted MRI in a patient with notch 3 gene and pathologically proven disease.

*Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* (CADASIL) is caused by mutations in the notch 3 gene<sup>234</sup> that lead to hyalinization and thickening of the arterial media of small blood vessels in the brain. Other organs are not affected, although asymptomatic vascular changes can be detected on skin biopsy.<sup>235</sup> Studies in CADASIL patients provide strong evidence that cerebral small-vessel disease can cause WMH. MRI reveals lacunar infarcts with extensive WMH burden (Fig. 20). The anterior temporal WM and

external capsule are frequently involved—sites uncommonly affected by sporadic age-related WMH<sup>236</sup>—making CADASIL unusual in that it has a relatively specific spatial distribution of lesions. CADASIL causes impaired cognition and progressive dementia.<sup>237,238</sup> Affected individuals present in their 30s and 40s with migraines, memory loss, psychiatric symptoms, or stroke.<sup>239</sup> Notably, however, studies of radiographic correlates of cognition in CADASIL show that WMH alone is not associated with global cognitive function after controlling for



**Figure 21.** MRI in the axial plane in cerebral amyloid angiopathy. **(A)** Gradient echo MRI demonstrating multiple punctuate areas of hemorrhage (microbleeds, arrow) at the cortico-subcortical junctions. **(B)** MRI FLAIR sequence in a patient with lobar intraparenchymal hemorrhage in the left occipital lobe (double arrows), as well as periventricular WMH (single arrow) and subcortical WMH (arrowheads).<sup>221</sup>

volume of lacunar infarcts,<sup>238</sup> indicating that tissue infarction may be required to produce more severe forms of cognitive impairment. This is exemplified by a 41-year-old patient (Schmahmann, unpublished) with notch 3-confirmed presymptomatic CADASIL, whose cognition is presently entirely preserved in the setting of diffuse and prominent WMH.

*Cerebral amyloid angiopathy* (CAA) is characterized by amyloid deposition in the media and adventitia of small arteries of the cerebral cortex and meninges. Rare hereditary cases may be caused by mutations in the amyloid precursor protein, resulting in deposition of  $\beta$ -amyloid, or by mutations in other genes including cystatin C, transthyretin, and gelsolin.<sup>240</sup> Affected individuals present in their 30s and 40s with cognitive impairment or intracerebral hemorrhage. Extensive WMH are typically present. Unlike CADASIL, CAA also exists as a sporadic disease. In contrast to hereditary CAA, sporadic CAA appears to be exclusively a disease of  $\beta$ -amyloid. It is a major cause of intracerebral hemorrhage in the elderly<sup>241</sup> (Fig. 21). Because the cerebral vascular pathology is almost exclusively limited to cerebral cortex, CAA-related

hemorrhages occur in lobar brain regions (i.e., within the cortex or at the cortico-subcortical junction) but not in deep hemispheric brain regions such as the putamen or thalamus.<sup>242</sup> The presence of multiple or recurrent lobar brain hemorrhages, in the absence of coagulopathy or other secondary causes such as vascular malformations, is highly specific for the presence of CAA pathology.<sup>241</sup> MRI with gradient echo sequence is sensitive to the presence of small hemosiderin deposits from previous hemorrhages, also called microbleeds, and can suggest the diagnosis of CAA.<sup>241</sup>

There is increasing recognition that sporadic CAA is associated with cognitive dysfunction, even though many patients with CAA-related intracerebral hemorrhage do not have severe cognitive impairment or dementia.<sup>243</sup> A population-based autopsy study showed that CAA pathology was associated with antemortem cognitive performance, controlling for the extent of AD pathology.<sup>244</sup> These subjects did not have symptomatic stroke. The same study showed that the prevalence of CAA in those older than 80 years is more than 10%,<sup>244</sup> which is much greater than the population

prevalence of symptomatic brain hemorrhage but may be similar to the population prevalence of asymptomatic lobar microbleeds.<sup>245</sup> These data suggest that CAA contributes to cognitive decline in the elderly and that the clinical effect of CAA is not limited to those with stroke. WMH burden is high in CAA and is associated with cognitive impairment independent of stroke.<sup>221</sup>

In contrast to CADASIL, there is no typical distribution of WMH suggestive of CAA.<sup>227</sup> WMHs appear to be a marker of CAA disease burden and progression, because they are associated with the number of lobar microbleeds<sup>221</sup> and predict new symptomatic intracerebral hemorrhages<sup>221</sup> and asymptomatic lobar microbleeds.<sup>246</sup> An interesting feature of CAA-related WMH is that the site of tissue pathology in the WM is remote from the site of vessel pathology in the cortex, potentially suggesting a flow-related mechanism of injury. DWI shows abnormalities in water diffusivity in brain regions not typically involved by WMH, suggesting that tissue microstructural changes may be more widespread than the changes in T2 hyperintensity.<sup>247,248</sup> The recent advent of molecular imaging of  $\beta$ -amyloid, using Pittsburgh compound B and other ligands,<sup>249</sup> offers the opportunity to address the relationship between extent and location of WMH, and extent and location of  $\beta$ -amyloid deposition.

### **Age-related WM Lesions, Cognition, and Behavior**

An association between WMH and cognitive dysfunction has long been recognized.<sup>196</sup> Research studies and clinical practice show, however, that only a modest amount of variance in cognition performance is explained by WMH. This conclusion is not surprising, perhaps, given the large amount of cognitive performance that remains unexplained by currently recognized brain pathologies, including AD.<sup>250</sup> Practicing clinicians are familiar with the situation where a patient displays consid-

erable incidentally discovered MRI WMH despite apparently normal cognition. Although within-individual decline from previous performance levels may be underappreciated, it appears that some individuals can compensate for high WMH burden through unknown mechanisms.

Population-based studies of aging report a relationship between WMH volume on MRI, determined by ordinal scales or by volumetric analysis, and cognitive performance, determined by psychological testing.<sup>201,204,251,252</sup> These populations were free of dementia and stroke at study onset. Longitudinal follow-up shows that those with higher baseline lesion burden have greater subsequent decline in test performance.<sup>253,254</sup> Further, those with higher WMH progression on follow-up MRI have greater decline in test performance than those with less lesion progression.<sup>253–255</sup> WM lesions are associated with subjective impression of cognitive performance, even in those with psychological test performance in the reference range, supporting their relevance to clinical practice.<sup>256</sup> There are few data to show whether a critical threshold of lesion severity exists, below which WMH can be considered insignificant and above which they should be considered clinically relevant to cognitive performance.

### **WMH and Risk of Cognitive Change**

Higher WMH burden is associated with the transition from normal cognition to mild cognitive impairment (MCI),<sup>257,258</sup> but not from MCI to dementia.<sup>258,259</sup> Whereas the severity of periventricular WMH predicts future dementia, predominantly AD, this relationship is reduced to a trend when also controlling for other MRI measures, such as brain atrophy.<sup>260</sup> Thus, MRI-identified WMH lesions appear to be sufficient to cause mild forms of cognitive dysfunction but rarely cause dementia in the absence of other brain pathologies. Nonetheless, these lesions have public health relevance because they are ubiquitous with

aging, and cumulative disability across the aging population may be large. By causing mild cognitive dysfunction, WM lesions may decrease cognitive reserve and predispose to dementia in the presence of additional brain pathologies. Autopsy-based studies of dementia emphasize the coexistence of vascular and AD pathology,<sup>261</sup> and these WMH lesions and other vascular pathologies may account for some of the otherwise unexplained variation between cognitive performance and burden of AD pathology.

### WM Changes in AD

Cerebral atrophy and loss of WM are marked in the later stages of AD,<sup>262,263</sup> and cerebral WM lesions in AD have the appearance of incomplete infarction.<sup>264,265</sup> Three mechanisms have been proposed for the WM findings in AD.

First, CAA occurs in up to 98% of AD cases and causes microvascular alterations, including WM ischemia and lacunar infarction.<sup>266</sup> Deposition of congophilic  $\beta$ -amyloid in cerebral arteries and arterioles predisposes to lobar hemorrhage and ischemic WM lesions via occlusive vascular disease,<sup>266</sup> and AD patients may have microbleeds on MRI, but they are not at increased risk of lobar hemorrhage.<sup>267</sup> The clinical effect of CAA-related WM lesions in AD is an area of active investigation because early evidence indicates that the amount of CAA pathology correlates with cognitive performance.<sup>268</sup>

Next is the controversial area of mixed AD and vascular dementia (VaD). Leukoaraiosis is probably of ischemic origin<sup>226</sup> and probably lies on a continuum with Binswanger's disease,<sup>269,270</sup> but its frequent presence in AD brains raises the question of a vascular contribution to AD. AD and VaD have been regarded as distinguishable clinically and neuropathologically, but substantial overlap of AD and VaD is now acknowledged.<sup>271</sup> Cerebrovascular risk factors have recently been suggested

to contribute etiologically to AD,<sup>271</sup> but these factors may simply reflect the co-occurrence of common age-related conditions rather than causal relationships.<sup>271</sup> Although much overlap exists, AD and VaD can be differentiated clinically when present in pure form.

A third explanation for WM changes in AD is Wallerian degeneration from loss of neocortical pyramidal neurons in affected cortical areas. More severe LA seen in AD patients has been suggested to result from Wallerian degeneration,<sup>272</sup> and DTI studies of AD have found microstructural WM damage in the CC and temporal, frontal, and parietal lobe WM consistent with Wallerian degeneration due to neocortical neuronal loss.<sup>273</sup> Disconnection of cerebral association areas from related cortical and subcortical regions by these WM changes may thus be an additional burden in AD and mixed dementia.

### Nature of Cognitive Impairment Associated with WMHs

WMHs most severely affect information processing speed and executive function.<sup>201,251,254,274–280</sup> Memory is affected to a lesser degree,<sup>255,276,281</sup> and therefore diagnostic instruments that are heavily weighted toward memory, such as the Mini-Mental State Exam, may underestimate the degree of dysfunction. However, the type of memory impairment may be critical because evidence suggests that WM disorders tend to display impaired memory retrieval rather than encoding, and WMH may be more usefully studied with measures that differentiate these memory components.<sup>116</sup> Impaired connectivity is presumed to be the mechanism by which WMHs cause cognitive dysfunction, although direct evidence to support this hypothesis is relatively scarce.<sup>281</sup> Some studies suggest that periventricular WMHs are of greater significance than subcortical lesions, perhaps reflecting the importance of long association fibers in brain networks subserving cognition, as discussed earlier.<sup>251</sup>

A substantial literature links WMH with depressive symptoms and major depressive disorder in the elderly.<sup>282,283</sup> Cognitive impairments associated with WMH, including impaired processing speed, are also described in depression. The association between WMH and depression does not seem to be restricted to those with mild cognitive impairment, dementia, or pseudodementia. This finding has given rise to a vascular depression hypothesis of late-onset depression,<sup>284</sup> supported by the observation that response to antidepressant treatment may be worse in those with higher burden of WMH.<sup>285,286</sup> This clinical scenario also raises the issue of pseudodepression, that is, apathy and abulia from WM disease masquerading as a primary affective disorder.

Studies examining the relationship between cognition and WMH have been almost entirely limited to global measures of WMH volume or global WMH severity. However, if WMHs do cause WM dysfunction by disrupting specific WM tracts, then these lesions in specific anatomic locations, rather than global extent, should more closely be linked with neuropsychological test performance. One study correlated frontal and temporal WMHs with executive function and memory, respectively,<sup>274</sup> but the use of large regions of interest encompassing the entire lobar WM did not allow for more precise localization of the WM tracts potentially involved. Another approach was to grade abnormalities in a specific WM pathway related to memory.<sup>287</sup> Some investigators have used anatomically coregistered images to produce statistical parametric maps of WM regions where WMH frequency correlates with depressive symptoms.<sup>288,289</sup> WM lesions in the prefrontal cortex have been associated with impaired functional MRI activation of dorsal prefrontal cortex.<sup>281</sup> Also, several studies have attempted to link regional WMH, grouped by lobe, with regional cortical metabolism or perfusion.<sup>277,290</sup> In general, there has been agreement that frontal lobe hypometabolism is a feature of subcortical small-vessel disease including WMH,<sup>277,290–293</sup> and a link with frontal

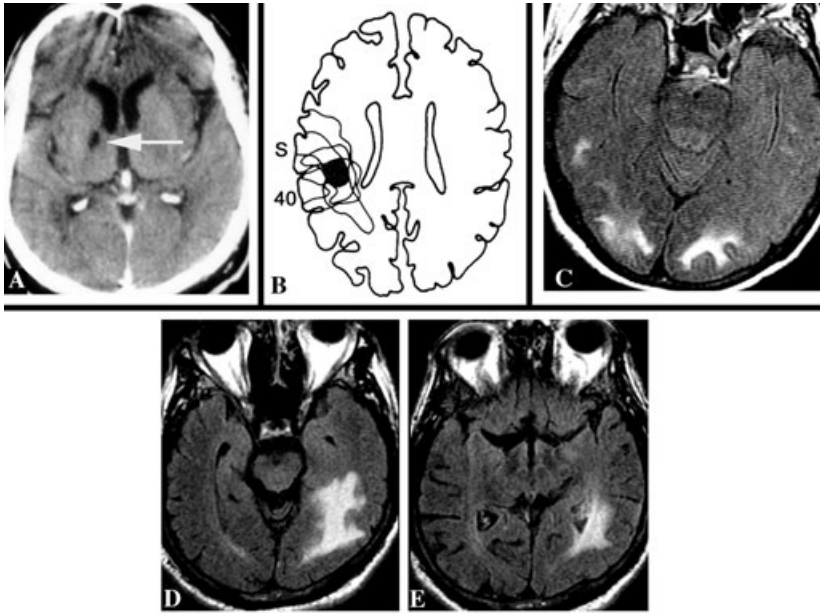
WMH has sometimes been found<sup>292</sup> but not uniformly established.<sup>290</sup>

## Synopsis of Neurobehavioral Syndromes of Cerebral WM

The disorders that lead to alterations in cerebral WM are remarkably heterogeneous, but they may reasonably be considered as a group with respect to their neurobehavioral manifestations. The available literature indicates that these disorders are associated with focal neurobehavioral syndromes, neuropsychiatric conditions, and cognitive dysfunction or dementia.

### Focal Neurobehavioral Syndromes

The neurobehavioral syndromes related to focal WM lesions are familiar to neurologists from the classic literature describing aphasia, apraxia, agnosia, callosal disconnection, and related syndromes.<sup>4,5,116</sup> Most result from stroke, although occasionally focal tumors and demyelinative plaques are responsible. These cases are comparatively rare; well-defined, isolated focal WM lesions that correlate convincingly with a given neurobehavioral deficit are unusual. These are exemplified by neglect syndromes from lesions in the anterior limb and genu of the IC<sup>2,52,53</sup> (Fig. 22A), pseudothalamic pain from lesions of the parietal WM deep to SII<sup>294</sup> (Fig. 22B), frontal behavioral disturbances in Marchiafava–Bignami disease of the CC,<sup>295</sup> fornix lesions that impair memory,<sup>296,297</sup> alexia without agraphia from the classic dual lesion (splenium and left occipital pole WM<sup>28</sup>) as well as from a single subcortical lesion undercutting Wernicke's area<sup>2</sup> (Fig. 22D and E), volitional facial paresis from premotor subcortical lesions,<sup>2</sup> visual loss from the WM lesions of posterior reversible encephalopathy syndrome (Fig. 22C), as well as the elementary deficits of visual loss from lesions of the geniculocalcarine pathway,<sup>298</sup> and sensory loss<sup>299</sup> and weakness<sup>300</sup> from lesions of the posterior limb of



**Figure 22.** Focal WM lesions with neurobehavioral manifestations. **(A)** Lacune in the genu of the right internal capsule (arrow) on CT presenting with hemineglect.<sup>2,52</sup> **(B)** Diagram of the WM lesion responsible for parietal pseudothalamic pain syndrome, thought to disrupt the second somatosensory cortex from thalamus.<sup>297</sup> **(C)** FLAIR MRI of posterior reversible encephalopathy syndrome producing visual loss.<sup>2</sup> **(D, E)** Focal WM lesion consisting of metastatic melanoma with surrounding edema, producing alexia without agraphia.

the IC. Behavioral neurology is founded on observations of this kind, which remain paradigmatic of the lesion method as applied to WM as well as GM regions.<sup>301</sup>

The location of the WM lesion affects the degree of recovery from deficit. Patients with aphasia recover more slowly when the lesion involves the area between the CC medially, the corona radiata laterally, and the caudate nucleus ventrally.<sup>302</sup> This is the territory of the (1) Muratoff Bundle immediately above the head and body of the caudate nucleus, that transmits fibers from dorsal cortical areas to the caudate nucleus, and (2) of the fronto-occipital fasciculus that links the dorsal and medial prefrontal and posterior parietal cortices with the dorsolateral prefrontal cortex. This finding provides support for the notion that location of lesion (i.e., which specific WM tracts are damaged) is crucial in recovery from aphasia. It also emphasizes the importance of intact communication between

the cortical and subcortical nodes in the distributed neural circuits that support language processing.

### Neuropsychiatric Syndromes

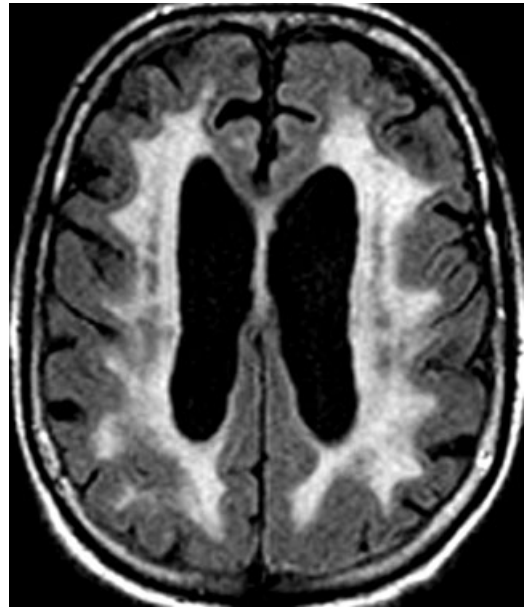
Several neuropsychiatric symptoms have been described in association with cerebral WM pathology. Although these presentations are diverse and etiologically puzzling, a postulated link between WM abnormalities and psychiatric dysfunction is common in the literature.<sup>116</sup> These associations have been pursued in two complementary ways. First, this idea has been pursued by exploring psychiatric phenomena in WM disorders, as in the case of MS, in which depression, mania, psychosis, and euphoria have all been examined.<sup>116</sup> Second, interest has developed in the potential relevance of WM dysfunction in psychiatric diseases, as exemplified by the study of myelin dysfunction in schizophrenia.<sup>303</sup>

and by a study showing abnormalities in the uncinate fasciculus in patients with schizophrenia and schizotypal personality disorder.<sup>304</sup>

In addition to acquired and genetically determined diseases, some neuropsychiatric disorders have been postulated to result from disruption of the natural phenomenon of pruning of excess axons in the developing brain.<sup>305,306</sup> This association has been observed in boys with early infantile autism in whom the volume of cerebral WM is greater than in age-matched control subjects.<sup>307</sup> Pruning of axonal connections during development appears necessary for optimal sculpting of neural circuits. Persistence into adulthood of excess and chaotically organized fiber systems may be as detrimental to healthy cognition as the loss of axonal connections is in the mature brain.

### WM Dementia

The most important neurobehavioral syndrome related to cerebral WM damage is WM dementia (WMD). This category was formally introduced in 1988 in an effort to define the dementia syndrome that occurs in patients with widespread cerebral WM involvement.<sup>6</sup> All the WM disorders can produce WMD (Fig. 23), representing an important source of disability, although milder cognitive dysfunction may be the presenting feature. WMD can be difficult to detect because early neurobehavioral features are often subtle, elemental neurologic manifestations are variably present, and establishing the diagnosis of the primary WM disorder can be challenging,<sup>116</sup> but attention to this syndrome and its earliest appearance are key clinical goals. A profile of neurobehavioral features typical of WMD has been postulated to include executive dysfunction, memory retrieval deficit, visuospatial impairment, and psychiatric disorder, with relatively preserved language, normal extrapyramidal function, and normal procedural memory. WMD is thus distinct both from cortical dementia, in which memory encoding and language are usually impaired,<sup>308</sup> and from subcortical GM de-



**Figure 23.** FLAIR MRI in the axial plane of an 80-year-old man with slowly evolving WM dementia. No single cause has been identified for the cognitive decline or WM hyperintensities.<sup>2</sup>

mentia, in which extrapyramidal function and procedural memory are typically affected.<sup>309</sup> Given the impressive number of WM disorders at all ages that produce WMD and other neurobehavioral syndromes, an awareness of the role of WM in cognition and behavior will enhance understanding of brain–behavior relationships and improve patient care.

### Summary and Conclusion

The distributed neural circuits that subserve behavior are topographically linked in a highly precise manner by five major groupings of fiber tracts: cortico–cortical association fibers; cortico–striatal fibers; commissural fibers across the hemispheres; and cortico–subcortical pathways linking cerebral cortex to thalamus, the pontocerebellar system, and the brain stem and spinal cord. Lesions of association fibers prevent communication between cerebral cortical areas engaged in different domains of behavior. Lesions of subcortical structures, or the projection/striatal fibers that link them with



the cerebral cortex, disrupt the contribution of subcortical nodes to the ultimate behavior. Disconnection syndromes may thus be regarded as resulting not only from lesions of the cerebral cortex but also from lesions of subcortical structures themselves, and of the WM tracts that link the nodes that make up the distributed circuits. The nature and the severity of the clinical manifestations of subcortical and WM lesions are determined, in large part, by the location, extent, and timing of onset of the underlying pathology. Discrete neurological and neuropsychiatric symptoms result from focal WM lesions. Cognitive impairment across multiple domains—WMD—is now recognized in the setting of diffuse WM disease. Unresolved issues relating to the significance and prevention of WMH in the elderly require further study. We hope that this synthetic review of WM diseases and their neurobehavioral manifestations may further the understanding, diagnosis, and treatment of these disorders.

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### Conflicts of Interest

The authors declare no conflicts of interest.

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