Comparing and contrasting white matter disorders: a neuropathological approach to pathophysiology

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Chapter 2

Genetic defect of glia maturation

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Leukoencephalopathy with vanishing white matter: a review

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Abstract
Vanishing white matter (VWM) is one of the most prevalent inherited childhood leukoencephalopathies, but this may affect people of all ages, including neonates and adults. It is a progressive disorder clinically dominated by cerebellar ataxia and in which minor stress conditions, such as fever or mild trauma, provoke major episodes of neurologic deterioration. Typical pathological findings include increasing white matter rarefaction and cystic degeneration, oligodendrocytosis with highly characteristic foamy oligodendrocytes, meager astrogliosis with dysmorphic astrocytes, and loss of oligodendrocytes by apoptosis. Vanishing white matter is caused by mutations in any of the genes encoding the 5 subunits of the eukaryotic translation initiation factor 2B (eIF2B), EIF2B1 through EIF2B5. eIF2B is a ubiquitously expressed protein complex that plays a crucial role in regulating the rate of protein synthesis. Vanishing white matter mutations reduce the activity of eIF2B and impair its function to couple protein synthesis to the cellular demands in basal conditions and during stress. Reduced eIF2B activity leads to sustained improper activation of the unfolded protein response, resulting in concomitant expression of proliferation, prosurvival, and proapoptotic downstream effectors. Consequently, VWM cells are constitutively predisposed and hyperreactive to stress. In view of the fact that VWM genes are housekeeping genes, it is surprising that the disease is primarily a leukoencephalopathy. The pathophysiology of selective glial vulnerability in VWM remains poorly understood.

Introduction

Leukoencephalopathy with vanishing white matter (VWM; OMIM number 603896) (van der Knaap et al., 1997), also referred to as childhood ataxia with central hypomyelination (Schiffmann et al., 1994) and myelinopathia centralis diffusa (Brück et al., 2001), is one of the most prevalent inherited childhood white matter disorders (van der Knaap et al., 1999a). Although initially described in children, later observations have demonstrated that VWM may affect people of all ages including adults. Vanishing white matter is prevalent among whites, but it has also been reported in non-white patients from South America (Rosemberg et al., 2002) and Asia (Sugiura et al., 2001; Wilson et al., 2005; Wong et al., 2008; Wu et al., 2009); however, its precise incidence has not been assessed. Vanishing white matter is due to mutations in any of the 5 genes encoding the eukaryotic translation initiation factor eIF2B (Leegwater et al., 2001; van der Knaap et al., 2002). Although the genetic defect resides in housekeeping genes, VWM is primarily a brain disorder in which oligodendrocytes and astrocytes are selectively affected. The basis of the glial vulnerability in VWM remains poorly understood.

Clinical Diagnosis

Vanishing white matter was initially recognized as a disease of young children (van der Knaap et al., 1997; Schiffmann et al., 1994; Hanefeld et al., 1993). The disease presents with cerebellar ataxia and less prominent spasticity. Cognition is often better preserved; optic atrophy with loss of vision and epilepsy may occur, but are mild or late signs (van der Knaap et al., 1997; Schiffmann et al., 1994; Hanefeld et al., 1993). Involvement of the peripheral nervous system has been described in only 2 children (Federico et al., 2006; Huntsman et al., 2007). Stresses act as provoking factors with respect to the onset of the disease and to the episodes of major and rapid neurologic deterioration, which typically characterize the clinical course. Such provoking factors include febrile infections, minor head trauma, and acute fright (van der Knaap et al., 1997 & 1998; Hanefeld et al., 1993; Vermeulen et al., 2005; Kaczorowska et al., 2006). During episodes of rapid deterioration hypotonia, irritability, vomiting, and epilepsy ensue or significantly increase. Consciousness is also impaired, ranging from somnolence to unexplained coma, and death may occur (van der Knaap et al., 1997 & 1998). Except for these episodes, the disease runs a slowly progressive course and is eventually fatal (van der Knaap et al., 1997 & 1998; Schiffmann et al., 1994; Hanefeld et al., 1993).

More recently, it has become apparent that VWM has a wider clinical spectrum than originally described with age at onset inversely related to clinical severity (van der Knaap et al., 1998 & 2003; Fogli et al., 2004a). Milder variants have been reported with onset in adolescence and adulthood in which the episodes of major deterioration are less prominent, and the courses were significantly more protracted (Leegwater et al., 2001; van der Knaap et al., 1998 & 2004; Labauge et al., 2009). The initial clinical signs in adults consist of epileptic seizures, complicated migraine, presenile dementia, and psychiatric symptoms (van der Knaap et al., 2004; Ohtake et al., 2004; Prass et al., 2001; Denier et al., 2007 Matsui et al., 2007; Riecker et al., 2007). Many affected women experience a combination of leukoencephalopathy and primary amenorrhea or premature ovarian failure, a condition named ovarioleukodystrophy (Schiffmann et al., 1997; Fogli et al., 2003; Mathis et al., 2008). The ovarian dysfunction may precede the neurologic decline (van der Knaap et al., 1997; Fogli et al., 2003; Biancheri et al., 2003). At the opposite side of the spectrum, the disease may also have an early infantile or antenatal onset (van der Knaap et al., 2003; Fogli et al., 2002a). A more severe variant of VWM has been reported among Cree and Chippewayan indigenous populations in northern Quebec and Manitoba. Cree encephalopathy affects infants as young as 3 months and is invariably fatal within the second year of life (Black et al., 1988 & 2002; Fogli et al., 2002b). Prenatal forms of disease have been described and are characterized by a variable combination of reduced fetal movements and oligohydramnios in the third trimester of gestation, primary microcephaly, and extraneurologic signs (including growth failure, congenital contractures, renal hypoplasia, hepatosplenomegaly, pancreatitis, and cataracts), in addition to ovarian dysgenesis and leukoencephalopathy (van der Knaap et al., 2003; Boltshauser et al., 2002).

The clinical diagnosis of VWM is strongly suggested by magnetic resonance imaging (MRI), which is diagnostic in the classic early childhood form (fig. 1A-C). Magnetic resonance imaging shows diffuse and symmetric involvement of the cerebral white matter that spares only the U fibers, the outer part of the corpus callosum, the internal capsules, and anterior commissure. These signal changes are also detected in presymptomatic patients (van der Knaap et al., 1997, 1998 & 2004; Rosemberg et al., 2002; Wu et al., 2007; da Costa Fontanelle et al., 2008). Over time, MRI demonstrates progressive rarefaction and cystic degeneration of the white matter, which is eventually totally replaced by fluid (van der Knaap et al., 1997 & 1998). Within the cystic areas, only radial stripes that stretch from the ventricular wall to the subcortical regions are faintly visible (van der Knaap et al.,

1997 & 1998) (fig. 1C). Contrast enhancement has not been reported. Complementary imaging techniques confirm the MRI findings of progressive replacement of tissue by fluid. In cerebral white matter diffusion-weighted images, there is increased diffusivity (Patay, 2005), and proton spectroscopy demonstrates progressive reduction and eventual disappearance of all major metabolites with the accumulation of glucose and lactate at cerebrospinal fluid-like concentrations (van der Knaap et al., 1997 & 1998; Schiffmann et al., 1994; Hanefeld et al., 1993; Tedeschi et al., 1995; Dreha-Kulaczewski et al., 2008). The cerebellar white matter may also be affected in VWM (typically without cystic degeneration). In the brainstem, abnormal signal intensity may be detected, particularly in the pontine central tegmental tracts (van der Knaap et al., 1997 & 1998). There is some cerebellar atrophy in late stages (van der Knaap et al., 1997 & 1998). The cortical gray matter is always spared, and minor and usually temporary signal changes have been reported in the thalamus and globus pallidus in some patients (van der Knaap et al., 1998).

In adult and early infantile variants of VWM, the MRI diagnosis is not as straightforward as it is in the classic childhood form. White matter cystic degeneration may be limited or even absent in teenagers and adults with VWM, and some degree of cerebral atrophy is common (van der Knaap et al., 1998 & 2004; Schiffmann et al., 1997). In neonates, the white matter appears swollen with little or no rarefaction. The gyral pattern is often immature for the age. Over time, there is considerable subcortical atrophy that eventually leads to collapse of the cortex on the ependymal lining (van der Knaap et al., 2003; Boltshauser et al., 2002). Basal ganglia and thalamus signal abnormalities accompany the white matter involvement in Cree leukoencephalopathy (Aloraini et al., 1999).

A few biochemical markers have been identified for VWM, including elevated cerebrospinal fluid glycine (Sugiura et al., 2001; van der Knaap et al., 1999b; Sinzig et al., 2004) and decreased asialotransferrin concentrations (Vanderver et al., 2005 & 2008). Asialotransferrin is thought to be produced exclusively in the brain, possibly by astrocytes and oligodendrocytes, and its reduction might reflect functional disturbances in these cells (Vanderver et al., 2008). However, in view of the high sensitivity and specificity of MRI findings, there is limited need for such biomarkers in common clinical practice.

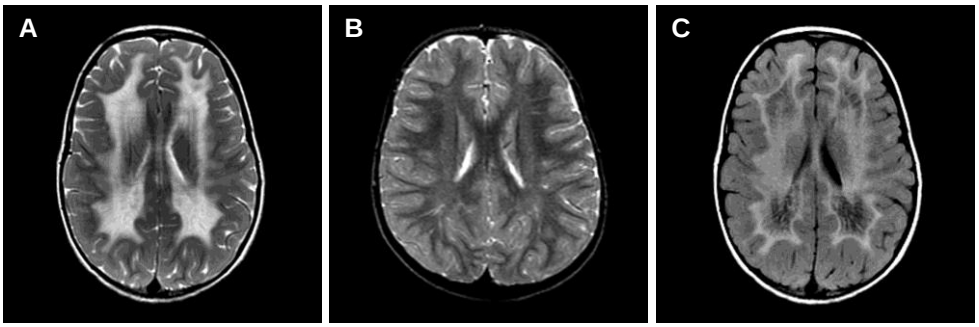

Figure 1. Magnetic resonance imaging findings in classic vanishing white matter (VWM) disease. (**A, B**) Axial T2-weighted image at the level of the centrum semiovale of a 3-year-old VWM patient shows a symmetric diffuse signal abnormality in the hemispheric white matter, partially sparing the U fibers (A). An axial T2-weighted image of an age-matched normal control is shown for comparison (B). (**C**) The cystic breakdown and cavitation of the white matter in VWM is seen in a fluid-attenuated inversion recovery sequence that shows that part of the affected white matter has a low-signal intensity, similar to that of cerebrospinal fluid. Radiating stripes stretching across the rarefied white matter are suggestive of remaining tissue strands.

Genetics and Genotype-Phenotype Correlation

Insight into the genetic cause of VWM was first achieved in 2001 when nucleotide changes in EIF2B5 were identified as the first disease-causing mutations in a small group of patients originating from the eastern part of the Netherlands who shared a common ancestor (Leegwater et al., 2001). Mutations in a second gene responsible for the disease, EIF2B2, were then recognized in patients from the southern part of the Netherlands (Leegwater et al., 2001). It soon became evident that mutations in any of the genes encoding the 5 subunits of eIF2B, EIF2B1 through EIF2B5, encoding eIF2Bα through eIF2Bε, can independently cause VWM (van der Knaap et al., 2002; Leegwater et al., 2003).

More than 120 mutations have been reported to date in more than 250 patients (Maletkovic et al., 2008); most reside in EIF2B5 and EIF2B2 (Fogli et al., 2004b; Pronk et al., 2006). No real mutational hotspots in specific domains of the different subunits have been found (50), although some recurrent mutations seem to occur in paired cytosine/guanine (CpG) dinucleotides (Leegwater et al., 2001; Maletkovic et al., 2008). Approximately 90% are missense mutations most often affecting nonconserved amino acid residues (Maletkovic et al., 2008; Fogli et al., 2004b). Frameshifts and nonsense mutations are rare and have been reported only in the compound-heterozygous state. Heterozygous mutations always affect the same

gene (Leegwater et al., 2001; van der Knaap et al., 2002 & 2003; Fogli et al., 2002a, 2002b, 2003 & 2004b; Maletkovic et al., 2008; Pronk et al., 2006; Fogli & Boespflug-Tanguy, 2006; Ohlenbusch et al., 2005; Scali et al., 2005).

The correlation between MRI findings typical of VWM and detection of mutations in the EIF2B1-5 genes is very high, again pointing to the sensitivity of MRI as an effective tool for establishing the diagnosis (van der Knaap et al., 1999a & 2006; Fogli et al., 2004b; Pronk et al., 2006). On the other hand, the genotype-phenotype correlation is limited because there is wide phenotypic variability among patients with the same mutations, and even among siblings (Leegwater et al., 2001; van der Knaap et al., 2004; Mierzewska et al., 2006; Damon-Perriere et al., 2008; Pineda et al., 2008), suggesting that environmental and/or other genetic factors can significantly influence the phenotype (van der Knaap et al., 2006). Interestingly, a stronger genotype-phenotype correlation has been found at the extremes of the clinical spectrum. The p.Arg113His variant in eIF2Bε, for example, is almost invariably reported in the homozygous state where there is a later onset and slow progression (van der Knaap et al., 2004; Fogli et al., 2004b); this variant is most frequently encountered in women with ovarioleukodystrophy (Fogli et al., 2003; Mathis et al., 2008; Damon-Perriere et al., 2008). Arg113 is not conserved even among mammals (i.e. the mouse and rat proteins have a histidine at the equivalent position), which could explain why p.Arg113His is responsible for a milder phenotype in humans (Fogli et al., 2003). p.Val309Leu in eIF2Bε has been reported only in combination with early onset in more severe cases (Fogli et al., 2002a & 2004b). Patients affected by Cree encephalopathy with very early onset and early death are homozygous for a mutation causing the p.Arg195His change in eIF2Bε (Fogli et al., 2002b & 2004b). Interestingly, the p.Arg113His compound with p.Arg195His seems to have a protective effect against the most severe phenotype (Fogli et al., 2004b). Several comprehensive reports of the VWM-causing mutations are reviewed elsewhere (Maletkovic et al., 2008; Fogli et al., 2004b; Pronk et al., 2006; Fogli & Boespflug-Tanguy, 2006; Ohlenbusch et al., 2005; Scali et al., 2005).

Pathology

External examination of the brain is unrevealing (van der Knaap et al., 1998; Rodriguez et al., 1999), except in infants and younger children in whom there usually is some swelling of the brain and flattening of the gyri (van der Knaap et al., 1997). Cerebral atrophy with enlargement of subarachnoid spaces and lateral

ventricles is seldom observed in children (van der Knaap et al., 1997; Rodriguez et al., 1999) but is common in adults. On cut slices, the white matter appears grayish and partly gelatinous to frankly cystic (fig. 2A) (van der Knaap et al., 1997 & 1998; Brück et al., 2001; Rodriguez et al., 1999; Wong et al., 2000; Francalanci et al., 2001). As observed by MRI, white matter rarefaction is more prominent in deep cerebral areas (van der Knaap et al., 1998). The gray matter structures including the cerebral cortex, basal ganglia, and brainstem nuclei appear macroscopically normal (fig. 2A) (van der Knaap et al., 1998).

Histopathologic examination reveals that the white matter involvement extends well beyond the limits recognized on gross examination (van der Knaap et al., 1997 Schiffmann et al., 1994). The U fibers are often affected (fig. 2B,C), whereas the outer rim of the corpus callosum, anterior commissure, fornix, optic tracts, internal capsules, and intrinsic fibers of the thalami are less severely affected (van der Knaap et al., 1997 & 1998; Schiffmann et al., 1994; Brück et al., 2001; Rodriguez et al., 1999; Wong et al., 2000; van Haren et al., 2004). In the mesencephalon, the cerebral peduncles are generally intact. In the pons, the ventral trigeminothalamic and central tegmental tracts may be affected. The deep cerebellar white matter shows discoloration that is most marked in the hilus of the dentate nucleus, but the myelin within the folia is usually normal. Discoloration is also observed in the hilus of the inferior olivary nucleus, pyramids, and corpus restiforme. The peripheral part of the cranial nerves appears normally myelinated. In the spinal cord, the posterior columns are only partially affected; there is a more marked myelin loss in the spinocerebellar tracts, lateral and anterior corticospinal tracts, and the anterolateral fascicles containing the spinoreticular and spinothalamic tracts (van der Knaap et al., 1997 & 1998; Rodriguez et al., 1999; Wong et al., 2000; Francalanci et al., 2001).

Histopathologic and immunohistochemical findings support the inclusion of VWM among orthochromatic sudanophilic leukoencephalopathies. Myelin stains of affected white matter show paucity of myelin sheaths, and the remaining sheaths appear thinned and dispersed by vacuoles giving rise to a spongiform appearance (van der Knaap et al., 1997 & 1998; Brück et al., 2001; Rodriguez et al., 1999; Wong et al., 2000). In semithin sections, these vacuoles correspond to focal areas of uncompacted myelin close to the axonal membrane (Rodriguez et al., 1999). Scattered phagocytic cells may be noted with orthochromatic and possibly Sudan black+ and periodic acid Schiff+ cytoplasm, which become sudanophilic and filled with myelin debris approaching the cavitated areas (van der Knaap et al., 1997 & 1998; Brück et al., 2001; Rodriguez et al., 1999); however, the amount of myelin

breakdown products appears disproportionately mild compared with the severity of the myelin lesions. In line with immunohistochemical data, biochemical studies show dramatically reduced myelin yields; the major myelin proteins (i.e. myelin basic protein, proteolipid protein [PLP], cyclic nucleotide phosphodiesterase, and myelin oligodendrocyte glycoprotein) are present, have a normal molecular weight, but are markedly reduced in amount (Schiffmann et al., 1994; Rodriguez et al., 1999; Francalanci et al., 2001). All myelin lipids, including galactocerebroside, sulfatide, and ethanolamine plasmalogens are reduced, whereas gangliosides are normal (Tedeschi et al., 1995). Data regarding cholesterol esters are contradictory (Tedeschi et al., 1995) (Marie Vanier, Lyon, France, personal communication; Ann Moser, Baltimore, MD, personal communication).

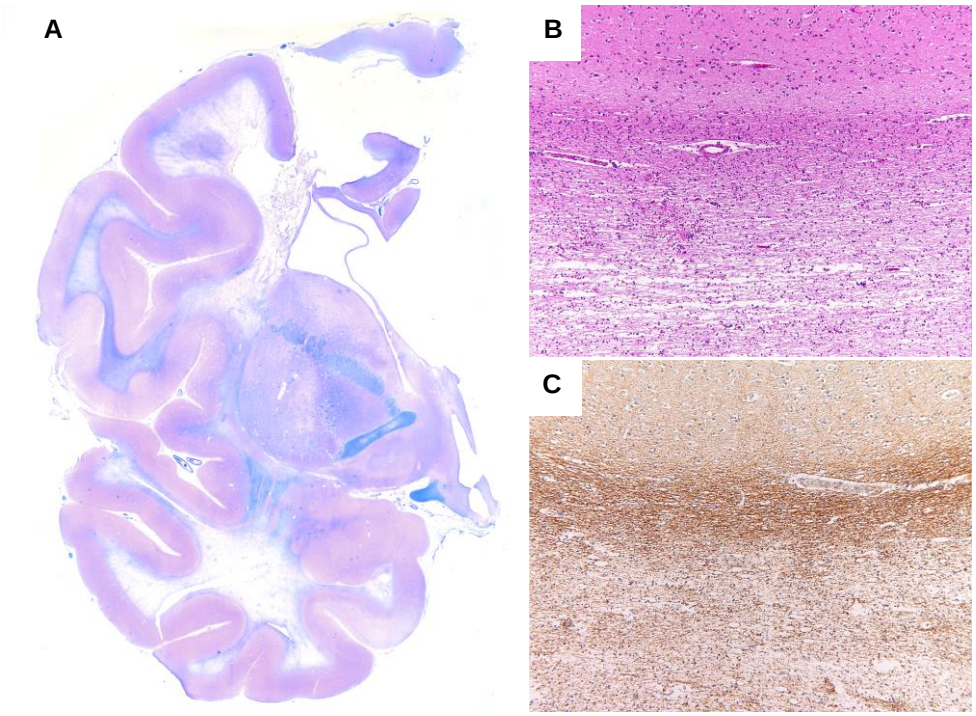

Figure 2. White matter cystic degeneration and tissue loss in vanishing white matter disease. (**A**) Coronal section of the left cerebral hemisphere stained with Luxol fast blue and periodic acid Schiff shows widespread loss of myelin and cystic rarefaction with preservation of optic chiasm, anterior commissure, capsulae, and, in places, subcortical myelin. There is a radial cobweb-like pattern of remaining fiber bundles in the frontal and temporal lobe. (**B, C**) Microscopic sections through the frontal lobe confirm that the U fibers are relatively preserved and myelinated compared with the deeper white matter where there is tissue rarefaction and myelin loss. The cortex is uninvolved. B: H&E; C: myelin basic protein immunohistochemistry. Original magnification: (B, C) 50x.

The number of axons in the white matter is decreased, which is usually commensurate with the decrease of myelin (Brück et al., 2001; van der Knaap et al., 1998; Wong et al., 2000). Axon loss is complete in areas of cavitation but variable in less involved areas (Rodriguez et al., 1999). Particularly in recent lesions, axons are devoid of myelin but microscopically preserved (Brück et al., 2001; van der Knaap et al., 1998; Fogli et al., 2002b; Rodriguez et al., 1999; Jansen et al., 2008) and show a normal cytoskeleton on ultrastructural analysis (Rodriguez et al., 1999; Wong et al., 2000); however, axonal swellings in and around cavitated areas have also been reported (Prass et al., 2001; Francalanci et al., 2001). These somewhat contradictory findings, together with the tract-like distribution of the myelin loss in the brainstem and the spectroscopy profile, have raised the debate as to whether VWM is a primary myelinopathy or an axonopathy (van der Knaap et al., 1998; Dreha-Kulaczewski et al., 2008; Wong et al., 2000; Rodriguez & Gelot, 1999; van der Knaap & Kamphorst, 1999; Sijens et al., 2005; Blüml et al., 2003). The degree of reactive gliosis is remarkably limited (van der Knaap et al., 1997 & 1998; Rodriguez et al., 1999; Wong et al., 2000; Francalanci et al., 2001). The radiating pattern of fine stripes within the rarefied white matter seen on MRI correlates with widened blood vessels accompanied by radial processes of reactive astrocytes (van der Knaap et al., 1997 & 1998; Rodriguez et al., 1999). The paucity of astrogliosis despite severe myelin loss and the dysmorphic appearance of astrocytes in areas of severe myelin loss suggest a deficiency in astrocytic function (Dietrich et al., 2005); it has been proposed that this contributes to the development of cavitated lesions. Only moderate numbers of macrophages/microglial cells are seen in VWM, and T and B lymphocytes are absent (Brück et al., 2001; Rodriguez et al., 1999; Kuhlmann et al., 2008). The lack of inflammatory changes may be helpful in distinguishing VWM from other childhood-onset leukoencephalopathies with active demyelination (e.g. X-linked adrenoleukodystrophy and Alexander disease), in which parenchymal and/or perivascular lymphocytic infiltrates may be seen together with numerous foamy macrophages that contain myelin degradation products (Kuhlmann et al., 2008).

The cerebral cortex appears almost entirely normal with normal neuronal architecture and lamination (van der Knaap et al., 1997; Rodriguez et al., 1999), but numbers of large neurons in the caudate nucleus can be decreased. Reduced numbers of Purkinje cells and cerebellar granular neurons has occasionally been observed, but only in younger children (Sugiura et al., 2001; Fogli et al., 2002b; Rodriguez et al., 1999). Neuronal loss in the hippocampus is a feature of Cree leukoencephalopathy (Fogli et al., 2002b) and may be due to severe seizures.

Involvement of dentate nuclei, inferior olives, and substantia nigra has been reported only once in a Japanese child (Sugiura et al., 2001).

The distinguishing histopathologic features of VWM pertain to macroglial cells. Around cavitated areas and in less affected regions, an increased cellular density is observed with cell numbers up to 200% to 300% with respect to controls (fig. 3A,B) (van der Knaap et al., 1998; Rodriguez et al., 1999; Francalanci et al., 2001; van Haren et al., 2004). This increased cellular density has been ascribed to oligodendrocytes, based on their morphology (i.e. small, round, dark nuclei, often with a small nucleolus, minimal cytoplasm, or perinuclear halo with rough endoplasmic reticulum [ER], and lack of intermediate filaments), their immunohistochemical properties (i.e. expression of carbonic anhydrase II and, to a lesser extent, of cyclic nucleotide phosphodiesterase, myelin basic protein, PLP, and myelin oligodendrocyte glycoprotein), and their failure to express glial fibrillary acidic protein (GFAP) and macrophage markers (Rodriguez et al., 1999; van Haren et al., 2004). Others have further defined these oligodendrocytes as mature cells (Wong et al., 2000) or myelinating glia (Rodriguez et al., 1999). The possible role of oligodendroglial precursors/progenitors in this phenomenon has been suggested (Brück et al., 2001), but not yet investigated.

Variable proportions of the oligodendrocytes display an unusually abundant, finely

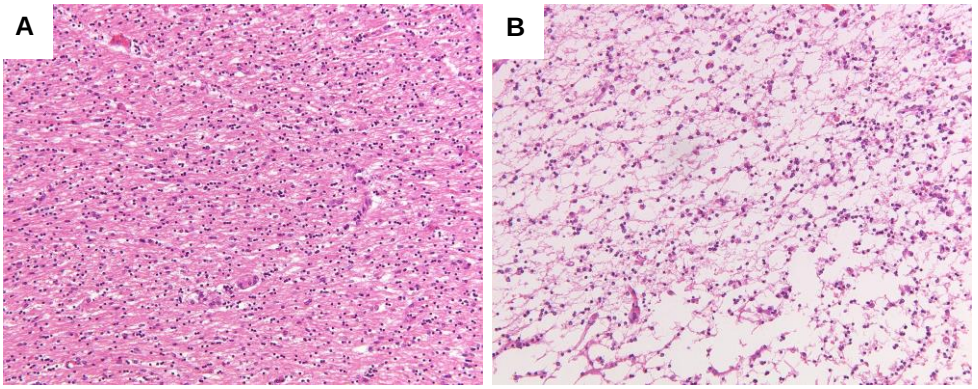

Figure 3. Myelin paucity and cystic degeneration coexist with oligodendrocytosis in the white matter in vanishing white matter disease. (**A**) The anterior commissure displays markedly increased oligodendrocyte density with minimal myelin pallor. (**B**) White matter rarefaction and myelin loss are prominent around cavitated areas in the frontal lobe but the density of oligodendrocytes is still high. (A, B) H&E; original magnification: 100x.

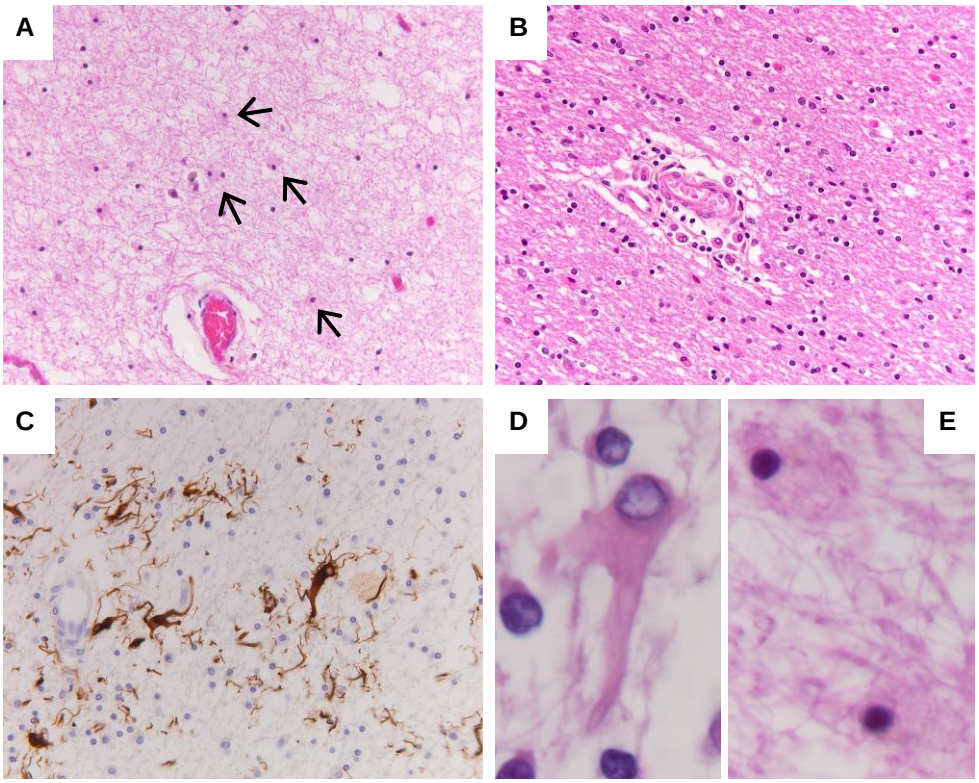

Figure 4. Macroglial cells in vanishing white matter disease. (**A**) Foamy oligodendrocytes (arrows) stand out as individual cells in deep brain regions that have marked myelin loss and spongy changes. (**B**) The foamy cytoplasm of oligodendrocytes is difficult to appreciate in subcortical regions in which the white matter is relatively preserved. (**C**, **D**) Astrocytes show atypical morphology with coarse, blunt processes that somehow clustered around blood vessels. (**E**) Higher magnification of the foamy oligodendrocytes demonstrates their homogeneous finely granular cytoplasm. A, B, D, E: H&E; C: glial fibrillary acidic protein. Original magnifications: (A-C) 200x; (D, E) 630x.

vacuolar to foamy cytoplasm (fig. 4A,B and E) (Rodriguez et al., 1999; Wong et al.,2000). These cells are present also in Cree leukoencephalopathy (Black et al., 2002; Fogli et al., 2002b) but are not seen in any other white matter disease (Wong et al., 2000).

At the ultrastructural level, the abnormal foamy oligodendroglial cells contain multiple membranous structures associated with mitochondrial membranes and, in places, are contiguous with myelin lamellae. Numerically increased and abnormal mitochondria and the absence of lysosomes were also reported (Wong et al.,

2000). In addition, in situ hybridization labeling of PLP mRNA in foamy oligodendrocytes appears more dense and extensive than in controls (Wong et al., 2000). On the basis of these data, it has been hypothesized that metabolic derangement of oligodendrocytes contributes to the myelin lesions (Wong et al., 2000). Fingerprint-like bodies have occasionally been observed in cells associated with myelin sheaths surrounding axons undergoing dissolution, which has been interpreted as a secondary phenomenon rather than storage material (van der Knaap et al., 1998; Wong et al., 2000). Positive staining for proliferation markers (MIB1/Ki67), antiapoptotic markers (survivin, bcl2), and proapoptotic markers (bac, bax, TUNEL, activated caspase-3) has been found in oligodendrocytes in several patients with variable combinations of immunoreactivity in different brain regions (Brück et al., 2001; van Haren et al., 2004). Collectively, these data suggest that conflicting proliferation, cell death, and survival signals affect oligodendrocytes in VWM (van Haren et al., 2004). It has been suggested that oligodendrocytic loss via apoptosis dominates in infants and younger children and, in general, in early lesion formation (Wong et al., 2000), whereas in older patients with long-standing disease, antiapoptotic mechanisms allow the proliferation of persisting oligodendrocytes, thus accounting for the striking increase in their numbers (van Haren et al., 2004).

Astrocytes in affected white matter are dysmorphic, with large blunt processes and often multiple nuclei (fig. 4C,D) (Prass et al., 2001; Fogli et al., 2002b; Rodriguez et al., 1999; Wong et al., 2000; van der Voorn et al., 2005; Schiffmann & Elroy-Stein, 2006; van Kollenburg et al., 2008). There is a reduction in the numbers of astrocytes with perivascular clustering in severe variants (Francalanci et al., 2001). In primary cell cultures from the brain of an individual with VWM, there were few GFAP+ astrocytes, generation of new astrocytes was compromised, and the few astrocytes generated showed an abnormal morphology and antigen phenotype (Dietrich et al., 2005). Similarly, RNA interference targeting of EIF2B5 compromised the induction of GFAP+ cells from normal human glial progenitors (Dietrich et al., 2005), raising the possibility that a deficiency in astrocytic maturation might contribute to abnormal white matter in VWM. In Cree leukoencephalopathy, numerous nests of atypical gliofibrillar cells are scattered throughout the white matter (Fogli et al., 2002b), a feature absent in classic VWM.

Except for a recently reported case in which there was a moderate reduction in the density of large diameter myelinated fibers in the absence of axonal degeneration and storage material in the Schwann cells (Federico et al., 2006), the sural nerve has been unaffected (van der Knaap et al., 1997).

Pathologic studies of extraneural tissues in VWM are limited, but the few available reports include ovarian dysgenesis (van der Knaap et al., 1997 & 2003; Boltshauser et al., 2002) and nonspecific findings in the liver (van der Knaap et al., 2003).

The neuropathologic literature since the 1960s includes several descriptions of patients who most probably were affected by VWM (Eicke et al., 1962; Watanabe & Muller, 1967; Girard et al., 1968; Macchi et al., 1968; Anzil & Gessaga, 1972; Deisenhammer & Jellinger, 1976; Gautier et al., 1984; Graveleau et al., 1985). The clinical pictures of these patients (including recognition of minor head trauma and febrile infections as possible provoking factors) largely overlaps with those of the more recently recognized adult-onset cases (Eicke, 1962; Watanabe & Muller, 1967; Girard et al., 1968; Macchi et al., 1968; Anzil & Gessaga, 1972; Gautier et al., 1984; Graveleau et al., 1985). The association of leukoencephalopathy with premature ovarian failure was also noted (Eicke, 1962). The only child in these reports presented with symptoms suggestive of classic childhood VWM (Deisenhammer & Jellinger, 1976). The main neuropathologic features in the earlier reported cases consisted of a sudanophilic leukodystrophy with large cavitations, increased density of oligodendrocytes, negligible myelin breakdown, and scanty astrogliosis. An increase in numbers of oligodendroglia was compared with tumors (Watanabe & Muller, 1967); lamellar fingerprint-like inclusions were noted in the oligodendrocytes from 2 patients (Gautier et al., 1984; Graveleau et al., 1985). Hypertrophic and atypical astrocytes around cystic cavities were described (Eicke, 1962; Watanabe & Muller, 1967). Although the authors of these reports provided accurate case descriptions, they did not recognize the cases as a single disease entity.

Pathophysiology

The basic defect of VWM resides in a protein complex, eIF2B, which is involved in the regulation of the first steps of protein synthesis (fig. 5) (Proud, 2001; Scheper et al., 2006 & 2007). It consists of 5 nonidentical subunits, α through ε. Subunit ε is catalytic, whereas subunits α through δ are regulatory (Price et al., 1996; Webb & Proud, 1997). The essential function of eIF2B is reflected by evolutionary conservation of the complex in eukaryotes (Dever, 2002). Yeast null mutant for each of the 5 subunits (except eIF2Bα) are not viable (Dever, 2002). Mutations that completely abrogate eIF2B activity are never observed in the homozygous state in VWM patients.

In eukaryotes, translation initiation is a multistep process, in which the interplay of the mRNA, initiator methionyl-tRNA (tRNAiMet), the ribosomal subunits, and several multiple translation initiation factors (eIFs), ensures start of the translation process at the AUG start codon of the mRNA (Proud, 2001; Scheper et al., 2007). One of the first steps in this initiation process involves the formation of a ternary complex consisting of tRNAiMet, eIF2 and GTP, which binds to the ribosome. On recognition of the start codon of the mRNA, the eIF2-bound GTP is hydrolyzed, and eIF2 is released in its inactive GDP-bound form. The coding information of the mRNA is then translated into a new protein, and finally, the ribosome dissociates from the mRNA and the newly synthesized protein is released. Active eIF2 must be regenerated by exchange of GDP for GTP to enable the formation of another ternary complex and initiate the synthesis of another protein. This GDP/GTP exchange is required for each round of translation initiation and is catalyzed by eIF2B (Dever, 2002). Thus, the eIF2B-catalyzed step is rate-limiting in translation initiation (Proud, 2001), that is, the step that governs the rate of global protein synthesis in a cell. The activity of eIF2B is tightly controlled by different mechanisms under diverse conditions (Hinnebusch, 2000). One of the main mechanisms involves phosphorylation of its substrate eIF2 on the α-subunit. In its phosphorylated form, eIF2 acts as a competitive inhibitor of eIF2B.

Inhibition of protein synthesis is part of the cellular stress response, a process aimed at enhancing cell survival under stress by preserving cellular energy and limiting the accumulation of denaturated proteins (Welch, 1992). A variety of cellular stresses, such as amino acid starvation, viral infection, iron deficiency, oxidative and ER stress, and thermal and mechanical trauma, lead to phosphorylation of eIF2α (Scheper et al., 1997; Duncan & Hershey, 1989; Petrov et al., 2001; Clemens, 2001; Harding et al., 2002). Phosphorylated eIF2 binds eIF2B and in that way inhibits the GDP/GTP exchange activity of eIF2B and, as a consequence, mRNA translation in general (fig. 5) (Rowlands et al., 1988; Krisnamoorthy et al., 2001).

The functional effect of VWM mutations on eIF2B activity has been investigated in different cell culture systems (Fogli et al., 2004b & 2006; Li et al., 2004; Richardson et al., 2004; van Kollenburg et al., 2006a; Kantor et al., 2005 & 2008). Frameshifts and nonsense mutations result in truncated polypeptides with a complete loss of function of the affected subunit and failure to form complexes with the other 4 subunits (Li et al., 2004; Richardson et al., 2004). Missense mutations confer only a partial loss of eIF2B function, which is either due to a decreased intrinsic GDP/GTP exchange activity or to an impaired structure or stability of the protein

eIF2/eIF2B holocomplex (Li et al., 2004; Richardson et al., 2004; Horzinsky et al., 2008).

In patient-derived lymphoblasts or fibroblasts, all mutations investigated reduce eIF2B activity by 20% to 70%. The severity of the decrease seems to correlate with the clinical severity, although inconsistently (Fogli et al., 2004b; Horzinsky et al., 2008 & 2009). Interestingly, in such cells, decreased eIF2B activity does not affect the rate of global protein synthesis, the regulation of protein synthesis during or after stress, or the ability of these cells to proliferate and survive (Li et al., 2004; van Kollenburg et al., 2006a; Kantor et al., 2005). Thus, it seems that basal eIF2B activity by itself cannot explain the disease.

To address this issue, several authors have investigated the hypothesis that the decreased eIF2B activity might impair the cellular stress response and improperly activate the unfolded protein response (UPR) (fig. 5).

The UPR is a compensatory intracellular signaling pathway that responds to accumulation of unfolded or denaturated proteins in the ER (Paschen, 2003; Liu & Kaufman, 2003; Schroder & Kaufman, 2005). Activation of this pathway restores cell homeostasis by reducing the rate of protein synthesis, abating the effects of ER stress, and promoting protein degradation. As part of the UPR, the pancreatic ER kinase is activated, resulting in phosphorylation of eIF2α and global inhibition of translation. Some mRNAs are exempt from inhibition through specific features in their 5' untranslated regions (Harding et al., 1999). One of these mRNAs encodes activating transcription factor 4 (ATF4), a transcription factor that leads to activation of numerous target genes, including C/EBP homologous protein (CHOP) and growth arrest and DNA damage protein 34 (GADD34) (Harding et al., 2000; Lu et al., 2004). The full efficiency of this process is essential because the balance between the UPR downstream effectors under stress conditions determines the ultimate fate of the cell, either (GADD34-mediated) survival and growth or (CHOP-related) cell cycle arrest and apoptosis (Novoa et al., 2001; Oyadomari & Mori, 2004). Decreased eIF2B activity in VWM would be expected to lead to a constitutive upregulation of ATF4 and its downstream effectors. This could be confirmed in the cerebral white matter of VWM patients (van der Voorn et al., 2005; van Kollenburg et al., 2006b) and cultured cells with VWM mutations (Kantor et al., 2005), which show activation of the UPR with increased activity of pancreatic ER kinase, phosphorylated eIF2α, ATF4, and CHOP. C/EBP homologous protein is known to further sensitize cells to ER stress (McCullough et al., 2001). In these cells, even minor stresses could further decrease eIF2B activity leading to

exaggerated expression of ATF4 and CHOP. Thus, VWM cells are innately predisposed and hyperreactive to stress (van der Voorn et al., 2005; Kantor et al., 2005).

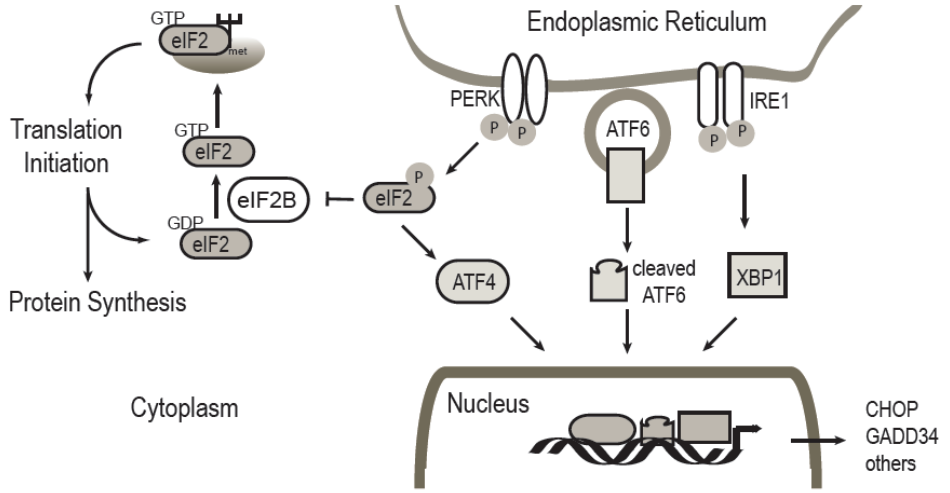

Figure 5. The physiologic role of eIF2B in translation initiation (left) and in the unfolded protein response (right). ATF4 indicates activating transcription factor 4; ATF6, activating transcription factor 6; CHOP, C/EBP homologous protein; eIF2B, eukaryotic translation initiation factor 2B; GADD34, growth arrest and DNA damage protein; PERK, pancreatic endoplasmic reticulum kinase; XBP1, X-box binding protein-1.

Vanishing white matter affects exclusively or predominantly the brain in which neurons are spared and the white matter is exclusively affected. Indeed, selective glial vulnerability is another major component of VWM pathophysiology. In VWM patients, it has been documented that activation of all 3 branches of the UPR is restricted to brain white matter (van Kollenburg et al., 2006b). Activation of the UPR was found to be most obvious in oligodendrocytes but was also observed in astrocytes (van Kollenburg et al., 2006b). In astrocytes, permanent upregulation of CHOP induces cell death by apoptosis in response to ER stress (Benavides et al., 2005). No signs of UPR activation were found in other brain cells, including neurons (van Kollenburg et al., 2006b). The selective activation of the UPR in glial cells has yet to be explained. It is possible that eIF2B expression in glial cells is

lower than that in other cells, such as lymphoblasts and fibroblasts. Alternatively, the ER load in astrocytes and oligodendrocytes could be higher than in other cell types, making them more vulnerable to conditions that predispose to ER stress (McCullough et al., 2001; Benavides et al., 2005). Another possible explanation is that glia-specific expression of ER stress target mRNAs is increased by decreased eIF2B activity, thereby affecting the balance between cell survival and cell death pathways under normal and stress conditions.

Concluding Remarks

Vanishing white matter is a fascinating, yet perplexing, disease. Its clinical, pathological, and molecular features are unique. It is the only brain disease recognized to date that involves a translation initiation factor, eIF2B. Although VWM is linked to housekeeping genes, the disease manifests primarily as a leukoencephalopathy. Within the white matter, oligodendrocytes and astrocytes are selectively involved. The insufficient myelin deposition and myelin loss seem to contradict the striking oligodendrocytosis. Astrocytes are dysmorphic and gliosis is insufficient to contain the severity of white matter damage, resulting in a remarkable degree of cystic cavitation. Several reports point to an aberrant activation of the UPR restricted to the macroglial cells. These findings suggest that the UPR plays an important role in VWM, but the pathophysiology of the disease remains poorly understood.

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