Delayed posthypoxic demyelination

Association with arylsulfatase A deficiency and lactic acidosis on proton MR spectroscopy

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Article abstract—Delayed demyelination is a rare and poorly understood complication of hypoxic brain injury. A previous case report has suggested an association with mild-to-moderate deficiency of arylsulfatase A. We describe a 36-year-old man who recovered completely from an episode of hypoxia related to drug overdose, and 2 weeks later progressed from a confusional state to deep coma. MRI showed diffuse white matter signal changes, and brain biopsy demonstrated a noninflammatory demyelinating process. Proton magnetic resonance spectroscopy revealed elevated choline and lactate and reduced N-acetyl aspartate signal in the affected white matter, consistent with demyelination and a shift to anaerobic metabolism. Arylsulfatase A activity from peripheral leukocytes was approximately 50% of normal, consistent with a "pseudodeficiency" phenotype. These findings confirm the hypothesis that relative arylsulfatase A deficiency predisposes susceptible individuals to delayed posthypoxic leukoencephalopathy and implicates lactic acidosis in the pathogenesis of this disorder.

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Delayed posthypoxic demyelination is a rare and poorly understood complication of hypoxic brain injury. In the original descriptions, comatose patients found after a hypoxic insult would regain consciousness within 1 to 2 days, only to relapse irreversibly into coma days to weeks later.[1,2] Concurrent histologic studies identified areas of pathology restricted to central white matter, with demyelination and relative axonal sparing.[1,2] Despite the scarcity of this complication, a retrospective analysis of 2,360 victims of carbon monoxide (CO) poisoning indicates that as many as 2.75% of patients suffer from delayed neurologic sequelae.[3] Although initially associated with CO intoxication, the syndrome may occur with hypoxia of any cause, including asphyxiation, cardiac arrest, and drug overdose. Its pathogenesis remains obscure.

The phenomenon of delayed posthypoxic demyelination spurs two intriguing questions. First, why is cerebral myelin damaged in the relative absence of other neuropathology? Hypoxia is a well-established mechanism of neuronal degeneration but less commonly targets myelin.[4] Second, what accounts for the delay in the leukoencephalopathy? A recent case report has proposed that "pseudodeficiency" of arylsulfatase A, with consequent dysfunction of myelin metabolism, could be a critical factor in predisposing some individuals to delayed demyelination after hypoxia.[5] In this report we describe a patient with delayed posthypoxic demyelination following a drug overdose, in whom proton magnetic resonance (MR) spectroscopy and lysosomal enzyme analysis were used to elucidate the pathogenesis of this disorder.

Case report. The patient is a 36-year-old man with a 20-year history of polysubstance abuse who was found by a family member lying face down in his bedroom, unconscious and cyanotic with shallow breathing. He was taken to a local hospital, where he was intubated for airway protection. Urine toxicology screen was positive for benzodiazepines, opiates, and amphetamines; respiratory arrest was attributed to an overdose of morphine sulfate. The patient awakened from coma after 48 hours, and thereafter his condition improved rapidly. He was discharged on hospital day eight after making a complete neurologic recovery.

On day 24 after the overdose, the patient began to behave strangely. His speech was idiosyncratic and bizarre. He became withdrawn, forgetful, and confused, attempting to open a car door with a quarter. The following day his behavior worsened. He developed persistent myoclonic jerks in his right thigh. He was unable to feed or dress himself, required the careful attendance of family members, and became incontinent. The patient refused to go to sleep without clutching the same quarter in his hand.

When he was readmitted on day 26 after the overdose, a repeat toxicology screen was negative, and serum electrolytes and blood counts were normal. The CSF contained 2 WBC and 249 RBC per mm^3 with normal protein and glucose. CSF cultures were negative. MRI revealed extensive bilateral hyperintensities on T2-weighted images throughout hemispheric white matter. Over the next 3
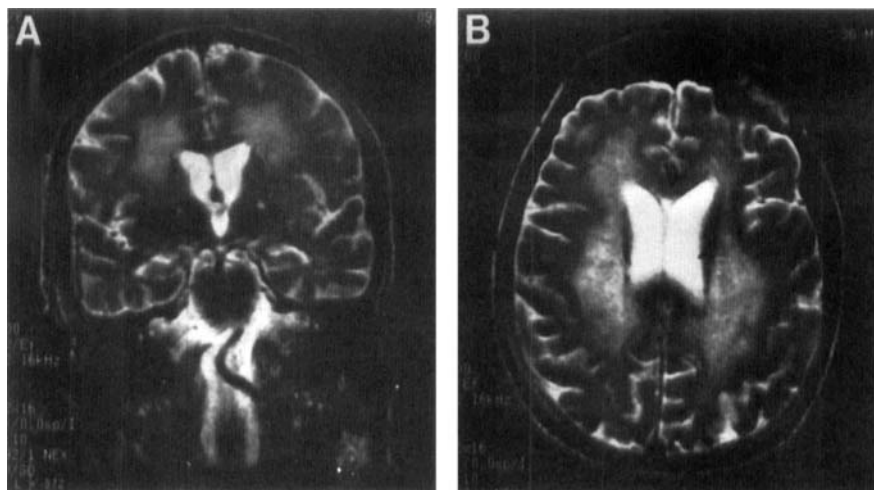
Figure 1. Coronal (A) and axial (B) T2-weighted MRI showing severe widespread demyelination of the corona radiata and centrum semiovale. Two discrete foci of increased T2 signal involving the globus pallidus are also evident in panel A.

days the patient became stuporous and developed spastic quadraparesis.

On day 34 after the overdose he was intubated and transferred to the Columbia-Presbyterian Neuro-ICU for further care. On admission, temperature was 101.4 °F, heart rate 140, blood pressure 132/70 mm Hg, and respirations 30 and labored. He was deeply comatose and profoundly diaphoretic, with severe spastic quadraparesis, spontaneous knee and ankle clonus, and flexion-withdrawal responses to noxious stimuli. Pupillary, oculocephalic, corneal, and gag reflexes were intact. Snout, palmomental, and glabellar reflexes were prominent. His hospital course was complicated by dysautonomia with central hyperventilation, paroxysmal tachycardia, and high fevers. MRI revealed widespread increased T2 signal changes throughout the deep hemispheric white matter, and bilateral 0.5-cm diameter foci of increased T2 and decreased T1 signal in globus pallidus (figure 1). Biopsy of the right anterior temporal lobe was performed on day 36

after the overdose to exclude acute disseminated encephalomyelitis. The specimen showed normal cortex, but widespread patchy demyelination with axonal sparing in the underlying white matter (figure 2). Immunohistochemical staining demonstrated numerous reactive astrocytes and macrophages scattered throughout the white matter, with no evidence of acute or chronic inflammation. Until the results of the biopsy were available, the patient was treated with high-dose methylprednisolone, without clinical effect. HIV-1 titers, heavy-metal screen, and CSF oligoclonal bands were negative.

Multisection ^{1}H magnetic resonance spectroscopic imaging (MRSI) was performed on day 65 after the overdose using a 1.5-T GE Signa scanner with a standard quadrature head coil (GE Medical Systems, Milwaukee, WI), according to the method of Duyn et al.[6] A section-interleaved spin echo sequence with octagonally tailored outer volume presaturation pulses was used to suppress fat signals from the scalp, skull, and calvarial marrow. Water suppression
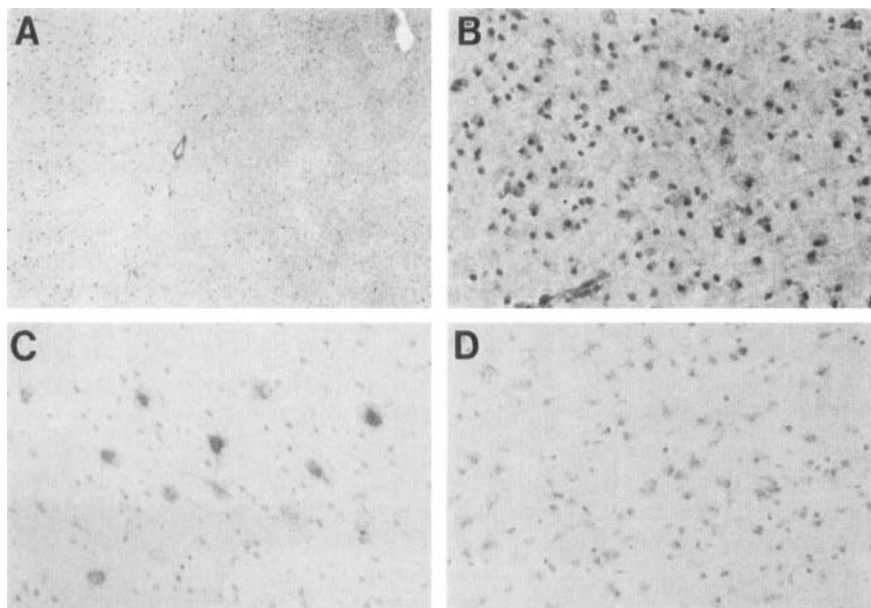
Figure 2. (A) Open brain biopsy sample demonstrates normal cortex (left); however, subcortical white matter (right) is hypercellular with patchy loss of myelin (Luxol Fast Blue/PAS, 4× magnification). (B) Hypercellular white matter with numerous gemistocytic astrocytes and macrophages. Although stain shows paucity of myelin, Bielschowsky stain (not shown) indicates relative preservation of axons (Luxol Fast Blue/PAS, 20× magnification). (C) Scattered gliofibrillar acidic protein (GFAP) positive, stellate shaped reactive astrocytes in white matter (GFAP immunostain, 20× magnification). (D) Numerous cells with cytoplasmic reactivity for MAC-1 (a macrophage marker) are found throughout white matter as a response to myelin loss/degradation (MAC-1 immunostain, 20× magnification). (All magnifications are before 14% reduction.)
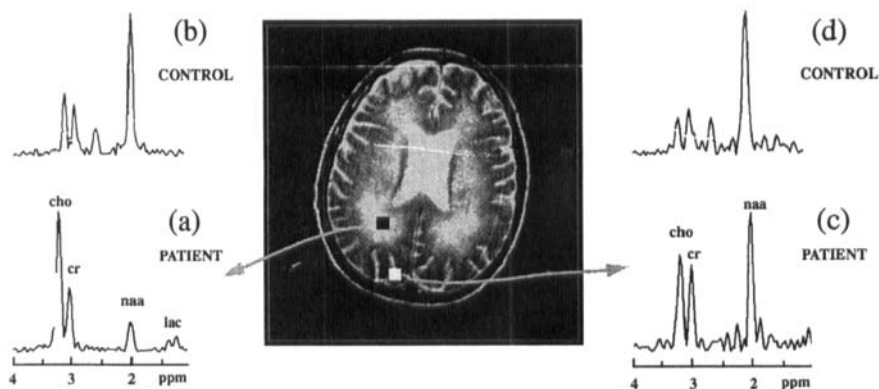
Figure 3. Representative ^1H MRSI spectra selected from volume elements in the periventricular white matter (a) and the occipital gray matter (c). For comparison, spectra obtained from corresponding locations in the brain of a normal volunteer are shown in panels (b) and (d). Note the lactate (lac) methyl peak at 1.33 ppm and the dramatic decrease of N-acetyl-aspartate (naa) (2.02 ppm) and increase of choline (cho) (2.23 ppm) in the white matter of the patient compared with control.

Although relative metabolite levels are also abnormal in the gray matter spectra of the patient compared with control, they are better preserved than in the white matter, and the lactate methyl peak is absent.

was achieved with a single chemical shift selective (CHESS) pulse followed by spoiler gradients. Four 15-mm brain sections, with 3.5-mm intersection gaps, were selected along the anterior commissure-posterior commissure line. MRSI data were recorded using a TE of 280 ms, a TR of 2,300 ms, a field of view of 240 mm, 32 × 32 phase-encoding steps with circular k-space sampling, and 256 points along the signal acquisition domain. The data were zero-filled once along the acquisition domain and then processed by standard fast Fourier transform algorithm. The nominal size of each of the resulting array of 32 × 32 volume elements was 0.84 ml (0.75 × 0.75 × 1.5 cm). Routine MR images were obtained to provide an accurate anatomic correlation of the MRSI images. Compared with the spectrum of a healthy age-matched volunteer, ^1H-MR spectroscopy of the deep hemispheric white matter of our patient showed reduced N-acetyl-aspartate (NAA), markedly elevated choline, and elevated lactate (figure 3). By contrast, these spectra were relatively normal throughout the gray matter of the cerebral cortex.

Blood was collected and the patient's cultured leukocytes were analyzed for leukodystrophies (Mayo Medical Laboratories, Rochester, MN). Arylsulfatase A activity was measured using an artificial substrate and determined to be 2.1 units/10^{10} cells, which is approximately 50% of normal activity (normal range >2.5 units/10^{10} cells). By contrast, enzymatic activities of hexosaminidase A, β-galactosidase, and galactosyl-ceramide β-galactosidase were normal, as were plasma levels of very long chain fatty acids and phytanic acid.

Three months after the overdose, the patient regained the ability to follow commands consistently. Six months after the overdose, he was alert and conversant but intermittently disoriented, with severe anterograde and retrograde amnesia. He had persistent spasticity with limited dexterity of the arms and legs but was able to walk with assistance. Percutaneous gastrostomy and tracheotomy tubes had been removed, although he remained unable to feed himself.

Discussion. Our patient's relapsing clinical course and radiologic findings are consistent with delayed posthypoxic demyelination.[1,2] In particular, the MRI signal abnormalities in deep hemispheric white matter and globus pallidus (see figure 1) closely overlap the distinctive histopathology described in previous

case reports of this disorder.[2] Brain biopsy confirmed the presence of noninflammatory demyelination of the deep white matter without neuronal or axonal involvement (see figure 2).

Although the pathologic hallmarks of delayed posthypoxic demyelination are well described, the pathophysiology of this disorder is poorly understood. Investigators initially believed that CO was directly myelinotoxic, but observation of the syndrome after a variety of hypoxic insults led to the consideration of other possibilities, including cerebral edema, vascular injury, and delayed-type hypersensitivity reactions.[1,2] Although researchers have successfully reproduced selective white matter injury in a number of animal models,[7-9] the underlying mechanism remains elusive.

Weinberger et al.[5] have proposed that an impairment of myelin metabolism might play a role in the pathogenesis of delayed posthypoxic demyelination. In their case report, a 34-year-old man who developed this disorder after a drug overdose was shown to have a reduction of arylsulfatase A activity to 10 to 30% of normal values. Arylsulfatase A is a lysosomal enzyme that is responsible for the hydrolysis of cerebroside sulfate and other sulfolipids (sulfatides) that comprise up up to 4% of myelin lipid in both the central and peripheral nervous systems. The sulfatides are anionic glycolipids that may be essential to membrane integrity and may participate as cofactors for the Na^+/K^+-ATPase and the GABA, serotonin, and opiate receptors.[10]

Complete absence of arylsulfatase A causes a lysosomal accumulation of sulfatide within oligodendrocytes and Schwann cells and disrupts myelin metabolism, resulting clinically in metachromatic leukodystrophy (MLD), a congenitally acquired disease that is inherited as an autosomal recessive trait.[10] A relative reduction of arylsulfatase A activity may occur in MLD heterozygotes but is more often found in healthy individuals in a condition called arylsulfatase A "pseudodeficiency," which is caused by allelic mutations of the gene that gives rise to MLD. This allele occurs commonly in the general population, with a frequency of up to 15%,[10] and contains a pair

of mutations (A to G transitions), one that causes loss of an N-glycosylation site, the other that disrupts a polyadenylation signal.[11] The enzymatic product of this mutated gene is catalytically intact, but is 3 to 4 kD smaller, underglycosylated, and more unstable than the normal protein. Despite these structural differences, the residual arylsulfatase A activity (between 10 to 50% of normal) is generally sufficient to prevent the accumulation of sulfatide, and carriers of this allele are asymptomatic.[10]

The identification of arylsulfatase A "pseudodeficiency" in a patient with delayed posthypoxic demyelination prompted Weinberger et al.[5] to speculate that this normally asymptomatic condition might predispose a small percentage of patients exposed to hypoxia to delayed white matter loss. The authors proposed that the suboptimal arylsulfatase A activity in these individuals would be unable to sustain an accelerated period of remyelination following the initial hypoxic injury; moreover, the persistent failure of myelin metabolism would gradually permit the accumulation of lysosomal sulfatides to toxic proportions, a hypothesis that would elegantly account for the paradoxical delay of demyelination.[5]

In this case report, we provide evidence for a second patient with delayed posthypoxic demyelination who was found to have a reduction of arylsulfatase A activity to approximately 50% of normal. This finding supports the idea that relative arylsulfatase A deficiency might predispose individuals to delayed leukopathy after hypoxic injury. We emphasize that while "pseudodeficiency" has not been directly linked to clinical symptoms, there is some evidence implicating relative arylsulfatase A deficiency in certain forms of neuropathology, including neuropsychiatric illness,[12] movement disorders,[13] multiple sclerosis,[14] and neurologic complications of alcoholism.[15]

The [1]H-MR spectrum derived from our patient (see figure 3) is consistent with a robust demyelinating process but differs from other white matter diseases in that a prominent lactate signal was identified. NAA, a neuron-specific marker,[16] was reduced in deep white matter and is indicative of neuronal loss, or conversely, of a gain of non-neuronal (NAA-negative) cells. This latter possibility seems likely, given the degree of reactive astrocytosis observed pathologically (see figure 2). Choline is a measure of membrane turnover and lipid metabolism,[16] and its elevation in our patient is consistent with demyelination, which was corroborated by pathologic examination. Proton MR studies of multiple sclerosis and lupus erythematosus involving the CNS have failed to identify elevated lactate in involved white matter.[17,18]

The spectral peak of lactate in our patient suggests a conversion of aerobic metabolism to anaerobic energy production and complements previous findings in cats, whereby the application of subtotal brain ischemia elicited a preferential increase of lactate in central white matter.[9] Either decreased energy substrate (e.g., hypoxia) or increased energy demands (e.g., neuronal stimulation or remyelination) may favor glycolysis and lactate production[19]; our patient's clinical course satisfies both of these conditions. Alternate explanations for the increase in lactate include reductions of cerebral blood flow or lactate sequestration within cellular elements that diminish its efflux from the brain.[19] The abundance of macrophages detected in deep white matter is consistent with this latter idea.

Is lactate more a cause or a consequence of the white matter deterioration? Using rats exposed to mitochondrial neurotoxins, Jenkins et al.[20] showed that the spectroscopic detection of lactate preceded evidence of neuronal lesions on T2-weighted MRI, implicating a causal role for lactate in the onset of neurodegenerative disease. It is intriguing to speculate that in the setting of relative enzyme deficiency, failure of oxidative metabolism might sufficiently disable arylsulfatase A activity to compromise myelin metabolism. The shift to glycolytic energy production and consequent reduction of ATP might interrupt a variety of cellular events essential to normal sulfatide turnover, such as lysosomal acidification, which may be critical to arylsulfatase A dimerization and function.[10] On the other hand, the presence of lactate per se might interfere with myelin turnover. For example, a number of anions behave as inhibitors of arylsulfatase A, including sulfate, phosphate, and fluoride[10]; it is possible that lactate anion might reduce sulfatide hydrolysis to a clinically significant level. Alternatively, the presence of lactic acid in the millimolar range might reduce local intracellular pH and impair arylsulfatase A activity. In this regard, it is notable that the activity of arylsulfatase A (in multiple sulfatase deficiency) is dramatically reduced at low pH.[10]

Further studies are necessary to elucidate the biochemical basis for delayed posthypoxic demyelination. With the presentation of a second case report of arylsulfatase A deficiency in a patient with this disorder, we hope that our findings will stimulate research in this area.

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The 5-year risk of MS after optic neuritis

Experience of the Optic Neuritis Treatment Trial

Optic Neuritis Study Group*

Article abstract—The objective of our study was to assess the 5-year risk of and prognostic factors for the development of clinically definite multiple sclerosis (CDMS) following optic neuritis. In a prospective cohort study design, 388 patients, who did not have probable or definite MS at study entry enrolled in the Optic Neuritis Treatment Trial between 1988 and 1991, and were followed for the development of CDMS. The 5-year cumulative probability of CDMS was 30% and did not differ by treatment group. Neurologic impairment in the patients who developed CDMS was generally mild. Brain MRI performed at study entry was a strong predictor of CDMS, with the 5-year risk of CDMS ranging from 16% in the 202 patients with no MRI lesions to 51% in the 89 patients with three or more MRI lesions. Independent of brain MRI, the presence of prior nonspecific neurologic symptoms was also predictive of the development of CDMS. Lack of pain, the presence of optic disk swelling, and mild visual acuity loss were features of the optic neuritis associated with a low risk of CDMS among the 189 patients who had no brain MRI lesions and no history of neurologic symptoms or optic neuritis in the fellow eye. The 5-year risk of CDMS following optic neuritis is highly dependent on the number of lesions present on brain MRI. However, even a normal brain MRI does not preclude the development of CDMS. In these patients with no brain MRI lesions, certain clinical features identify a subgroup with a particularly low 5-year risk of CDMS.

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The Optic Neuritis Treatment Trial (ONTT), funded by the National Eye Institute of the National Institutes of Health, assessed the efficacy of corticosteroids as treatment for optic neuritis. A secondary objective was to investigate the relationship between optic neuritis and MS. The cohort of patients who did not have MS at the time of study entry has now been followed for 5 years. After 2 years of follow-up we reported that MRI was a strong predictor of the early risk of MS and that treatment with intravenous followed by oral corticosteroids transiently reduced the rate of new MS attacks.[1] We now report the 5-year risk of MS, prognostic factors for the development of MS, and the degree of neurologic disability among the patients developing MS.

Methods. Fifteen clinical centers in the United States enrolled 457 patients between July 1, 1988, and June 30,

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