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The Syndrome of Delayed Post-Hypoxic Leukoencephalopathy

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Abstract

Delayed post-hypoxic leukoencephalopathy (DPHL) is a demyelinating syndrome characterized by acute onset of neuropsychiatric symptoms days to weeks following apparent recovery from coma after a period of prolonged cerebral hypo-oxygenation. It is diagnosed, after excluding other potential causes of delirium, with a clinical history of carbon monoxide poisoning, narcotic overdose, myocardial infarction, or another global cerebral hypoxic event. The diagnosis can be supported by neuroimaging evidence of diffuse hemispheric demyelination sparing cerebellar and brainstem tracts, or by an elevated cerebrospinal fluid myelin basic protein. Standard or hyperbaric oxygen following CO poisoning may reduce the likelihood of DPHL or other neurologic sequelae. Bed rest and avoidance of stressful procedures for the first 10 days following any prolonged hypoxic event may also lower the risk. Gradual recovery over a 3 to 12 month period is common, but impaired attention or executive function, parkinsonism, or corticospinal tract signs can persist. Stimulants, amantadine or levodopa may be considered for lasting cognitive or parkinsonian symptoms. Anticipation and recognition of DPHL should lead to earlier and more appropriate utilization of health care services.

Keywords

delayed post-anoxic leukoencephalopathy; delayed post-hypoxic encephalopathy; delayed neurologic sequelae; carbon monoxide

Introduction

Delayed post-hypoxic leukoencephalopathy (DPHL) is a rare condition that can occur following any event that causes a period of prolonged cerebral hypo-oxygenation. DPHL is important to recognize, as failure to do so could lead to unnecessary treatments or investigations, including brain biopsy. In the classic biphasic presentation, there is a full recovery from an obtunded or comatose state. This is typically followed days or weeks later by an acute onset of neuropsychiatric findings including disorientation, amnesia, hyper-reflexia, frontal release signs, parkinsonism, akinetic-mutism or psychosis. Magnetic resonance imaging (MRI) of the brain at this time often demonstrates diffuse demyelination involving white matter of the cerebral hemispheres, usually sparing the posterior fossa. However; the literature surrounding the DPHL is scant and exists only in the form of case reports and case series. Thus, the following review is based upon the authors' experience and a comprehensive review of the literature, where DPHL has also been referred to as "delayed post-anoxic leukoencephalopathy," "delayed post-anoxic encephalopathy", "delayed post-

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hypoxic encephalopathy", "and "delayed neurologic sequelae" of CO poisoning or other anoxic events.

Epidemiology

The exact incidence of DPHL is not known. Formal epidemiological studies have not been conducted due to the rarity of the condition. The earliest relevant epidemiologic study, a retrospective review of New York City hospital records from 1925-1935, found that 13 of 32 cases with neuropsychiatric sequelae of CO poisoning had a delayed onset (consistent with DPHL) [1]. The extremely low reported incidence of CO related neurologic sequelae (39 per 21,000) might have been due in part to the study design: only records of admission to mental hospitals for "psychosis due to drugs and other exogenous toxins" (carbon monoxide or natural gas) were reviewed in detail. It may also be related to the fact that, with the standard therapy at the time ("prone pressure artificial respiration and inhalation of 93% oxygen and 7% carbon dioxide"), mortality from CO poisoning was 33%. The United States case fatality rate declined by 2001 to only about 3% of non-fire related CO poisonings [2]. Thus, many individuals who would otherwise have succumbed (before advent of standard of care oxygen therapies) might still be at increased risk for delayed neurologic sequelae of CO. A 1982 prospective study of 2360 victims of CO poisoning in Korea found neurologic symptoms in 5.5% (129 cases), with delayed onset in 2.8% overall (65 cases) [3]. In these studies, between 1/3 to 1/2 of all neurologic sequelae of CO poisoning occurred in delayed fashion. There have been no studies of incidence for DPHL from other causes.

Clinical Features

History

A common key feature of all cases of DPHL is a preceding event with a suspected period of prolonged cerebral anoxia. The earliest and most extensively described cases of DPHL were caused by carbon monoxide (CO) poisoning [1,3]. Case series by Plum and Posner demonstrated a remarkably similar presentation in association with surgical anesthesia complications, cardiac arrest or asphyxial gas poisoning [4]. Subsequently, delayed leukoencephalopathy has been described in the setting of strangulation [5], hemorrhagic shock [6], and overdoses of opiates and/or benzodiazepines [7,8]. All of these events fit into one of three main categories defined by Plum and Posner [9]: anoxic anoxia (oxygen fails to reach the blood due to low environmental tension or pulmonary function), anemic anoxia (low oxygen carrying capacity of blood as in CO poisoning), or ischemic anoxia (failure of cerebral blood flow). In some instances, there can be a combination of factors. For example hemorrhagic shock would cause both anemic and ischemic conditions while heroin overdose could lead to both respiratory failure (anoxic anoxia) and critical hypotension (ischemic anoxia).

With the exception of cases preceded by CO poisoning, DPHL is always preceded by a period of unconsciousness [4,7,8,10-17]. About 10% of CO-associated cases may have no initial period of unconsciousness [3,18]. Patients usually recover within 24 hours, and in many cases return to work. This lucid interval usually lasts between 7 to 21 days, but the possible range is from 2 to 40 days [1,3,18]. One case of insidiously progressive cerebellar, upper motor neuron, parkinsonian symptoms and dystonia beginning several months after cardiac arrest was suggested to have been an atypical case of DPHL [10], however neuroimaging or neuropathological data (necessary to support this contention) were not reported. In all cases of DHPL, the lucid interval is followed by an abrupt onset of neuropsychiatric symptoms, which progress within days such that the patient becomes unable to attend to their typical daily needs.

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Clinical Findings

DPHL, as described by Lee and Marsden (the latter of who is commonly viewed as one of the founders of movement disorders as a neurologic subspecialty), classically conforms to one of two general categories of clinical presentation: parkinsonism or akinetic-mutism [19]. In addition to characteristic parkinsonian motor features (masked facies, rigidity, short stepped gait, tremor) dystonic posturing, agitation, apathy, hallucinations, or odd behaviors may also be present. All had extremely slow verbal responses with varying degrees of impaired cognition or emotional lability. Akinetic-mute patients were profoundly apathetic and developed functional bowel and bladder incontinence, minimal primitive responses to pain, and pathologic laughter or crying. From an anecdotal experience of one of the authors (DS) who cared for a patient of this type with DHPL following a methadone overdose, the history of major depression and presence of repetitive stereotyped behaviors (stereotypies) and rigidity might have been mistaken for catatonia, were it not for the classic MRI findings (discussed below) [17]. More severe symptoms, including quadriparesis and near-blindness, have been reported with more severe insults such as hemorrhagic shock or prolonged respiratory arrest during complications of anesthesia [6]. Common examination findings may include frontal release signs (eg, snout, glabellar) and corticospinal tract signs (hyper-reflexia, Babinski response). Early on, cognitive symptoms are so profound that detailed testing is difficult to obtain. During the course of rehabilitation, tests of frontal-executive function and intelligence can be useful.

Differential Diagnosis and Diagnostic Testing

There are no widely accepted formal criteria for diagnosis of DPHL, however it can be made with appropriate clinical history and supplemental testing provided alternative diagnoses have been ruled out. Depending upon individual circumstances, the differential diagnosis can be quite broad, particularly if circumstances surrounding the initial hypoxic event are unclear. Therefore, all potential causes of delirium relevant to the individual case need to be explored. In the setting of psychosis, fluctuating level of consciousness, or odd repetitive behaviors, EEG should be obtained to consider non-convulsive status epilepticus. Generalized delta range slowing, indicative of diffuse encephalopathy, can be seen in more than half of cases [18].

Serum analysis should be employed to rule out medical causes of both dementia and delirium. For example, uremic encephalopathy, parkinsonism related to liver failure and/or manganese neurotoxicity, or bismuth toxicity from overdose of over-the-counter sub-salicylate (“Peptobismal”) can all cause profound mental status changes [20-23]. Empiric testing should include complete blood counts and chemistries, B12, TSH, and toxicology studies. Among patients at high risk for B12 deficiency (potential abusers of inhaled nitric oxide, post-bariatric surgery patients, vegans), methymalonic acid level should also be measured. If any evidence of infection is noted blood cultures, chest x-ray and urinalysis should be performed.

In most cases, lumbar puncture to rule out encephalitis will be indicated. In keeping with established clinical guidelines, encephalitis is viewed as a potential symptom of increased intracranial pressure. Hence, neuroimaging (discussed below) should be obtained before proceeding, findings from which are typically very informative with respect to the likelihood of DPHL. Protein, glucose, cell count, bacterial cultures and herpes simplex virus polymerase chain reaction are routine for ruling out encephalitis. Myelin basic protein, a marker of acute widespread demyelination, can be a valuable test in considering suspected DPHL. In all three of our cases, we reported levels of greater than 40ng/ml (normal range in our lab was 0.07 to 4.1 ng/ml) [17].

Computed tomography (CT) is readily obtained in most community hospitals and is the initial imaging modality in the evaluation of persons presenting for evaluation of altered mental status,

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particularly when rapid imaging is required not only for diagnosis but also as a pre-requisite to lumbar puncture. Diffuse hypodensity of white matter, particularly if unexpected (for example in a younger individual) can be strongly suggestive of acute demyelination. Prior scans for comparison (such as those at initial presentation) can be confirmatory if they demonstrate that the more recent finding is new. Otherwise, supplemental magnetic resonance imaging (MRI) with diffusion weighted imaging (DWI) sequences may be necessary.

The MRI findings of DPHL are nearly pathognomonic. Among individuals with this condition, diffuse hyperintensity of cerebral white matter will be present on T2-based sequences, particularly in the region of the dorsal frontal and parietal lobes known as the centrum semiovale. In contrast, posterior reversible encephalopathy syndrome usually has a predilection for the white matter regions supplied by posterior cerebral arteries. Inhaled heroin, in reports, can cause spongiform leukoencephalopathy that is associated with a pattern of T2 hyperintensity involving dorsal hemispheric white matter, posterior limb of the internal capsule, cerebellum, and brainstem corticospinal tracts. It characteristically spares the ventral frontal and temporal lobar white matter, anterior limb of the internal capsule, and cerebellar dentate nuclei [24-27].

The predictive value of early neuroimaging on DPHL is uncertain. One reported case had mild T2 hyperintensity of white matter within the first 24 hours following the hypoxic event (drug overdose), becoming more pronounced following onset of neuropsychiatric symptoms [28]. MRI with diffusion weighted imaging (DWI) sequences can clarify extent of brain injury and hence provide some prognostic information. An apparent diffusion coefficient (ADC), calculated from the T2-based DWI sequence, is used to create an image that reflects the rate of diffusion of water molecules. Neuronal death under hypoxic conditions is accompanied by a failure of ATP-dependent ion channels. The resulting loss of ion gradients and translocation of water from extracellular to intracellular compartments causes restricted movement of molecules. This is reflected as a low ADC, known as “diffusion restriction” [29]. Abnormalities in deep grey matter structures are common in CO poisoning. Globus pallidus, which exists at arterial border zones is usually affected, but thalamus or midbrain can also be involved. T2 hyperintensity and diffusion restriction (reflecting cytotoxic edema) in these grey matter regions appears within 48 hours after the initial hypoxic insult [30,31]. Similar to cytotoxic edema following a stroke [32], this early diffusion restriction usually resolves within 7-10 days. Restricted diffusion in white matter has a different origin, because axons and oligodendroglia are largely spared in DPHL [4,15]. ADC in affected white matter gradually declines, reaching a nadir at about 7 weeks [33-35]. More data is required to confirm, but it appears that homogeneous prolonged restriction may portend a worse prognosis than patchy restriction with early resolution [17,36].

There are potential explanations for the longer duration of diffusion restriction of cerebral white matter in DPHL. First, it may be due to trapping of water molecules within areas of defective myelin (dysmyelination.) Persistent diffusion restriction of the same white matter tracts is seen with metachromatic leukodystrophy (MLD) [37]. MLD is a progressive leukodystrophy in which autosomal recessive deficiency of arylsulfatase-A (an enzyme required for metabolism of sulfatides in myelin turnover) causes dysmyelination. Second, oligodendrocyte apoptosis or other inflammatory changes have been proposed to occur [33].

While clinical history and distribution of white matter changes are generally sufficient to make a diagnosis of DPHL once alternative differential diagnoses have been excluded, MR-spectroscopy (MRS) and diffusion tensor imaging (DTI) are of interest for purposes of research. The classic finding on MRS is a choline peak which indicates increased lipid turnover (as seen in acute demyelination) [12,17]. A fall in the neuronal marker n-acetyl-aspartate may reflect a gain of non-neuronal cells (astrocytes and macrophages) known to occur [15]. An elevated

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lactate peak, suggesting a shift from aerobic to anaerobic metabolism within affected white matter, has also been reported [15,38]. DTI has shown that severe disruption of axonal function and structural integrity in these regions gradually resolves over a period of 5 months [15].

DPHL can generally be diagnosed when the clinical history, laboratory assessments, and neuroimaging features are concordant with those described above. Alternative diagnoses should be considered if white matter lesions are non-continuous, enhancing, extend to overlying cortex, and are accompanied by seizures or constitutional symptoms. In rare circumstances, brain biopsy may be necessary in order to guide therapy if alternate diagnoses such as progressive multifocal leukoencephalopathy, neoplasm, or autoimmune phenomena (such as CNS vasculitis or acute disseminated encephalomyelitis) are suspected.

Pathophysiology

The pathophysiology of DPHL had not been delineated fully. CO or heroin may be directly myelinotoxic, yet DPHL from these exposures is remarkably similar to that from other forms of anoxia. Inhaled heroin (“chasing the dragon”) causes a spongiform leukoencephalopathy can present in delayed fashion [39], but differs in both neuroimaging and neuropathologic characteristics from DPHL [39]. This route is unique in that it is the only method that involves heating of the heroin (to inhale the vapor), and thus a toxin formed from impurities or the heroin itself may be involved. Heroin overdose by IV route [40] or due to rupture of container in a “drug mule/carrier” [41] can cause rapid onset of coma and diffuse cerebral edema. Duration of obtundation (or respiratory arrest) is rarely clear in these cases, and so it is unclear whether neurotoxicity from heroin or other impurities in addition to hypoxia alone is involved. Overdose of heroin or other narcotics causes severe respiratory suppression and consequent vasodilation and hypotension. Hence hypoxemia and cerebral hypoperfusion are sufficient to cause DPHL without a specific toxic mechanism.

CO is known to impair tissue oxygenation due to tight binding of hemoglobin than oxygen. However; additional toxicity may be a factor that causes DPHL to be more common after CO poisoning, even in cases with no loss of consciousness. CO is known to bind and inhibit function of cytochrome oxidase (an enzyme essential for aerobic respiration). DPHL can be reproduced in animals using injections of potassium cyanide, which impairs cellular respiration through binding of cytochrome c. Therefore, it may be that the myelinotoxicity of CO exposures is mediated in part by impairment of ATP-dependent enzymes responsible for myelin turnover.

It has thus been suggested that pseudodeficiency of arylsulfatase-A, an enzyme essential for the turnover of myelin, predisposes to DPHL. In metachromatic leukodystrophy, an autosomal recessive disorder due to very low production of arylsulfatase-A, there is a progressive leukodystrophy which is associated with a diffuse pattern of cerebral white matter restriction on DWI MRI. This restriction is thought to be the result of dysmyelination [37]. In other words, water protons become trapped within pockets of abnormal myelin, resulting in DWI abnormalities throughout the white matter. While we and others have reported cases of DPHL with normal arylsulfatase-A levels [11,16,17,28], genetic variability in other enzymes important for myelin turnover has yet to be explored. If any of these enzyme systems can be disrupted by a period of cerebral hypoxia, then the resulting demyelination would be expected to have a delayed presentation.

Common to all known causes of DPHL is the potential to cause a prolonged period not just of impaired oxygenation, but also of vasodilatation and/or hypotension. Cerebral white matter is supplied primarily by widely spaced arterioles with few anastomoses and thus may be less able than grey matter or posterior fossa to compensate for hypoxia or hypoperfusion [42]. The fact that age is a risk factor for both vascular disease and DPHL may thus be closely related. Both cases with low arylsulfatase-A levels, but none in the large post-CO cases series, were under

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age 36. Thus, a combination of genetic and age-associated vascular risk factors could be responsible in most cases.

Another possible explanation for DPHL, and one that is not mutually exclusive to the others, is that oligemia and/or hypo-oxygenation restricted to hemispheric white matter may result in delayed apoptosis of the oligodendrocytes responsible for myelin production [36]. Oligodendrocytes are uniquely vulnerable to glutamate-induced excitotoxicity [43]. ATP depletion may lead to release of glutamate from oligodentrocytes and axons, which in turn triggers calcium influx and a further apoptotic cascade. Thus, a moderate but prolonged period of reduced cerebral blood flow or oxygenation could cause disruption of ATP production sufficient to trigger death of oligodendrocytes in hemispheric white matter. Finally, inflammatory responses to damaged myelin, or other effects of CO or hypoxemia may have a role. Rodent models of CO poisoning show increased brain microglial activation [44], and tissue studies from DPHL victims are similarly interesting.

Neuropathology

Plum and Posner reported autopsy findings of severe diffuse demyelination, which only partially spared the subcortical ‘U’ fibers. Tissue examination demonstrated the presence of reactive astrocytes and lipid laden macrophages within affected areas [4]. In a separate report, open brain biopsy performed in a drug-overdose DPHL case revealed patchy loss of myelin in subcortical white matter. The involved regions had similar hypercellularity due to infiltration by gemistocytic (swollen, reactive) astrocytes and macrophages [15]. In all cases, the axons and oligodendrocytes were preserved, and no vacuolar edema (such as that reported from inhaled heroin) [24,39] was present to suggest direct damage to the myelin.

Prognosis

The likelihood of recovery appears to be inversely related to the age of the patient. A prospective study of 86 post-CO cases of DPHL found that the mean age of those recovered within one year was 10 years younger than those who did not. Most improved within 3 to 6 months (mean 4.2 months) [18]. Some cases have been reported with a biphasic course that had severe decompensation with fatal outcomes [4]. A majority of those who survive the initial rehospitalization period demonstrate significant recovery [3], yet most have at least some lasting cognitive deficits or other neurologic signs [4,11,17,28,45,46]. Lasting deficits in frontal-executive functions such as attention, mental flexibility or alternating responses, working memory and control of emotions (temper) are most common.

Treatment and future directions

Early Supportive Care

Supportive care is the mainstay of treatment during the first two weeks after the neuropsychiatric symptoms of DPHL begin. For cases that rapidly progress to coma, there is no known treatment to reverse the course. Based upon evidence for microglial inflammation in DPHL (discussed above), immunotherapy (with steroids and plasmapheresis) was tried, unsuccessfully, in a rapidly fatal case associated with drug overdose.

Rehabilitation

As with the care of persons with other demyelinating syndromes, rehabilitation is an integral component of the care process and is appropriate to initiate as soon as the patient becomes able to participate in rehabilitation therapies. These interventions, including physical therapy, occupational therapy, speech therapy, recreation therapy, and (when necessary) respiratory therapy should assess the patient's functional status and integrate information derived from

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neurorehabilitation assessment to develop treatment goals. Ideally, these goals are individualized to target specific neurological impairments in the service of improving the patient's functional abilities. When remediation of impairments is not possible or fails to occur, the development and implementation of compensatory strategies is prudent and adjustment of the type and/or schedule of post-DPHL roles (e.g., at home, at work, interpersonally and socially) may be necessary.

Cognitive symptoms

Clinical trials data are not available to guide treatment of cognitive symptoms in DPHL. However, an “n of 1” trial design may identify benefits from treatments of relatively low risk to an individual patient. For example, a double-blind placebo controlled trial of donepezil with a 6-week washout period was conducted for a patient with fixed amnesic syndrome attributable to history of CO poisoning. It was determined that donepezil 5 mg per day did not improve this problem and long term treatment was avoided [47]. Nonetheless, acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine, dimebolin) may still be worthy of study for cognitive sequelae of DPHL in other patients, including those who develop this syndrome after other (non-CO) hypoxic-ischemic brain injuries. Given that cognitive deficits attributable to the subcortical pathology of DPHL frequently can include impairment of attention and working memory [17,28], stimulant medication (methylphenidate, dextroamphetamine, modafanil) would also be rational for study. Amantadine has shown promise for treatment of these frontal-subcortical deficits in association with traumatic brain injury [48], and thus (along with other n-methyl-daspartate antagonists such as memantine) could also be considered in DPHL. In one DPHL case report, persistent DHPL-induced impairments in attention and executive function improved during treatment with amantadine, declined after self-discontinuation of this agent, and improved again following resumption of this therapy [28].

Parkinsonism

Parkinsonian symptoms such as tremor or rigidity may also benefit from treatment with amantadine, particularly if this agent is used to treat concomitant cognitive deficits. Levodopa and anticholinergics have generally had unclear benefit in post-CO parkinsonism [19], but could still be considered. At least one case report exists of dramatic benefit from levodopa for pain associated with parkinsonism due to post-MI DPHL [13]. Given the potential for exacerbation or induction of parkinsonism in DPHL, symptoms of hallucinations, delusions, or even nausea should generally not be treated with dopamine blocking agents.

Prevention

Preventive therapy against DPHL and other neurologic sequelae is most relevant concerning CO poisoning. Oxygen is a commonly employed treatment to lessen neurologic complications of CO, but there has been considerable debate about whether hyperbaric oxygen therapy (HBT) is more effective than normobaric (100% oxygen by face mask) therapy (NBT) in this regard. Though NBT results in normalization of carboxyhemoglobin levels, HBT may provide better elimination of CO from brain mitochondrial cytochrome c oxidase [49]. It also may inhibit carbon monoxide-induced brain lipid peroxidation and microglial proliferation [50,51]. Thus HBT could mitigate processes such as ATP depletion and inflammatory response implicated in DPHL. The first-double blind sham controlled placebo controlled trial of HBT for acute CO poisoning (191 subjects) actually showed potential harm from the procedure; all 5 of the delayed neurologic syndromes in this trial occurred in the treatment group ($p=0.03$). It was complicated by a 46% drop-out rate, and there was concern that continuous 100% face mask oxygen delivered between treatments over the 3 to 6 days of the study could have been neurotoxic [52]. A double-blind sham-controlled clinical trial of 152 subjects did show significantly lower 6-week incidence of neuropsychiatric symptoms after HBT vs. NBT.

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(Essentially all confirmed cases of DPHL have occurred within 40 days, and hence this was the primary outcome measure.) Guidelines from the American College of Emergency Physicians (ACEP) on Clinical Policies Subcommittee on Critical Issues in the Management of Adult Patients are drawn from a review of these as well as several other less rigorously designed studies. They state that risk-benefit ratio for use of HBT should be carefully considered in individual cases of CO poisoning, but the evidence base is insufficient to mandate HBT in these guidelines [53]. Risks of HBT to consider include ear barotrauma, claustrophobia, seizures [52,54] and those associated with transfer of an unstable patient to the hyperbaric facility.

Electroconvulsive therapy (ECT) is sometimes considered for refractory depression following a suicidal attempt with CO poisoning or drug overdose. One such case was reported with onset of DPHL after a series of ECT treatments [42]. The patient experienced very poor outcome, with persistence of amnesia, mutism, parkinsonism years later. While she also had an underlying anemia which might have predisposed to a poor outcome, the authors wondered whether the increased metabolic demands on damaged white matter posed by ECT could have been partly responsible. They suggested that, in addition to optimal medical management of acidosis or electrocardiographic abnormalities, bed rest for 2 to 4 weeks after CO poisoning and avoidance of ECT might minimize risk of DPHL. Plum and Posner also recommended 10 days of empiric bed rest following any severe hypoxic event. The evidence to support their recommendation is purely anecdotal, but intuitive. They managed 100 consecutive hypoxic-ischemic injury patients, and the only one who developed DPHL had been out of bed (to chair) by day 6 after the event [4].

Future Directions

Clinical trials design to identify a treatment that alters the prognosis of DPHL or outcome of rapidly progressive forms may not be practical. While there is clearly equipoise about the role of HBT for CO poisoning, those who completed the positive trials now view it as standard of care and might have ethical objections to repeating them. Future research should also explore the prognostic value of specific neuroimaging measures, myelin basic protein, or arylsulfatase-A levels. It is also of interest whether DPHL may occur due to a failure of oligodendrocyte resistance to hypoxic/ischemic injury [43]. Most importantly, education of clinicians about this well-characterized syndrome will lead to early diagnosis and appropriate tailoring of treatment.

Conclusion

Clinicians should be aware of the variety of presenting neurologic symptoms of DPHL. We expect that more cases of this condition will be diagnosed with the expanding availability of MRI. This rare but potentially devastating post-hypoxic demyelinating syndrome has been recognized clinically for nearly a century, and should not be a “medical mystery” to the average clinician. With prompt recognition of DPHL, appropriate supportive care and rehabilitative services can effectively be utilized.

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