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The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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SYSTEMATIC REVIEWS

Spectrum of delayed post-hypoxic leukoencephalopathy syndrome: A systematic review

Bahadar S Srichawla, Maria A Garcia-Dominguez

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Abstract

BACKGROUND

Delayed post hypoxic leukoencephalopathy syndrome (DPHLS), also known as Grinker's myelinopathy, is a rare but significant neurological condition that manifests days to weeks after a hypoxic event. Characterized by delayed onset of neurological and cognitive deficits, DPHLS presents substantial diagnostic and therapeutic challenges.

AIM

To consolidate current knowledge on pathophysiology, clinical features, diagnostic approaches, and management strategies for DPHLS, providing a comprehensive overview and highlighting gaps for future research.

METHODS

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes guidelines, we systematically searched PubMed, ScienceDirect and Hinari databases using terms related to delayed post-hypoxic leukoencephalopathy. Inclusion criteria were original research articles, case reports, and case series involving human subjects with detailed clinical, neuroimaging, or pathological data on DPHLS. Data were extracted on study characteristics, participant demographics, clinical features, neuroimaging findings, pathological findings, treatment, and outcomes. The quality assessment was performed using the Joanna Briggs Institute critical appraisal checklist.

RESULTS

A total of 73 cases were reviewed. Common comorbidities included schizoaffective disorder, bipolar disorder, hypertension, and substance use disorder. The primary causes of hypoxia were benzodiazepine overdose, opioid overdose, polysubstance overdose, and carbon monoxide (CO) poisoning. Symptoms frequently include decreased level of consciousness, psychomotor agitation, cognitive decline, parkinsonism, and encephalopathy. Neuroimaging commonly revealed diffuse T2 hyperintensities in cerebral white matter, sometimes involving

the basal ganglia and the globus pallidus. Magnetic resonance spectroscopy often showed decreased N-acetylaspartate, elevated choline, choline-to-creatinine ratio, and normal or elevated lactate. Treatment is often supportive, including amantadine, an antioxidant cocktail, and steroids. Hyperbaric oxygen therapy may be beneficial in those with CO poisoning. Parkinsonism was often treated with levodopa. Most of the patients had substantial recovery over the course of months and many cases had some residual neurocognitive deficits.

CONCLUSION

DPHLS remains a complex and multifaceted condition with various etiologies and clinical manifestations. Early recognition and appropriate management are crucial to improving patient outcomes. Future research should focus on standardizing diagnostic criteria, using advanced imaging techniques, and exploring therapeutic interventions to improve understanding and treatment of DPHLS. Conducting prospective cohort studies and developing biomarkers for early diagnosis and monitoring will be essential to advance patient care.

Key Words: Delayed post hypoxic leukoencephalopathy syndrome; Anoxic encephalopathy; Delayed post hypoxic leukoencephalopathy; Hypoxic-ischemic brain injury; Grinker's myelinopathy; Toxic leukoencephalopathy; Toxic leukoencephalopathy; Delayed postanoxic encephalopathy; Carbon monoxide poisoning

Core Tip: Delayed post hypoxic leukoencephalopathy syndrome (DPHLS) manifests days to weeks after a hypoxic event, presenting with neurological and cognitive deficits. This systematic review consolidates current knowledge on DPHLS, highlighting the complexity of its pathophysiology and the challenges in diagnosis and treatment. Common causes include benzodiazepine and opioid overdose, and carbon monoxide (CO) poisoning. Neuroimaging typically shows diffuse T2 hyperintensities in cerebral white matter sometimes involving subcortical structures such as the basal ganglia and thalamus. Early recognition and supportive management are crucial. Hyperbaric oxygen therapy may be beneficial in CO poisoning.

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INTRODUCTION

Delayed post hypoxic leukoencephalopathy syndrome (DPHLS), also known as Grinker's myelinopathy, is an intriguing and often under-recognized neurological condition that typically manifests after a latent period following a hypoxic event. This syndrome is characterized by delayed onset of neurological and cognitive deficits, often presenting several days to weeks after the initial hypoxic insult[1]. Despite its rarity, DPHLS poses significant diagnostic and therapeutic challenges due to its unpredictable course and diverse clinical manifestations[2]. Hypoxic events, such as cardiac arrest, carbon monoxide (CO) poisoning, and prolonged hypotension, can result in various forms of brain injury. Although the immediate consequences of such events are well documented, the delayed effects on the brain's white matter, leading to DPHLS, remain less understood. The pathophysiology of DPHLS involves a complex interplay of factors, including demyelination, inflammatory responses, and metabolic disturbances, which ultimately leads to altered neuronal communication[3].

The clinical spectrum of DPHLS is broad, ranging from mild cognitive impairment to severe neuropsychiatric disturbances and motor dysfunction[4]. This variability in presentation often leads to misdiagnosis or delayed diagnosis, complicating patient care and prognosis. Neuroimaging, particularly magnetic resonance imaging (MRI), plays a critical role in the identification and characterization of white matter changes associated with DPHLS, but there is a paucity of standardized diagnostic criteria[5]. Typically, confluent hyperintensities involving the centrum semiovale are observed in T2-weighted fast spin echo and T2-fluid attenuated inversion recovery (T2-FLAIR). Given the critical need for increased awareness and understanding of DPHLS, this Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guideline directed systematic review aims to consolidate current knowledge on the pathophysiology, clinical characteristics, diagnostic approaches, and management strategies for DPHLS. By synthesizing data from various studies, we seek to provide a comprehensive overview of this syndrome, highlight gaps in the existing literature, and propose directions for future research. Through this review, we hope to enhance the recognition and treatment of DPHL, ultimately improving outcomes for affected individuals.

MATERIALS AND METHODS

This systematic review will be conducted in accordance with the PRISMA guidelines[6]. The review protocol will be preregistered on the International Prospective Register of Systematic Reviews to ensure transparency and methodological rigor (CRD42024550991).

Three electronic databases will be systematically searched: PubMed, ScienceDirect, and Hinari. The search strategy will include terms related to delayed post-hypoxic leukoencephalopathy, hypoxic brain injury, and white matter damage. The following keywords and Medical Subject Headings terms will be used: 'Delayed post-hypoxic leukoencephalopathy', 'Grinker's myelinopathy', and 'delayed encephalopathy' (Table 1).

Inclusion and exclusion criteria

Studies will be included if they meet the following criteria: (1) Original research articles, case reports, and case series; (2) Studies involving human subjects diagnosed delayed post-hypoxic leukoencephalopathy; (3) Articles published in English; and (4) Studies demonstrating detailed clinical, neuroimaging, or pathological data on DPHLS.

Studies will be excluded if they meet the following criteria: (1) Reviews, editorials, conference abstracts, and animal studies; and (2) Studies not related to DPHL or without sufficient clinical or radiographic data (Figure 1).

Study selection

Two independent reviewers (Srichawla and Garcia-Dominguez) will screen the titles and abstracts of all articles retrieved for relevance. Full-text articles will be obtained for all potentially eligible studies and will be assessed for inclusion based on the predefined criteria. Any discrepancies between the reviewers will be resolved through discussion and a third reviewer will be consulted if necessary.

Data extraction

A standardized data extraction form will be used to collect the following information from each included study: (1) Study characteristics (author, year, country, study design); (2) Characteristics of the participants (age, sex, underlying cause of hypoxia); (3) Clinical features (symptoms, time of onset); (4) Neuroimaging findings; (5) Pathological findings; and (6) Treatment and results.

Quality assessment

The quality of the included studies will be assessed using the Joanna Briggs Institute (JBI) critical evaluation checklist for case reports and case series. Two reviewers (Srichawla and Garcia-Dominguez) will independently assess the quality of each study, and disagreements will be resolved through discussion.

Statistical analysis

Data will be synthesized descriptively due to the anticipated heterogeneity in study designs, patient populations, and outcome measures. A narrative synthesis will be provided, summarizing key findings related to the epidemiology, pathophysiology, clinical characteristics, diagnostic approaches, and DPHL management strategies. Where possible, data will be presented in tables and figures to facilitate comparison between studies.

Ethical considerations

As this study involves the synthesis of previously published data, no ethical approval is required. However, the review will be conducted in accordance with ethical guidelines for systematic reviews, ensuring transparency, objectivity, and reproducibility.

RESULTS

A total of 74 cases were procured and summarized in Table 2[7-55]. Of those with the gender recorded, 30 occurred in men and 15 in women. The most common reported comorbidities included schizoaffective disorder, bipolar disorder, depression, hypertension, hyperlipidemia, substance use disorder, and hepatitis C.

The most common causes of hypoxia are benzodiazepine overdose, opioid overdose, polysubstance overdose, and CO poisoning. Other lesser reported causes included cervical spinal cord injury, severe acute respiratory syndrome-coronavirus 2, acute respiratory distress syndrome, asphyxiation, unilateral internal carotid artery occlusion, traumatic brain injury, ethanol abuse, cardiopulmonary arrest, and myocardial infarction. Symptoms often reported included 13 decreased level of consciousness, 14 psychomotor agitation (*e.g.*, akinetic mutism, *etc.*), 7 cognitive decline, 1 Anton-Babinski syndrome, 3 catatonia, 13 encephalopathy. Other reported symptoms included aphasia, malignant catatonia, hyperreflexia, rigidity, clonus, parkinsonism, pseudobulbar affect, and choreoathetosis. The onset of symptoms ranged from a few days to around 60 days after hypoxia, with many cases showing symptoms around 14-30 days.

The most common neuroimaging findings included: The 44/72 diffuse increase in T2 signal throughout the cerebral white matter, 4 basal ganglia, 1 thalamus, and 5 pallidus globus. The case by Jang and Kwon[27] had a completed diffusion tensor tractography showing dysconnectivity between the ascending reticular activating system, the basal ganglia, and the thalami. Jingami *et al*[29] completed N-isopropyl-(123I)-p-iodoamphetamine SPECT imaging showing hypoperfusion involving the frontal lobe. The case by Meyer[36] had a complete magnetic resonance spectroscopy (MRS)

Table 1 Databases queried as well as respective search string

Database	Search string
PubMed	("Delayed post-hypoxic leukoencephalopathy" OR "delayed encephalopathy ") AND ("human" OR "case report" OR "case series")
ScienceDirect	("Delayed post-hypoxic leukoencephalopathy" OR "delayed encephalopathy") AND ("human" OR "case report" OR "case series")
Hinari	("Delayed post-hypoxic leukoencephalopathy" OR "delayed encephalopathy") AND ("human" OR "case report" OR "case series")

showing an increase in creatinine and choline signals. The case of Gottfried *et al*[20] (1994) demonstrated a decrease in N-acetylaspartate (NAA), elevated choline, and lactate. Betts *et al*[11] reported a case series of 3 patients. MRS demonstrated a decrease in NAA, an elevated choline-to-creatinine ratio, and normal lactate within cerebral white matter. One case had diffuse cerebral atrophy, one follow-up imaging nine months later.

Newburn *et al*[39] (2024) presented a case series of two patients who showed increased signal intensity at divided subtracted inversion recovery (dSIR). In the case series by Zamora *et al*[54], all cases had confluent cerebral white matter hyperintensities involving the centrum semiovale and two cases had associated diffusion restriction. Furthermore, histopathological evaluation of case 5 from the Zamora *et al*[54] case series showed significant loss of myelin, axonal swelling, and reactive astroglia with a sparing of the U fibers. Other cases reported nonspecific lesions involving subcortical structures, including the basal ganglia and the thalamus.

The 20 cases had a decreased apparent diffusion coefficient signal consistent with cytotoxic edema or ischemia, most frequently involving: The 10 cerebral white matter, 4 globus pallidus, 1 basal ganglia and thalamus. There was at least one case of cerebral microbleeds on susceptibility-weighted imaging. Only a few cases showed contrast enhancement. When an electroencephalogram was performed, it often showed diffuse slowing, polymorphic delta activity involving the frontal region, diffuse delta activity, and paroxysmal epileptiform activity. Cerebrospinal fluid studies when completed were often normal. There were few reported cases of elevated myelin basic protein and elevated protein.

The complications reported included herniation syndromes from elevated intracranial pressure, sympathetic hyperactivity after a trial of electroconvulsive therapy (ECT), and mechanical ventilatory and/or hemodynamic support. Management was largely supportive, including physiotherapy. Other proposed treatments included high-dose intrave-nous methylprednisolone, amantadine, and hyperbaric oxygen therapy (HBOT) (due to CO poisoning). Few cases reported using an antioxidant cocktail including vitamin E, vitamin C, and magnesium sulfate. There were few cases that utilized ECT and one case of levodopa for rigidity/parkinsonism. The case of Hamlin *et al*[22] had a clinical sequela of malignant catatonia and was managed with combination pharmacotherapy of propranolol, clonidine and lorazepam. In particular, the patient had worsening sympathetic 'storming' after ECT. In the case of Huarcaya-Victoria *et al*[25] the symptoms of catatonia were managed with aripiprazole 30 mg/day and diazepam 30 mg/day. Of the reported cases with outcomes measured, 4 died. Twenty-five showed significant improvement, seven showed only mild to moderate improvement, and 13 showed no significant improvement (functionally dependent).

Hsiao *et al*[24] (2004) retrospectively reviewed 12 patients with DPHLS after CO intoxication, selected from 89 cases. These patients, averaging 54.4 years, initially showed severe disturbances of consciousness and were treated with high flow oxygen or HBOT. They regained consciousness within a week, but developed delayed encephalopathy 14 days to 45 days later, presenting with cognitive impairment, akinetic mutism, sphincter incontinence, gait ataxia, and various movement disorders. Brain MRI revealed lesions mainly in the subcortical white matter and basal ganglia, especially the globus pallidus. During follow-up, sphincter incontinence resolved first, cognitive function improved significantly over months, but involuntary movements showed minimal improvement, with some patients experiencing persistent symptoms such as dystonia. Follow-up MRI indicated steady improvement. Overall, delayed encephalopathy typically developed 2 weeks to 1.5 months after acute CO poisoning, with clinical and neuroimaging improvements roughly cor-related [24].

Quality and risk of bias assessment was completed using the 8-point questionnaire from the JBI assessment tool for case reports and series. A total of 41 records had a low risk of bias and five had a moderate risk of bias. The complete score breakdown is provided in Table 3[7-19,21-55].

DISCUSSION

This systematic review encompassed 72 cases of DPHLS, summarizing key demographic, clinical, neuroimaging, and outcome data. The analysis highlights the significant variability in patient presentations, etiologies, and outcomes, underscoring the complexity of this condition. The presence of symptoms in DPHLS was often correlated with neuroimaging findings, providing information on the pathophysiological changes underlying clinical manifestations. For example, cognitive decline and a decrease in level of consciousness were frequently associated with diffuse T2-hyperintensities in the cerebral white matter. Akinetic mutism, observed in several cases, corresponded to lesions in the basal ganglia and the globus pallidus, regions critical for motor control and behavioral regulation. In particular, the globus pallidus is particularly susceptible to CO and exists in an arterial border zone, making it susceptible to hypoxia[4]. Encephalopathy, a common symptom, was often associated with widespread changes in white matter, reflecting the global impact of hypoxic injury on brain function. Psychomotor agitation and catatonia, including malignant catatonia, were correlated with basal ganglia and thalamic involvement, highlighting the role of these structures in the regulation of movement and behavior.

Table 2 Cases of delayed-post hypoxic leukoencephalopathy reported

Ref.	Year of publication	Age	Gender	Cause of hypoxia	Comorbidities	Symptomatology	Time to onset of symptoms	Neuroimaging findings	Other neurodiagnostics	Therapeutic interventions	Complications	Outcomes
Aljarallah and Al-Hussain[7]	2015	19	M	Benzodiazepine overdose	None	Comatose	21 days	T2WI: Diffusely increased signal intensity in cerebral white matter. DWI/ADC: Diffuse and symmetric diffusion restriction within the subcortical cerebral white matter and the right globus pallidus. T1WI: Patchy enhancement within cerebral white matter	EEG: Diffuse slowing at 2-3 Hz	Osmolar therapy	Tonsillar herniation and brain death	Death (23rd day of hospitalization)
Arciniegas *et al*[8]	2004	24	M	Opioid and benzodiazepine overdose	NA	21 days	Executive dysfunction	T2WI: Diffusely increased signal intensity in cerebral white matter	NA	Amantadine	NA	Did not return to baseline
Arimany *et al*[9]	2017	43	M	Heroin overdose	Schizoaffective disorder	Akinetic mutism and ataxia	21 days	T2WI: Diffuse and symmetric increase in T2 signal	NA	Supportive	NA	Significant improvement at 16 weeks after overdose
Beeskow *et al*[10]	2018	51	F	Carbon monoxide poisoning	Hypertension, obesity, sleep apnea syndrome, and depression	Agitation, reduced psychomotor activity, strange behavior. Progressed to mutism	21 days	T2WI: Diffusely increased the T2 signal of the bilateral cerebral hemispheres and the basal ganglia	NA	Supportive	NA	Discharged from neurological rehabilitation in 6 weeks. At nine months improvement in leukoencephalopathy with cerebral atrophy
Betts *et al*[11]	2012	46-59	--	Benzodiazepine overdose, ETOH abuse	Cognitive decline, speech disturbance, and memory loss		17 days, 24 days, and 5 days	T2WI: Diffusely increased T2 signal of the bilateral cerebral hemispheres, including the globus pallidi. MRS: Decreased NAA, increased Cho/Cr ratio	EEG: Diffuse slowing	Supportive	NA	Significant improvement in one patient. Persistent memory dysfunction in other two patients
Brovelli *et al*[12]	2022	55	F	Opioid intoxication	None	Psychomotor slowing, apathy, cognitive decline, akinetic mutism	14 days	T2WI: Diffusely increased T2 signal within the frontal regions. DWI/ADC: The corresponding diffusion restriction	EEG: Global slowing	Logopedic and physiotherapic treatment	None	Awake and collaborative, with mild hypomimia and decreased spontaneous speech upon discharge

								was confirmed on the ADC maps			
Cardona Quiñones *et al*[13]	2022	26	M	Opioid intoxication with cardiac arrest	None	Anton-Babinski syndrome	Few days	T2WI: Bilateral cerebral hemisphere hyperintensities including corpus callosum	NA	Supportive	None	NA
Chachkhiani *et al*[14]	2022	46	M	Opioid intoxication with respiratory failure	Hepatitis C, substance use disorder, mesial temporal lobe epilepsy	Psychomotor agitation and abulia	27 days	T2WI: Bilateral cerebral hemisphere hyperintensities	EEG: Diffuse polymorphic delta activity. CSF: Normal	High dose IVMP, and amantadine	None	Discharged on day 48 with mild abulia and day 138 with a normal clinical exam, except hyperreflexia. Radiographic resolution of cerebral white matter disease
Chen *et al*[15]	2022	64	M	Nitrite poisoning. Comatose on initial presentation	None	Cognitive decline and mental and behavioral abnormalities	60 days	T2WI: Hyperintensities of the bilateral cerebral hemisphere, involving the basal ganglia and the thalamus. DWI/ADC: Corresponding diffusion restriction involving	NA	Supportive	None	Did not regain functional independence at 6-month follow-up
Choi *et al*[16]	2013	37	M	Traumatic cervical cord injury	None	Akinetic mutism	7 days	T2WI: Bilateral fronto temporal and basal ganglia hyperintensities	NA	Supportive	None	At 2 months of follow-up, they continued to show cognitive disability and disorientation
Fong *et al*[17]	2019	61	F	Benzodiazepine overdose	None	Neuropsychiatric symptoms	41 days	T2WI: Confluent cerebral white matter changes DWI/ADC: Associated diffusion restriction	EEG: Generalized slowing. CSF: Normal	Supportive	None	Clinical improvement at follow-up (MoCA: 26/30). Repeat neuroimaging at 3 months showed improvement
Garzón-Hernández *et al*[18]	2022	68	M	Severe acute respiratory syndrome-coronavirus 2related hypoxia	None	Unresponsiveness	17 days	T2WI: Confluent cerebral white matter hyperintensities. SWI: Cerebral microbleeds	EEG: isolated polymorphic delta waves in the frontal region without epileptiform activity	Supportive	None	Discharged to rehab on day 30 of hospitalization
Geraldo *et al*[19]	2014	61	M	Carbon monoxide poisoning	None	Disorientation, incoherent speech, and behavior disturbances	39 days	T2WI: Confluent cerebral white matter hyperintensities	CSF: Normal	Hyperbaric oxygen therapy (90 minutes daily sessions, 100 % oxygen at 2.5 atmospheres with a total of 40 sessions)	None	Mild to moderate improvement and discharged to a rehabilitation facility

Gottfried *et al*[20]	1994	36	M	Opioid overdose	NA	Quadriparesis, myoclonic jerks, encephalopathy, cognitive decline	24 days	T2WI: Increased supratentorial white matter signal. Hyperintense foci within globus pallidi. MRS: Decreased NAA; elevated choline and elevated lactate	NA	NA	NA	Significant improvement
Hakamifard *et al*[21]	2021	39	M	Opioid (methadone) overdose	Substance use disorder	Aphasia and decreased level of consciousness	Approximately 30 days	T2WI: Confluent cerebral white matter hyperintensities	CSF: Normal	Vitamin E 400 mg/day, vitamin C 1000 mg/day, magnesium-sulfate 1000 mg/day and vitamin B complex	None	Significant improvement in two months
Hamlin *et al* [22]	2020	29	M	Opioid overdose	Substance use disorder	Malignant catatonia, paroxysmal sympathetic hyperactivity	Approximately 30 days	T1WI and T2WI: Confluent hyperintensities involving the bilateral centrum semiovale	EEG: No epileptiform discharges	Propranolol, clonidine, and lorazepam	Akinetic mutism and sympathetic hyperactivity after electroconvulsive therapy (ECT)	Moderate improvement in 30 days
Hori *et al*[23]	1991	13		Asphyxiation	NA	Pseudobulbar paralysis, choreoathestosis	7 days	Lesion involving the putamen and caudate nuclei	NA	NA	NA	Significant improvement at 1.5 years
Hsiao *et al* [24]	2004	11-79		Carbon monoxide poisoning	NA	Cognitive impairment, akinetic mutism, and parkinsonism	14-45 days	T2WI: Increased signal within the subcortical white-matter, basal ganglia, and globus pallidus	NA	NA	NA	Moderate to considerable improvement
Huarcaya-Victoria[25]	2018	37	F	Carbon monoxide poisoning	None	Progressive psychomotor agitation, catatonia, and cognitive decline	Approximately 30 days	T2WI: Confluent cerebral white matter hyperintensities	NA	Hyperbaric oxygen therapy (29 feet for one hour, 2.2 absolute atmospheres, 20 sessions). Aripiprazole and diazepam for the management of catatonia	None	Significant improvement and discharge to rehabilitation facility
Huisa *et al* [26]	2013	19, 32	--	Opioid overdose	NA	Decreased level of arousal, and encephalopathy	58 days and 112 days	T2WI: Confluent cerebral white matter hyperintensities. ADC: Diffusion restriction in both cases with normalization at follow-up in case two	NA	NA	NA	Persistent deficits in both cases
Jang *et al*[27]	2017	50	M	Carbon monoxide poisoning	None	Myoclonus, dysarthria,	26 days	T2WI: Bilateral basal ganglia hyperin-	NA	Supportive	None	Discharge to rehabilitation facility six

						decreased level of consciousness		tensities. DTT: Dysconnectivity involving the ascending reticular activating system				weeks from initial presentation. No significant improvement
Jayakrishnan *et al*[28]	2021	68	F	Myocardial infarction	Hypertension, hyperlipidemia, and myocardial infarction	Drowsiness, behavioral changes, urinary incontinence	21 days	T2WI: Diffuse hyperintensities involving the cortex. ADC: Diffusion restriction involving the basal ganglia	NA	Supportive	None	Discharge to hospice
Jingami *et al* [29]	2024	47	M	Opioid intoxication	None	Decreased level of consciousness	20 days	T2WI: Confluent cerebral white matter hyperintensities. N-isopropyl-(123I)-p-iodoamphetamine	CSF: Elevated myelin basic protein 135.5 pg/mL	Hyperbaric oxygen (2.0 ATA, 60 minutes, 63 total)	None	Improvement in mini-mental status exam from unmeasurable to 15 on day 40 of hospitalization
Kim *et al* [30]	2002	54-71		Carbon monoxide poisoning	NA	Memory loss, confabulations, and akinetic mutism	1-4 weeks	T2WI: Confluent white matter hyperintensities in the brain	NA	NA	NA	4 patients with significant improvement
Law-ye *et al* [31]	2018	58	M	Carbon monoxide poisoning	None	Encephalopathy	14 days	T2WI: Confluent white matter hyperintensities in the brain. ADC: Diffusion restriction in the corresponding area	CSF: Normal	Supportive	None	Significant improvement
Lee *et al*[32]	2001	71	F	Benzodiazepine overdose	None	Encephalopathy	14 days	T2WI: Confluent cerebral white matter hyperintensities	CSF: Normal. EEG: Diffuse delta wave pattern	Supportive	None	Significant improvement with discharge to rehabilitation facility on day 47
Lou *et al*[33]	2009	62	F	Cardiac arrest after gastrointestinal hemorrhage	NA	Akinetic mutism, rigidity	14-21 days	T2WI: Confluent cerebral white matter hyperintensities involving the globus pallidi, and basal ganglia	NA	NA	NA	No significant improvement
Manjunath *et al*[34]	2021	76	M	Acute respiratory distress syndrome	NA	Cognitive decline	Few weeks	T2WI: Confluent cerebral white matter hyperintensities. ADC: Diffusion restriction in corresponding area	NA	Supportive	None	Significant clinical improvement over 3 months. With significant radiographic improvement in 4 months
Mazo *et al* [35]	2020	66	M	Carbon monoxide poisoning	None	Encephalopathy	12 days	T2WI: Increased signal within the bilateral	CSF: Normal	Supportive	None	No significant improvement

								globus pallidus			
Meyer *et al* [36]	2013	43	F	Benzodiazepine overdose	None	Encephalopathy	--	T2WI: Confluent cerebral white matter hyperintensities. MRS: High peak for choline and creatinine	EEG: Generalized slowing	Supportive	None	Significant improvement in a few months
Mittal *et al* [37]	2010	38	M	Polysubstance abuse	NA	Encephalopathy, akinetic mutism	21 days	T2WI: Confluent cerebral white matter hyperintensities	NA	Steroids and antiox-idants	None	Significant improvement
Molloy *et al* [38]	2006	40	F	Opioid overdose	NA	Agitation, echolalia	17 days	T2WI: Confluent cerebral white matter hyperintensities. ADC: With associated restricted diffusion	CSF: Normal	Supportive	None	Significant improvement over 6 months
Newburn *et al*[39]	2024	19	M	Benzodiazepine overdose	Developmental delay	Cognitive decline	--	DSIR: High signal in the white matter of the brain	NA	Supportive	None	Mild improvement
Newburn *et al*[39]	2024	20	M	Suicide attempt (hanging)	Substance abuse	Cognitive decline	--	DSIR: High signal in the white matter of the brain	NA	Supportive	None	Mild improvement
Nzwalo *et al* [40]	2011	55	F	Benzodiazepine overdose	NA	Akinetic mutism	NA	T2WI: Confluent cerebral white matter hyperintensities	CSF: Normal	Supportive	NA	No significant improvement
Pfaff *et al*[41]	2022	81	M	Unilateral internal carotid artery occlusion	Acute myeloid leukemia, hypertension, hyperlipidemia	Encephalopathy	13 days	T2WI: Increased signal within the left centrum semiovale	NA	Supportive; mechanical thrombectomy	None	Clinical and radiographic improvement on day 92 of hospitalization
Quinn *et al* [42]	2014	56	F	Opioid overdose	Schizoaffective disorder, cirrhosis	Catatonia	21 days	T2WI: Confluent cerebral white matter hyperintensities	EEG: generalized polymorphic theta waves, 2-3 Hz delta waves, and superimposed beta waves	ECT, methylpred-nisolone	None	No significant improvement
Rozen *et al* [43]	2012	59	--	Opioid overdose	NA	Akinetic mutism	21 days	T2WI: Confluent cerebral white matter hyperintensities including the globus pallidi	NA	IV Magnesium	None	Significant improvement
Salazar *et al* [44]	2012	54	M	Opioid overdose	NA	Encephalopathy, and rigidity	21 days	T2WI: Confluent cerebral white matter hyperintensities. ADC: Diffusion restriction involving the globus pallidi	NA	Levodopa for rigidity	None	Significant improvement

Singu *et al* [45]	2017	66	M	Left main coronary artery occlusion	Hypertension, hyperlipidemia, diabetes mellitus, myocardial infarction	Aphasia, dysexecutive syndrome	35 days	T2WI: Cerebral white matter hyperintensities involving the L MCA territory. ADC: Corresponding region hypointense. SPECT: 60%-70% decrease in CBF	CSF: Elevated protein	Supportive	None	Moderate improvement
Smolinsky *et al*[46]	2018	16	F	Traumatic brain injury	None	Encephalopathy	8 days	DWI/ADC: Restricted diffusion involving right frontoparietal lobes, right temporal lobe, and left parietal lobe, and corpus callosum	None	Amantadine	None	Mild improvement
Tahir and Islam[47]	2021	43	M	ETOH abuse	None	Encephalopathy	6 days	DWI/ADC: Diffusion restriction involving the bilateral centrum semiovale	CSF: Normal. EEG: Paroxysmal epileptiform activity	Supportive	None	Death
Tainta *et al* [48]	2018	43	M	Polysubstance abuse	Schizophrenia	Decreased level of consciousness	21 days	T2WI: Confluent cerebral white matter hyperintensities. DWI/ADC: Diffusion restriction involving the bilateral centrum semiovale	NA	Supportive	None	Significant improvement in 2.5 months
Tan and Teo [49]	2023	64	M	Carbon monoxide poisoning	NA	Psychomotor agitation	7 days	T2WI: Hyperintensities involving the bilateral globus pallidus	NA	Supportive	None	NA
Tormoehlen *et al*[50]	2013	46	F	Carbon monoxide poisoning	NA	Pseudobulbar affect	14 days	T2WI: Confluent cerebral white matter hyperintensities	NA	Supportive	NA	Unknown
Wallace *et al* [51]	2009	28	M	Polysubstance abuse	ETOH abuse	Encephalopathy	35 days	T2 BLADE: Hyperintensities involving the bilateral centrum semiovale	EEG: Normal	Supportive	Ventilatory and hemodynamic support	Significant improvement at 12 months
Wang and Yang[52]	2003	15	M	Substance abuse	NA	Seizures, dysphagia, dystonia, and altered mental status	NA	T2WI: Bilateral globus pallidi hyperintensities	NA	Supportive	NA	NA
Weinberger *et al*[53]	1994	34	--	Benzodiazepine overdose	NA	Encephalopathy, hyperreflexia, clonus, primitive reflexes, and	24 days	Increased signal within the supratentorial white matter	NA	NA	NA	Persistent cognitive decline

						frontal lobe release sign						
Zamora *et al* [54]	2015	64	M	Cardiopulmonary arrest	NA	Psychomotor agitation	23 days	T2WI: Confluent cerebral white matter hyperintensities. ADC: Increased signal less extensive than T2WI	NA	NA	None	Moderate improvement
Zamora *et al* [54]	2015	32	M	Opioid abuse	NA	Encephalopathy	32 days	T2WI: Confluent cerebral white matter hyperintensities. ADC: More extensive than T2WI	NA	NA	None	Significant improvement
Zamora *et al* [54]	2015	63	F	Polysubstance abuse	NA	Akinetic mutism	35 days	T2WI: Confluent cerebral white matter hyperintensities.ADC: Matched signal to T2WI	NA	NA	None	Significant improvement
Zamora *et al* [54]	2015	65	M	Polysubstance abuse	NA	Encephalopathy	14 days	T2WI: Confluent cerebral white matter hyperintensities. ADC: Increased signal less extensive than T2WI	NA	NA	None	Significant improvement
Zamora *et al* [54]	2015	59	F	Opioid abuse	NA	Catatonia	14 days	T2WI: Confluent cerebral white matter hyperintensities. ADC: Matched signal to T2WI	NA	NA	None	Deceased
Shprecher *et al*[55]	2008	39-56	--	Polysubstance abuse	NA	Catatonia, memory loss, disorientation, encephalopathy	31 days-38 weeks	T2WI: Confluent cerebral white matter hyperintensities. ADC: Diffusion restriction in 2 cases. MRS: Decreased NAA	NA	NA	NA	No significant improvement

DWI/ADC: Diffusion-weighted imaging/apparent diffusion coefficient; EEG: Electroencephalogram; ETOH: Ethanol; MRS: Magnetic resonance spectroscopy; NAA: N-acetylaspartate; ADC: Apparent diffusion coefficient; CSF: Cerebrospinal fluid; IVMP: Intravenous methylprednisolone; ECT: Electroconvulsive therapy; DSIR: Divided subtracted inversion recovery; NA: Not applicable; F: Female; M: Male.

Pathophysiology of delayed post-hypoxic leukoencephalopathy syndrome

The pathophysiology of DPHL is not fully understood but is believed to predominantly involve hypoxic-ischemic injury to the brain's white matter. White matter, composed of myelinated axons, is highly susceptible to hypoxic damage due to its high metabolic demand and lower capacity for anaerobic metabolism compared to gray matter[56]. Additionally, widely spread anastomoses within the white matter may also influence neuronal injury in the setting of hypoxia[57]. This review highlighted diffuse increases in the T2 signal in cerebral white matter in a significant proportion of cases, indicating widespread demyelination and axonal injury. Lesions in the basal ganglia, thalamus, and globus pallidus were

Table 3 Joanna Briggs Institute critical appraisal and risk of bias results for case reports/series

Ref.	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall	Risk
Aljarallah and Al-Hussain[7]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Arciniegas *et al*[8]	Y	Y	Y	Y	Y	N	N	Y	6	Moderate
Arimany *et al*[9]	Y	Y	Y	Y	N	N	N	Y	5	Moderate
Beeskow *et al*[10]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Betts *et al*[11]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Brovelli *et al*[12]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Cardona Quiñones *et al*[13]	Y	Y	Y	Y	N	N	N	Y	5	Moderate
Chachkhiani *et al*[14]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Chen *et al*[15]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Choi *et al*[16]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Fong *et al*[17]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Garzón-Hernández *et al*[18]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Geraldo *et al*[19]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Hakamifard *et al*[21]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Hamlin *et al*[22]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Hori *et al*[23]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Hsiao *et al*[24]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Huarcaya-Victoria [25]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Huisa *et al*[26]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Jang and Kwon[27]	Y	Y	Y	Y	N	Y	Y	Y	7	Low
Jingami *et al*[29]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Kim *et al*[30]	Y	Y	Y	Y	Y	N	Y	Y	8	Low
Law-ye *et al*[31]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Lee *et al*[32]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Lou *et al*[33]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Manjunath *et al*[34]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Mazo *et al*[35]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Meyer *et al*[36]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Mittal *et al*[37]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Molloy *et al*[38]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Newburn *et al*[39]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Nzwalo *et al*[40]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Pfaff *et al*[41]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Quinn *et al*[42]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Rozen *et al*[43]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Salazar *et al*[44]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Singu *et al*[45]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Smolinsky *et al*[46]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low

Tahir and Islam[47]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Tainta *et al*[48]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Tan and Teo[49]	Y	Y	Y	Y	Y	N	N	Y	6	Moderate
Tormoehlen *et al*[50]	Y	Y	Y	Y	Y	N	N	Y	6	Moderate
Wallace *et al*[51]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Wang and Yang[52]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Weinberger *et al*[53]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Zamora *et al*[54]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low
Shprecher *et al*[55]	Y	Y	Y	Y	Y	Y	Y	Y	8	Low

Q1: Were the patient's demographic characteristics clearly described? Q2: Was the patient's history clearly described and presented as a timeline? Q3: Was the current clinical condition of the patient on presentation clearly described? Q4: Were diagnostic tests or assessment methods and the results clearly described? Q5: Was the intervention(s) or treatment procedure(s) clearly described? Q6: Was the post-intervention clinical condition clearly described? Q7: Were adverse events (harms) or unanticipated events identified and described? Q8: Does the case report provide takeaway lessons? Overall: Sum of points. Y: Yes; N: No.

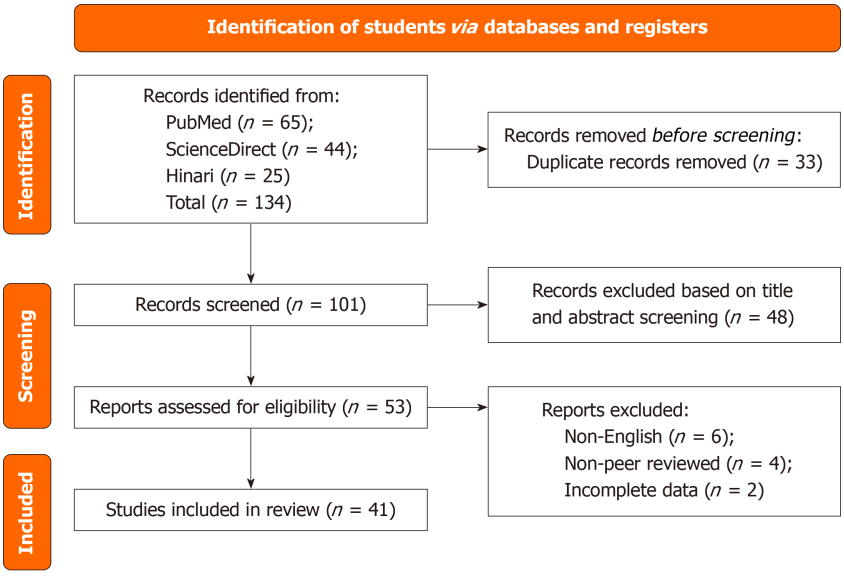

Figure 1 Identification of students *via* databases and registers.

commonly observed, suggesting that these subcortical structures are particularly vulnerable to hypoxic injury. These regions are involved in motor control, cognition, and behavioral regulation, which explains the frequent occurrence of symptoms such as akinetic mutism, psychomotor agitation, and cognitive decline. The involvement of these areas underscores their sensitivity to oxygen supply disruptions and subsequent metabolic disturbances. The delayed onset of symptoms, which ranges from 14 days to 60 days after hypoxia, suggests that secondary injury mechanisms play a crucial role in the pathogenesis of DPHL.

CO poisoning leads to hypoxia by binding to hemoglobin with an affinity 200-250 times greater than oxygen, forming carboxyhemoglobin (COHb), which alters oxygen transport and release to tissues[58]. This hypoxic state particularly affects tissues of high metabolic demand, such as the brain. The resulting hypoxic injury initiates a cascade of cellular events, including oxidative stress, excitotoxicity, and inflammatory responses, which contribute to neuronal damage and white matter demyelination[59]. In DPHLS, the delayed onset of symptoms after an acute hypoxic episode, such as that induced by CO poisoning, suggests secondary injury mechanisms. These include the activation of microglia and astrocytes, leading to further degradation of myelin and axonal damage. Advanced imaging often reveals diffuse white matter hyperintensities and basal ganglia lesions, indicating widespread demyelination and axonal injury[60]. The primary treatment for CO poisoning-induced brain injury is the administration of 100% oxygen, through a non-rebreather mask or endotracheal intubation, to improve the dissociation of CO from hemoglobin and accelerate the elimination of COHb from the bloodstream[61]. HBOT is considered for patients with severe CO poisoning or neurological symptoms, as it further increases the amount of dissolved oxygen in the blood, reduces the half-life of COHb, and mitigates oxidative stress and inflammatory responses in the brain[62]. Supportive care, including intravenous fluids, seizure management, and monitoring for potential complications such as cardiac arrhythmias, is essential[61]. Long-term neurological rehabil-

itation may be necessary in patients with persistent cognitive or motor deficits[63].

Neuroimaging and neuropathology

Initial hypoxic insult can trigger a cascade of cellular and molecular events, including inflammation, oxidative stress, and excitotoxicity, which evolve over time and lead to progressive damage to white matter. Neuroimaging overlaps between delayed DPHLS and metachromatic leukodystrophy (MLD) reveal significant similarities and differences that offer insights into their pathophysiology and diagnostic challenges. Both conditions commonly present with diffuse white matter hyperintensities on T2-FLAIR MRI sequences, reflecting extensive demyelination[64,65]. Despite these similarities, the pathophysiological mechanisms underlying DPHLS and MLD differ significantly. DPHLS results from hypoxic episodes leading to delayed demyelination and axonal damage, characterized by oxidative stress, excitotoxicity, and inflammation[64]. On the contrary, MLD is a genetic disorder caused by mutations in the *ARSA* gene, leading to deficient arylsulfatase A enzyme activity and subsequent accumulation of sulfatides, resulting in progressive demyelination[65]. The progression of white matter changes in DPHLS is typically subacute, with symptoms appearing weeks to months after the hypoxic event, while MLD has a more insidious onset, with gradual progression over months to years[66]. Advanced imaging techniques, such as MRS and diffusion tensor imaging (DTI), have revealed further similarities and distinctions. Both conditions show reduced levels of NAA, indicating neuronal loss, and elevated levels of choline, reflecting increased membrane turnover and gliosis[67]. However, MLD can show additional unique metabolic markers due to the specific biochemical abnormalities associated with sulfatide accumulation[68]. DTI studies reveal altered white matter integrity under both conditions, with decreased fractional anisotropy and increased mean diffusivity, although the pattern of white matter tract involvement can differ[66]. Histopathological evaluations revealed significant loss of myelin, axonal swelling, and reactive astroglia, indicating an inflammatory response to hypoxic injury[67]. These findings point to a substantial role for inflammation and immune activation in the progression of DPHL, contributing to the primary and secondary phases of white matter injury.

Limitations and future directions

The cases included in this review exhibit significant heterogeneity in terms of patient demographics, causes of hypoxia, symptomatology, and treatment approaches. This variability makes it difficult to draw definitive conclusions and limits the generalizability of the findings. Most of the included studies are retrospective case reports and series, which can introduce selection bias and limit the ability to establish causality. The retrospective design also relies on the accuracy and completeness of medical records. The absence of standardized diagnostic criteria for DPHLS results in variability in diagnosis and reporting, which can lead to inconsistencies in case identification and classification. Incomplete or inconsistent reporting of clinical results, neuroimaging findings, and therapeutic interventions in included studies limits the ability to perform a comprehensive and uniform analysis. Many studies lack long-term follow-up data, which is crucial for understanding the full path of DPHLS, including the persistence of symptoms, long-term outcomes, and the potential for recovery. Conducting prospective cohort studies with standardized diagnostic criteria and protocols will provide more robust data on the incidence, risk factors, and natural history of DPHLS. These studies can also help establish causality and improve understanding of disease progression. Developing and adopting standardized diagnostic criteria for DPHLS will improve the consistency and reliability of diagnosis and reporting across studies, facilitating more accurate comparisons and meta-analyses. Identifying and validating biomarkers for DPHLS, such as specific neurochemical or inflammatory markers, can aid in early diagnosis, monitor disease progression, and evaluate treatment response.

The findings of Newburn *et al*[39] suggest that DPHL may be underdiagnosed due to the reliance on conventional MRI and stringent diagnostic criteria. Future research should aim to broaden the diagnostic criteria for DPHL to include less severe cases and recognize the spectrum of clinical presentations. The use of dSIR sequences, as highlighted in the study, may provide greater clinical utility than conventional MRI techniques. Future studies should explore the routine use of advanced MRI sequences like dSIR to improve the detection and characterization of white matter changes in DPHL[39].

CONCLUSION

Delayed post-hypoxic leukoencephalopathy syndrome (DPHLS), or Grinker's myelinopathy, is an under-recognized neurological condition that manifests after a latent period after a hypoxic event. It is characterized by delayed onset of neurological and cognitive deficits, which typically present day to weeks after the injury. This systematic review highlights the significant variability in the presentations, etiologies, and outcomes of patients with DPHLS. Commonly reported symptoms include encephalopathy, akinetic mutism, psychomotor agitation, cognitive decline, catatonia, and parkinsonism. MRI often shows confluence cerebral white matter hyperintensities involving the corona radiata and centrum semiovale. Sometimes extending into subcortical structures including the basal ganglia and thalamus. Most common causes of hypoxia include CO poisoning, cardiac arrest, benzodiazepine, and opioid overdose. Treatment is often supportive, including amantadine, an antioxidant cocktail, and steroids. Parkinsonism was often treated with levodopa. Most of the patients had substantial recovery over the course of months and many cases had some residual neurocognitive deficits.

FOOTNOTES

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