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ORIGINAL COMMUNICATION

Different routes of heroin intake cause various heroin-induced leukoencephalopathies

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Abstract

Objective Toxic leukoencephalopathy is a rare but critical neurological disorder in heroin abusers. Our aim is to compare the clinical manifestations, brain MRIs and prognoses of heroin-induced leukoencephalopathy by different intake routes.

Methods We present two patients with toxic leukoencephalopathy caused by intravenous (IV) injection of heroin and 48 additional cases from systematic reviews of the literature published between 1994 and 2018.

Results Among the 50 heroin abusers who developed leukoencephalopathy, inhalation was the most popular route (60%), followed by IV injection (30%) and snorting (10%). Mental changes, mutism and urine/fecal incontinence were the major symptoms in patients who IV injected heroin, while cerebellar ataxia and dysarthria were more common among those who inhaled heroin. Delayed-onset encephalopathy uniquely occurred in those who IV injected heroin, whereas progressive encephalopathy was more commonly observed in those who inhaled heroin. Clinical improvement was observed in 60% of patients, the overall mortality rate was 12%, and higher mortality was observed in patients who used the inhalation route (16.7%). The hallmarks on the MRIs of those who inhaled heroin were posterior to anterior involvement of the cerebral white matter and lesions in the posterior limbs of the internal capsules, cerebellum and brainstem. In contrast, those who IV injected heroin had more frequent lesions in the subcortical U fibers and the genu of the internal capsules.

Conclusion These data could help physicians make an early diagnosis and predict prognosis and suggest that prompt antioxidative or symptomatic treatments might reduce the long-term consequences and mortality of heroin-induced leukoencephalopathy.

Keywords Heroin · Inhalation · Intravenous · Snorting · Leukoencephalopathy · MRI

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Introduction

Toxic leukoencephalopathy is a unique and rare disorder in heroin abusers. The differing clinical features and abnormal brain imaging of heroin-induced leukoencephalopathy occasionally lead to misdiagnoses and delays in treatment. In addition, there are various routes of heroin use, including inhalation, intravenous (IV) injection, snorting (intranasal), intramuscular injection, subcutaneous injection, oral and rectal routes. The inhalation of heroin is performed via the inhalation of heated vapors, i.e., heroin pyrolysate, which differs from snorting heroin powder. Due to the complexity of the clinical presentations of heroin abusers with different routes of heroin intake, making a prompt diagnosis of heroin-associated leukoencephalopathy is difficult.

Several previous case reports have described toxic leukoencephalopathy following heroin misuse by different routes [1–6]. However, the characteristic manifestations, brain imaging and prognostic outcomes are inconclusive. The purpose of this study was to analyze the clinical and imaging characteristics of heroin-induced leukoencephalopathy by different routes. We present two index cases of leukoencephalopathy after heroin IV injection and collected relevant cases through a systematic literature review for comparison and analyses.

Materials and methods

Case reports

Two patients with a diagnosis of heroin-induced leukoencephalopathy by IV injection were identified at Chang Gung Memorial Hospital, Lin-Kou Medical Center. We recorded the demographic and clinical symptoms at onset and during follow-up visits. The brain MRIs were obtained using a 3.0-Tesla machine (Siemens Magnetom Vision, Siemens Medical Systems, Erlangen, Germany) with the essential scan sequences, including T1-weighted images (T1WI), T2-weighted images (T2WI), fluid-attenuated inversion recovery (FLAIR) images, gadolinium-enhanced T1WI images, diffusion-weighted images (DWI) and apparent diffusion coefficient (ADC) maps.

Case 1

A 33-year-old male plumber had been addicted to IV injection of heroin for 4.5 years. He visited the emergency department at a local hospital due to an altered mental status, acute fulminate hepatitis and rhabdomyolysis. His vital signs and conscious level were not available. The urine screen was positive for heroin but negative for amphetamine, benzodiazepine (BZD) and alcohol. Acute heroin intoxication was diagnosed. The initial brain computed tomography (CT) was unremarkable. His consciousness and activities returned to normal within 1 week.

Acute mutism, bradykinesia, weakness in the lower extremities, purposeless repetitive behaviors and urine retention/fecal incontinence occurred 6 weeks after discharge. Upon admission, the neurological examinations showed a confused status, akinetic mutism, a silly smile and paraparesis. The toxicological screening at the emergency department was negative for morphine/opioids, amphetamine, BZD, ketamine, 3,4-methylenedioxy-methamphetamine (MDMA) and alcohol. The laboratory data revealed leukocytosis and rhabdomyolysis. The CSF analysis showed normal findings, and the HIV screen was negative. The EEG demonstrated continuous, diffuse theta and delta activities. The brain CT showed diffuse hypodensities in the white matter (Fig. 1a). The brain MRI on the 8th day after symptom onset revealed more detailed white matter involvement in the bilateral periventricular and subcortical regions extending to the U fibers, corpus callosum and genu of the internal capsules, with hyperintensities on FLAIR and T2WI (Fig. 1b) and hypointensities on T1WI, with no enhancement on post-contrast T1WI. The DWI exhibited increased signal intensities in the bilateral frontoparietal white matter (Fig. 1c) without water restriction on the ADC map. The brainstem, cerebellum and deep gray matter were apparently unaffected (Fig. 1d). The brain MR spectroscopy (MRS) exhibited an increased choline peak and a decreased N-acetylaspartate (NAA) peak with normal lactate in the bilateral periventricular white matter (Fig. 1e). However, the normal-appearing cortex revealed both a reduced NAA peak and an inverted doublet lactate peak, presumably reflecting the insidious hypoxic injury (Fig. 1f). The above clinical and imaging findings were consistent with delayed posthypoxic leukoencephalopathy (DPHL).

Antioxidative combined therapy with vitamin C (1000 mg BID), vitamin E (400 mg TID) and coenzyme Q10 (30 mg TID) was initiated on the 14th day. He gradually recovered to independent ambulation and oriented speech one month after the antioxidative therapy and rehabilitation. He was lost of follow up after discharge.

Case 2

A 32-year-old man had used heroin IV injection for several years. The patient lost consciousness and was found by friends lying on the floor with his eyes closed a few hours after an IV injection of heroin (the previous time the friends saw the patient was 4 h prior, and he appeared to be clear). At our emergency department, he was irritable and confused (Glasgow Coma Scale: E3V1M6) with mild hyperthermia and tachycardia (body temperature:

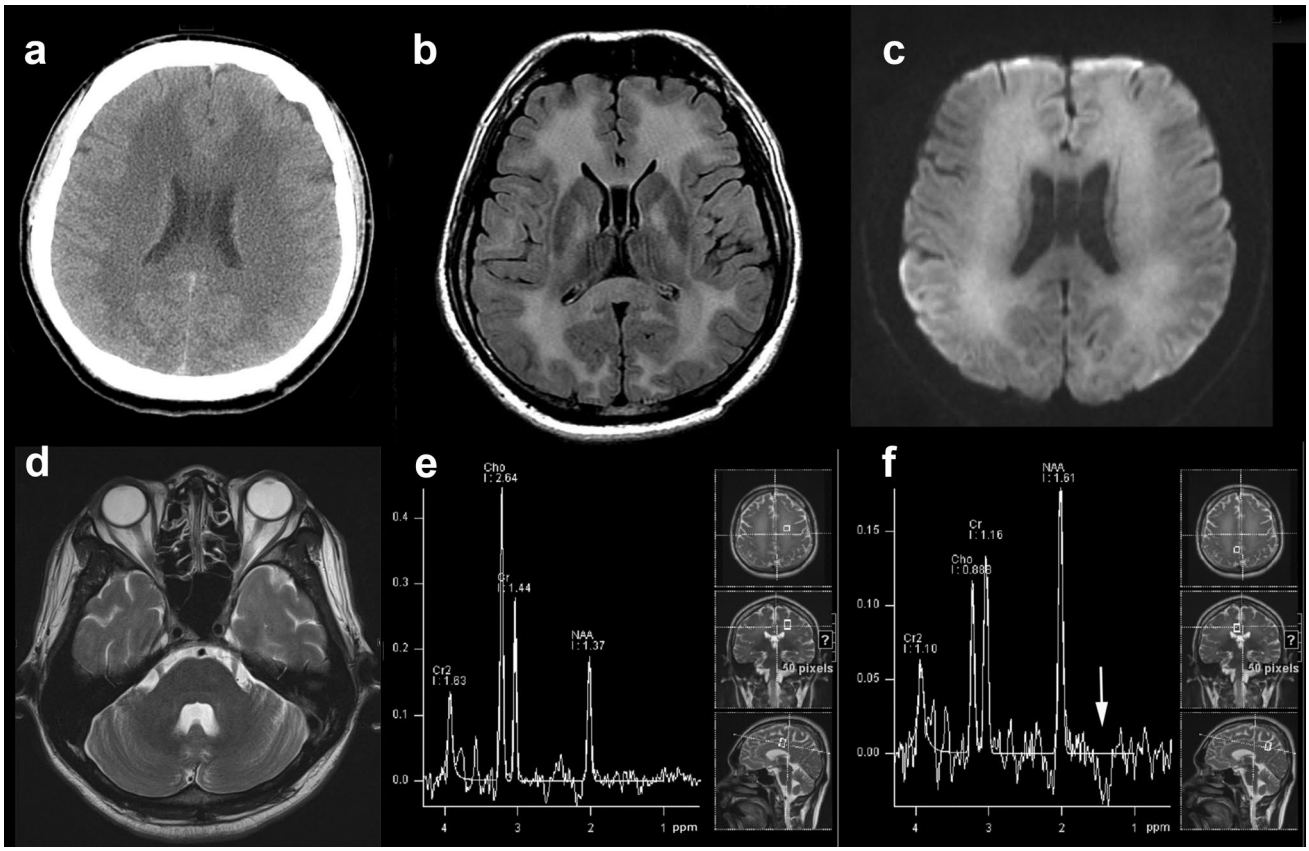

Fig. 1 The exceptionally clear distinction between the cortex and white matter is a common CT finding in ongoing white matter disease (**a**). The confluent white matter hyperintensities are compatible with severe leukoencephalopathy in the supratentorial cerebrum (**b** axial FLAIR images). Neither water restriction nor brainstem and cerebellum involvement was noted (**c** DWI; **d** axial T2WI). 1H-MR spectroscopy of hyperintense white matter revealed a markedly reduced NAA peak suggestive of axonal damage (**e**). The normal-appearing cortex also revealed not only a mildly reduced NAA peak but also a large inverted doublet lactate peak at 1.3 ppm (arrow) suggestive of a hypoxic phenomenon (**f**)

38 °C, heart rate: 96 bpm, respiratory rate: 18/min, blood pressure: 105/78 mmHg). Morphine/opioid was strongly detected in the urine (156,090 ng/ml). Acute renal failure was also simultaneously diagnosed. The CSF examination and amphetamine, alcohol, BZD, HIV, virological and autoimmune screening were all negative. The brain CT showed symmetrical but equivocal white matter hypodensities (Fig. 2a), while the EEG did not reveal any abnormalities. Upon admission, his consciousness gradually recovered, and the neurological examinations were unremarkable. He could move freely and was well oriented at discharge.

Rapidly progressive confusion, bradykinesia/bradyphrenia and urine incontinence were observed 1 month after discharge. The urine screening was positive for BDZ but negative for morphine/opioids and amphetamine. He had a dull response, disorientation and incoherent speech upon admission. Conscious deterioration, akinetic mutism, neck and limb rigidity, tremor and stimulation-induced generalized myoclonus ensued within 2 days. The EEG showed continuous, diffuse theta and delta waves. The brain CT showed diffuse and pronounced white matter hypodensities in the bilateral hemispheres (Fig. 2b). The brain MRI on the 9th day (Fig. 2c–f) exhibited features similar to those observed in case 1 and was consistent with DPHL. His cognition, fluency, content of speech and movement disorders gradually recovered to independent daily activity within 1 month after the initiation of piracetam, but his short-term memory was still impaired at the final out-patient clinic visit 2 months later.

Literature review

To analyze the clinical presentations and MRI findings of patients misusing heroin via different routes, a systematic review of the English literature was performed using PubMed and Journal at Ovid. To obtain sufficient data, especially brain MRI data, full-length articles and case reports published between January 1994 and January 2018 were included. The Medical Subject Heading (MeSH) terms “heroin” and “leukoencephalopathy” or “toxic

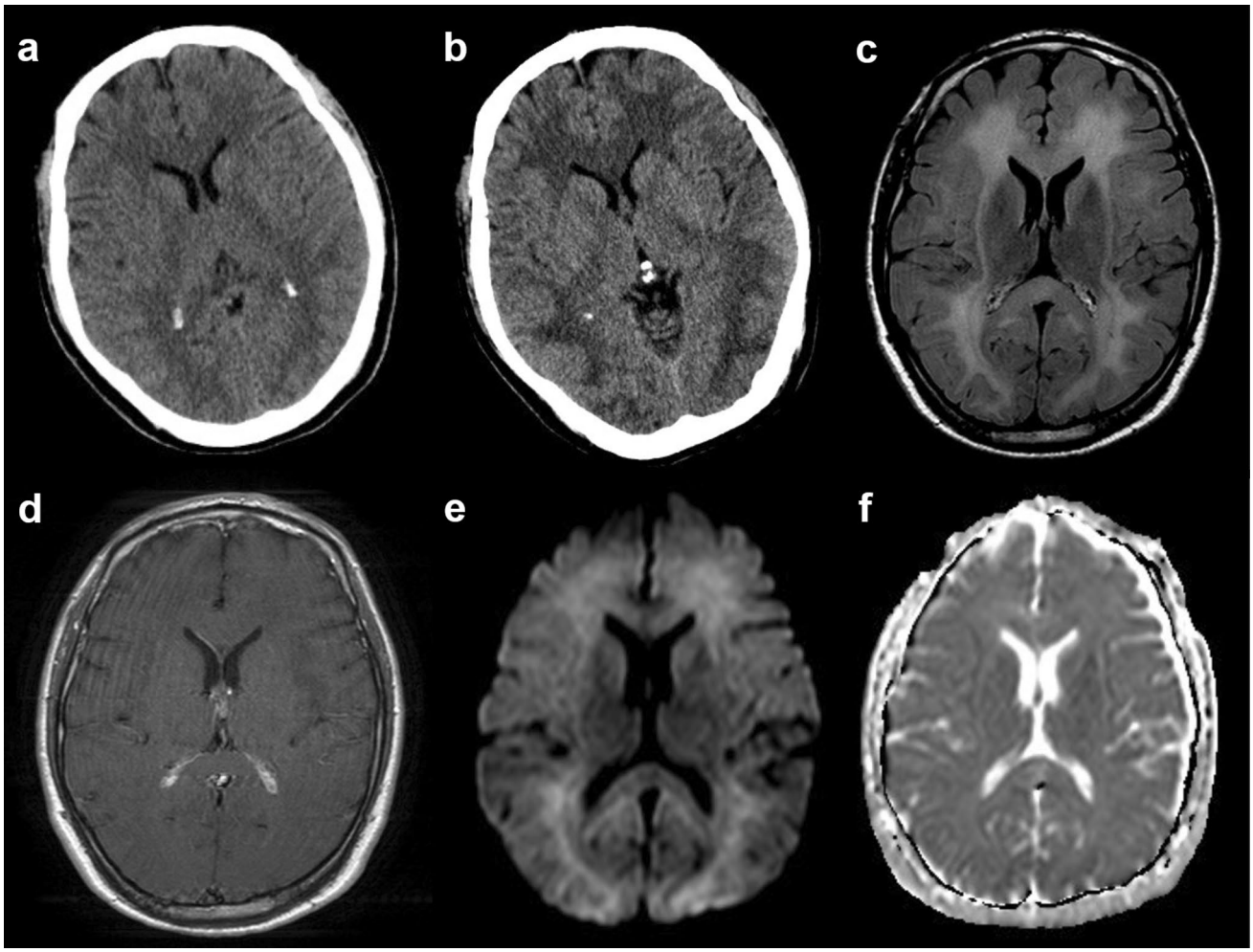

Fig. 2 Compared to the first brain CT images (**a**), the subsequent follow-up brain CT 1 month later (**b**) showed more pronounced white matter hypointensities. The diffuse white matter abnormality was distributed in the centrum semiovale and periventricular regions with extension to the subcortical U fibers and corpus callosum but did not involve the cortex or deep gray matter structures (**c** axial FLAIR images). This interval progressive change is consistent with delayed-onset leukoencephalopathy, which is a commonly observed finding in heroin leukoencephalopathy. The white matter abnormality did not have enhancement or water restriction (**d** enhanced T1WI; **e** DWI; **f** ADC). In this setting, the imaging findings were suggestive of a vasogenic, reversible white matter change

leukoencephalopathy" were used to acquire all accessible articles.

We recorded the clinical features and brain images of our two patients and previously reported cases of heroin-induced leukoencephalopathy. Depending on the temporal sequence between the heroin misuse and clinical manifestations, the onset pattern was classified into the following three types: (1) acute-onset encephalopathy: occurring rapidly after heroin consumption or overdose; (2) delayed-onset encephalopathy: occurring after a latent period following acute heroin intoxication; and (3) progressive encephalopathy: gradually escalating in chronic heroin abusers. The time of receiving the brain MRIs was divided into the acute phase (within 1 week of the occurrence of the initial signs/symptoms), subacute phase (between 1 week and 1 month) and chronic phase (after 1 month). According to their locations, the lesions on MRI were classified as supratentorial or infratentorial. The results of the DWI/ADC and MRS findings were also analyzed if the MRI data were available.

Statistical analysis

SPSS 22.0 (IBM, SPSS, Statistics, USA) was used for the statistical analyses. The categorical variables were compared using Pearson's Chi-squared test or Fisher's exact test. A one-way ANOVA was used to compare the unpaired groups. The level of significance was set at $p < 0.05$. All tests were two-tailed.

Results

In total, 50 patients with heroin-induced leukoencephalopathy were recruited, including our two subjects and 48 cases collected from 33 articles (Table 1). The male to female ratio was 46:4, and the mean age at onset was 33.2 and 31.8 years in the males and females, respectively. Patients were divided into three groups as follows: 15 patients (30%) in the IV injection group, five patients (10%) in the snorting group and 30 patients (60%) in the inhalation group (Table 2). The sex and mean age at onset did not differ among the three groups.

Overall, mental changes (decreased level of consciousness, cognitive deficits, or both) represented the most common symptom and were identified in 31 cases (100% of heroin use via IV injection, 80% of heroin use via snorting, and 40% of heroin use via inhalation); cerebellar ataxia (80% of heroin use via inhalation, 33% of heroin use via IV injection, and 20% of heroin use via snorting) and pyramidal dysfunction (80% of heroin use via IV injection, 53% of heroin use via inhalation, and 40% of heroin use via snorting) were the second most common symptoms and were identified in 30 cases each (Table 2). Furthermore, mental changes were more frequently observed in patients in the non-inhalation groups (IV injection and snorting) than in patients in the inhalation group. Mutism and urine/fecal incontinence were mostly found in the IV injection group. Cerebellar ataxia and dysarthria were more common in the inhalation group than in the non-inhalation groups. A notable improvement in the clinical signs/symptoms was observed in 60 percent of patients (30/50, 60%). The overall mortality rate was 12%, including five mortalities in the inhalation group (5/30, 16.7%) and one mortality in the IV injection group (1/15, 6.7%). Treatments were recorded in 18 cases, including eight patients who received antioxidative and ten patients who received symptomatic treatments (Tables 1, 2). The other 32 cases did not receive specific therapy or the data were not available. Antioxidants were more frequently prescribed to patients in the inhalation groups, while symptomatic treatments were more often used in patients in the non-inhalation groups (IV injection and snorting). Overall, patients who received treatment, including the antioxidative or symptomatic treatments, had a much higher rate of improvement and a lower rate of mortality than those who did not receive treatment ($p = 0.010$ and $p = 0.016$, respectively).

Most patients underwent brain MRIs during the acute phase (29 cases), and some patients underwent MRIs during the subacute and chronic phases (16 and 5 cases, respectively) (Table 2; details shown in Table 3). In the supratentorial regions, lesions in the posterior limbs of the internal capsules (PLIC) and posterior to anterior involvement of the cerebral white matter (P–A distribution) were more frequently observed in the inhalation group than in the non-inhalation groups (Table 2). In contrast, lesions in the subcortical U fibers and the genu of the internal capsules were more frequently found in the IV injection group than in the snorting and inhalation groups. In the infratentorial regions, compared with the non-inhalation groups, all brainstem lesions and most cerebellar lesions were observed in the inhalation group. None of the patients had a contrast-enhanced lesion. The DWI/ADC values were available for 26 patients, revealing water restriction (increased DWI with decreased ADC) in eight patients and T2 shine-through effects (increased DWI with normal or increased ADC) in 18 patients. The water restriction and T2 shine-through effects were not related to the routes of heroin use, the time of the brain MRIs, prognosis (improvement) or mortality ($p = 0.433$, $p = 0.789$, $p = 0.795$ and $p = 0.919$, respectively). Brain MRS data were only available for 12 patients (see details in Table 3). Decreased NAA or choline with increased lactate peaks in the periventricular white matter was observed in 11 patients in the inhalation group. One patient in the IV injection group (Case 1) showed decreased NAA and increased choline with normal lactate.

Documentation of the onset pattern was collected in 37 cases (Table 4; details shown in Table 1). The average latent period of delayed-onset encephalopathy was 24 days (range 21–45 days). Delayed-onset encephalopathy was more frequently observed in the IV injection heroin abusers, while progressive encephalopathy was found only in the inhalation group. Mutism and urine/fecal incontinence were more frequently found in patients with delayed-onset encephalopathy. Patients with acute-onset or delayed-onset encephalopathy tended to exhibit mental changes and water restricted brain lesions and receive symptomatic treatments. Patients with progressive encephalopathy frequently exhibited cerebellar ataxia, dysarthria, P–A distribution and lesions in the PLIC, cerebellum and brainstem and received antioxidative treatments.

Discussion

Among the 50 heroin abusers, inhalation was the most popular route of heroin administration, followed by IV injection and snorting. We found that the clinical symptoms, disease onset pattern and brain MRIs highly differed among the three groups (Table 5). For patients with a vague history of heroin intake routes, the topographic distribution on brain MRIs in addition to peculiar clinical symptoms in different subgroups of heroin abusers may offer insight for pursuing the correct diagnosis. Mental changes, mutism and urine/fecal incontinence were the most common symptoms in the abusers who IV injected heroin. The occurrence of mental changes was significantly higher in the heroin abusers using the IV injection or snorting routes and those with

Table 1 Demographics and clinical data of 50 patients with heroin-induced leukoencephalopathy

No.	Routes of heroin intake	Onset pattern	Clinical features							Improvement	Mortality	Treatment	References
			Mental changes	Cerebellar ataxia	Pyramidal	Mutism	Dysarthria	EPS	Incontinence				
1	IV injection	Delayed-onset (1.5 M)	+	−	+	+	−	−	+	+	−	Antioxidative[a]	Case 1
2		Delayed-onset (1 M)	+	−	−	+	−	+	+	+	−	Symptomatic[c]	Case 2
3		Delayed-onset (3 W)	+	−	+	+	−	−	+	+	−	N/A	Barnett [7]
4		Delayed-onset (3 W)	+	−	+	+	+	−	−	+	−	Antioxidative[a]	Pirompanich [8]
5		Delayed-onset (3 W)	+	+	+	−	−	−	−	−	+	N/A	Rizzuto [9]
6		Delayed-onset (3–6 W)	+	−	+	+	−	+	+	+	−	Symptomatic[d]	Chang [10]
7		Delayed-onset (3 W)	+	+	+	−	N/A	N/A	N/A	N/A	−	N/A	Blasel [2]
8		Acute-onset	+	NA	+	+	N/A	N/A	N/A	+	−	N/A	Chen [11]
9		Acute-onset	+	N/A	+	+	N/A	N/A	N/A	+	−	N/A	Maschke [12]
10		Acute-onset	+	N/A	+	N/A	−	−	N/A	+	−	N/A	Villella [13]
11		Acute-onset	+	+	+	+	−	−	+	+	−	Symptomatic[e]	Siu [14]
12		Acute-onset	+	−	−	−	−	+	−	−	−	Symptomatic[f]	Benassi [15]
13		Acute-onset	+	+	+	−	−	−	−	+	−	Symptomatic[g]	Long [16]
14		Unknown	+	−	−	−	−	+	−	−	−	N/A	Robertson [17]
15		Unknown	+	+	+	+	N/A	N/A	N/A	+	−	N/A	Blasel [2]
16	Snorting	Acute-onset	+	−	−	−	−	−	N/A	+	−	N/A	Bega [18]
17		Acute-onset	+	−	+	−	+	+	−	+	−	Symptomatic[h]	Schoser [19]
18		Acute-onset	−	+	−	−	+	−	−	+	−	Symptomatic[i]	Bach [20]
19		Delayed-onset (3 W)	+	−	−	−	N/A	−	−	+	−	Symptomatic[j]	Lefaucheur [21]
20		Unknown	+	−	+	−	−	N/A	N/A	N/A	−	N/A	Blasel [2]
21	Inhalation	Progressive	−	N/A	+	−	+	−	N/A	+	−	Antioxidative[a]	Jee [22]
22		Progressive	+	+	−	−	+	−	−	+	−	N/A	Celius [23]
23		Progressive	−	+	−	−	+	−	−	−	−	N/A	Tan [4]
24		Progressive	−	+	−	−	+	−	−	N/A	−	N/A	Tan [4]
25		Progressive	−	+	+	−	+	−	−	N/A	−	N/A	Tan [4]
26		Progressive	+	+	+	−	+	−	−	+	−	N/A	Tan [4]
27		Progressive	−	+	−	−	+	−	−	N/A	−	Antioxidative[b]	Bartlett [6]
28		Progressive	−	+	+	−	+	−	−	+	−	N/A	Bartlett [6]
29		Progressive	−	+	−	−	−	+	−	N/A	−	N/A	Keogh [5]
30		Progressive	−	+	−	−	+	+	−	N/A	−	N/A	Keogh [5]
31		Progressive	−	+	+	+	+	+	−	+	−	Antioxidative[b]	Kriegstein [3]
32		Progressive	−	+	+	−	+	−	−	+	−	Antioxidative[a]	Kriegstein [3]
33		Progressive	−	+	+	−	+	+	−	N/A	−	N/A	Weber [24]

Table 1 (continued)

No.	Routes of heroin intake	Onset pattern	Clinical features							Improvement	Mortality	Treatment	References
			Mental changes	Cerebellar ataxia	Pyramidal	Mutism	Dysarthria	EPS	Incontinence				
34		Acute-onset	+	+	+	N/A	N/A	+	N/A	−	+	N/A	Hill [25]
35		Acute-onset	+	N/A	+	N/A	N/A	N/A	N/A	−	+	N/A	Verma [26]
36		Acute-onset	−	+	−	−	+	+	−	−	−	N/A	Ropper [27]
37		Acute-onset	+	+	+	−	−	−	−	+	−	Symptomatic[k]	Gupta [28]
38		Acute-onset	−	+	+	−	+	−	−	+	−	N/A	Kass-Hout [29]
39		Acute-onset	+	+	+	N/A	N/A	N/A	N/A	+	−	Antioxidative[a]	Gacouin [30]
40		Delayed-onset (1 M)	+	−	−	−	−	+	−	+	−	Symptomatic[l]	Singh [31]
41		Unknown	+	+	−	−	−	+	+	+	−	Antioxidative[b]	Heales [32]
42		Unknown	−	+	+	−	−	−	−	−	+	N/A	Offiah [1]
43		Unknown	+	+	−	−	+	−	−	+	−	N/A	Offiah [1]
44		Unknown	−	+	+	−	−	−	−	+	−	N/A	Offiah [1]
45		Unknown	+	−	−	−	−	−	−	−	+	N/A	Offiah [1]
46		Unknown	−	+	−	−	+	−	−	+	−	N/A	Offiah [1]
47		Unknown	−	+	−	−	+	−	−	+	−	N/A	Offiah [1]
48		Unknown	+	−	+	−	−	−	−	−	+	N/A	Keogh [5]
49		Unknown	+	−	+	−	+	−	−	N/A	−	N/A	Chang [33]
50		Unknown	−	+	−	−	−	−	−	N/A	−	N/A	Kriegstein [3]

EPS extrapyramidal system, *N/A* not available

[a]Antioxidative treatment: combined therapy with vitamin C, vitamin E and coenzyme Q

[b]Antioxidative treatment: Coenzyme Q

[c]Piracetam

[d]Bromocriptine for parkinsonian symptoms and akinetic mutism

[e]Haloperidol and benzodiazepines

[f]Pimozide for movement disorder

[g]Mannitol, dexamethasone and surgery for acute hydrocephalus

[h]Trihexyphenidyl for movement disorder

[i]Acyclovir and ampicillin for initially suspected infectious etiology

[j]Escitalopram, alimemazine and pantoprazole

[k]Surgery for external ventricular drainage and posterior fossa decompression

[l]Madopar for movement disorder

Table 2 Clinical and MRI data of 50 patients with heroin leukoencephalopathy by different intake routes

Demographics	IV injection ($n=15$)	Snorting ($n=5$)	Inhalation ($n=30$)	p value
Sex (M/F)	15/0	4/1	27/3	0.294
Mean age at onset	35.5	31.2	32.1	0.386[a]
Acute/delayed/progressive	6/7/0	3/1/0	6/1/13	0.001*
Mental changes (+/−)	15/0	4/1	12/18	0.000*
Cerebellar ataxia (+/−)	5/7	1/4	24/4	0.002*
Pyramidal (+/−)	12/3	2/3	16/14	0.143
Mutism (+/−)	9/5	0/5	1/26	0.000*
Dysarthria (+/−)	1/10	2/2	18/9	0.006*
EPS (+/−)	4/7	1/3	8/20	0.867
Urine/fecal incontinence (+/−)	5/5	0/3	1/25	0.002*
Improvement (+/−)	11/3	4/0	15/7	0.373
Mortality (+/−)	1/14	0/5	5/25	0.426
Treatments (antioxidative/symptomatic)	2/5	0/3	6/2	0.046*
MRI				
Time: acute/subacute/chronic	10/5/0	4/1/0	15/10/5	0.339
White matter (+/−)	14/1	4/1	25/5	0.608
U fibers (+/−)	3/6	1/3	0/21	0.023*
PLIC (+/−)	3/10	0/3	19/9	0.006*
Genu (+/−)	4/6	0/3	0/26	0.002*
P–A (+/−)	0/13	0/4	18/9	0.000*
Cerebellum (+/−)	2/8	1/4	25/4	0.000*
Brainstem (+/−)	0/10	0/5	20/10	0.000*
WR/T2ST	4/7	2/2	2/9	0.433

+/−: with/without. The sum of the with and without cases might not match the total number in all groups due to missing data

EPS extrapyramidal system, *Genu* genus of the internal capsules, *P–A* posterior to anterior involvement of the cerebral white matter, *PLIC* posterior limbs of the internal capsules, *U fibers* subcortical U fibers, *WR/T2ST* water restriction/T2 shine-through effects

*Pearson chi-squared test, $p<0.05$

[a]One-way ANOVA

acute-onset or delayed-onset encephalopathy, which is consistent with previous reports [2, 21, 34]. Mutism, particularly akinetic mutism, has been found in all heroin abusers using the IV injection route in a previous study [8]. These clinical characteristics correspond to the diffuse symmetric supratentorial white matter lesions. However, cerebellar ataxia and dysarthria, which are related to infratentorial cerebellar or brainstem lesions, were hallmarks in patients using heroin by inhalation.

The pathophysiological mechanisms underlying encephalopathy induced by inhalation versus IV injection of heroin might be related to the chemical components of heroin, impurities, absorption or metabolites. In its base form, heroin is insoluble in water and can be used by inhalation, but in the hydrochloride form, heroin is water soluble and suitable for IV injection. "Chasing the dragon" is an inhalation route in which vapors are inhaled after heating heroin on aluminum foil above a flame. The heroin base is often mixed with additives, such as barbiturates and caffeine. The direct toxicity of heroin, the byproducts created by combustion and adulterants are considered mechanisms of toxic leukoencephalopathy caused by "Chasing the dragon" [35]. Symmetric lesions in the cerebral white matter, PLIC (sparing the anterior limbs), cerebellum and brainstem are common imaging findings in patients using heroin by inhalation. Reduced NAA and choline with increased lactate peaks indicating mitochondrial dysfunction or axonal injury have been observed in serial studies investigating leukoencephalopathy induced by heroin inhalation [1, 3, 6]. However, the risks of heroin-induced leukoencephalopathy in patients using heroin by inhalation are still uncertain, although a relative deficiency of arylsulfatase-A or genetic predispositions have been proposed [36, 37].

Delayed-onset encephalopathy represents a unique onset pattern, especially in heroin abusers who use by IV injection. By observing MRI findings, reversible delayed post-hypoxic leukoencephalopathy (DPHL) has been described in several case reports in which delayed-onset symptoms

Table 3 Brain MRI and MRS findings of 50 patients with heroin-induced leukoencephalopathy

No.	Routes of heroin intake	MRI time	Supratentorial lesions					Infratentorial lesions		DWI	ADC	Gd	MRS		
			White matter	U fibers	PLIC	Genu	P–A	Cerebellum	Brainstem				NAA	Choline	Lactate
1	IV injection	Subacute phase	+	+	−	+	−	−	−	↑	↑	−	↓	↑	−
2		Subacute phase	+	+	−	−	−	−	−	↑	↑	−	N/A	N/A	N/A
3		Acute phase	+	N/A	−	N/A	−	−	−	N/A	N/A	N/A	N/A	N/A	N/A
4		Acute phase	+	N/A	−	+	−	N/A	N/A	↑	N/A	−	N/A	N/A	N/A
5		Acute phase	+	−	+	N/A	N/A	+	−	N/A	N/A	N/A	N/A	N/A	N/A
6		Subacute phase	+	−	−	−	−	−	−	↑	↓	N/A	N/A	N/A	N/A
7		Acute phase	+	−	−	−	−	−	−	↑	↓[a]	−	N/A	N/A	N/A
8		Subacute phase	+	N/A	+	N/A	−	−	−	↑	↓	N/A	N/A	N/A	N/A
9		Acute phase	+	N/A	−	+	−	N/A	N/A	N/A	N/A	−	N/A	N/A	N/A
10		Acute phase	+	N/A	N/A	N/A	N/A	N/A	N/A	↑	N/A	N/A	N/A	N/A	N/A
11		Acute phase	+	N/A	+	+	−	N/A	N/A	↑	↓	−	N/A	N/A	N/A
12		Acute phase	+	−	−	−	−	−	−	N/A	N/A	N/A	N/A	N/A	N/A
13		Acute phase	−	−	−	−	−	+	−	↑	N/A	N/A	N/A	N/A	N/A
14		Subacute phase	+	−	N/A	N/A	−	N/A	N/A	↑	N/A	−	N/A	N/A	N/A
15		Acute phase	+	+	−	−	−	−	−	↑	N/A	−	N/A	N/A	N/A
16	Snorting	Acute phase	+	N/A	N/A	N/A	N/A	−	−	↑	↓	N/A	N/A	N/A	N/A
17		Acute phase	+	−	−	−	−	−	−	N/A	N/A	N/A	N/A	N/A	N/A
18		Acute phase	−	−	−	−	−	+	−	↑	↑	−	N/A	N/A	N/A
19		Acute phase	+	−	N/A	N/A	−	−	−	↑	↓	−	N/A	N/A	N/A
20		Subacute phase	+	+	−	−	−	−	−	↑	↑	−	N/A	N/A	N/A
21	Inhalation	Chronic phase	+	−	+	−	+	+	+	↑	↑	N/A	N/A	N/A	N/A
22		Chronic phase	−	−	−	−	−	+	−	N/A	N/A	−	N/A	N/A	N/A
23		Subacute phase	+	−	N/A	N/A	N/A	+	+	N/A	N/A	N/A	N/A	N/A	N/A
24		Chronic phase	+	−	+	−	+	+	−	N/A	N/A	N/A	N/A	N/A	N/A
25		Chronic phase	+	N/A	+	N/A	N/A	N/A	+	N/A	N/A	N/A	N/A	N/A	N/A
26		Chronic phase	+	N/A	+	N/A	+	+	+	N/A	N/A	N/A	N/A	N/A	N/A
27		Subacute phase	+	−	+	−	+	+	+	↑	↑	−	↓	↓	↑
28		Subacute phase	+	−	+	−	+	+	+	↑	↑	−	↓	↓	↑
29		Acute phase	+	−	+	−	+	+	+	N/A	N/A	N/A	N/A	N/A	N/A
30		Subacute phase	+	−	+	−	+	+	+	N/A	N/A	N/A	N/A	N/A	N/A
31		Subacute phase	+	−	+	−	+	+	+	N/A	N/A	N/A	↓	−	↑

Table 3 (continued)

No.	Routes of heroin intake	MRI time	Supratentorial lesions					Infratentorial lesions		DWI	ADC	Gd	MRS		
			White matter	U fibers	PLIC	Genu	P–A	Cerebellum	Brainstem				NAA	Choline	Lactate
32		Subacute phase	+	−	+	−	+	+	+	N/A	N/A	N/A	↓	−	↑
33		Acute phase	+	−	+	−	N/A	+	+	N/A	N/A	−	N/A	N/A	N/A
34		Acute phase	+	−	−	−	−	+	−	N/A	N/A	N/A	N/A	N/A	N/A
35		Subacute phase	+	−	−	−	−	−	−	↑	↓	N/A	N/A	N/A	N/A
36		Acute phase	−	−	−	−	−	+	−	N/A	N/A	N/A	N/A	N/A	N/A
37		Acute phase	−	−	−	−	−	+	−	N/A	N/A	N/A	N/A	N/A	N/A
38		Acute phase	−	−	+	−	−	+	−	N/A	N/A	N/A	N/A	N/A	N/A
39		Subacute phase	+	−	N/A	N/A	−	+	+	N/A	N/A	N/A	N/A	N/A	N/A
40		Acute phase	+	−	−	−	−	−	−	↑	↓	N/A	N/A	N/A	N/A
41		Subacute phase	+	−	−	−	+	−	−	N/A	N/A	N/A	N/A	N/A	N/A
42		Acute phase	+	N/A	+	−	+	+	+	↑	↑	−	↓	↓	↑
43		Acute phase	+	N/A	+	−	+	+	+	↑	↑	−	↓	↓	↑
44		Acute phase	+	N/A	+	−	+	+	+	↑	↑	−	↓	↓	N/A
45		Acute phase	+	N/A	−	−	+	+	−	↑	↑	−	N/A	N/A	N/A
46		Acute phase	+	N/A	+	−	+	+	+	↑	↑	−	↓	↓	↑
47		Acute phase	+	N/A	+	−	+	+	+	↑	↑	−	↓	↓	↑
48		Acute phase	+	−	+	−	+	+	+	N/A	N/A	N/A	N/A	N/A	N/A
49		Acute phase	+	N/A	+	−	+	+	+	N/A	N/A	N/A	↓	N/A	↑
50		Subacute phase	−	−	−	−	−	−	+	N/A	N/A	N/A	−	−	↑

Gd gadolinium contrast enhancement, *Genu* genus of the internal capsules, *NAA N*-acetylaspartate, *N/A* not available, *P–A* posterior to anterior involvement of the cerebral white matter, *PLIC* posterior limbs of the internal capsules, *U fibers* subcortical U fibers

[a]Elevated ADC values after 18 days

Table 4 Clinical and MRI data of patients with different onset patterns of heroin leukoencephalopathy

Demographics	Acute-onset ($n=15$)	Delayed-onset ($n=9$)	Progressive ($n=13$)	p value
IV/snorting/inhalation	6/3/6	7/1/1	0/0/13	0.001*
Mental changes (+/−)	12/3	9/0	2/11	0.000*
Cerebellar ataxia (+/−)	8/3	2/7	12/0	0.002*
Pyramidal (+/−)	11/4	6/3	7/6	0.471
Mutism (+/−)	3/8	5/4	1/12	0.026*
Dysarthria (+/−)	4/6	1/6	12/1	0.002*
EPS (+/−)	4/7	3/5	4/9	0.764
Urine/fecal incontinence (+/−)	1/7	4/4	0/12	0.019*
Improvement (+/−)	11/4	7/1	6/1	0.509
Mortality (+/−)	2/13	1/8	0/13	0.346
Treatments (antioxidative/symptomatic)	1/6	2/4	4/0	0.019*
MRI				
White matter (+/−)	10/5	9/0	12/1	0.073
U fibers (+/−)	0/10	2/5	0/11	0.060
PLIC (+/−)	3/9	1/7	11/1	0.001*
Genu (+/−)	2/9	2/4	0/10	0.081
P–A (+/−)	0/13	0/8	9/1	0.000*
Cerebellum (+/−)	7/5	1/7	12/0	0.001*
Brainstem (+/−)	1/11	0/8	11/2	0.000*
WR/T2ST	4/3	4/3	0/3	0.019*

(+/−): with/without. The sum of the with and without cases might not match the total number in all groups due to missing data

EPS extrapyramidal system, *Genu* genus of the internal capsules, *P–A* posterior to anterior involvement of the cerebral white matter, *PLIC* posterior limbs of the internal capsules, *U fibers* subcortical U fibers, *WR/T2ST* water restriction/T2 shine-through effects

*Pearson Chi-squared test, $p<0.05$

Table 5 Summary of the key clinical features and main MRI findings in heroin leukoencephalopathy by different intake routes

	IV injection	Snorting	Inhalation
Symptoms	Mental changes Mutism Incontinence	Mental changes	Cerebellar ataxia Dysarthria
Onset pattern	Acute-onset Delayed-onset	Acute-onset	Progressive
MRI	U fibers Genu		PLIC P–A Cerebellum Brainstem[a] NAA↓, choline↓, lactate↑

Genu genus of the internal capsules, *NAA* N-acetylaspartate, *P–A* posterior to anterior involvement of the cerebral white matter, *PLIC* posterior limbs of the internal capsules, *U fibers* subcortical U fibers

[a]Only observed in the inhalation group

after acute hypoxic events were caused by acute carbon monoxide intoxication [38] or overdoses of various substances, including heroin. After the initial conscious disturbances in patients with DPHL, the symptoms rapidly improve within a few days, followed by clinical deterioration several weeks after the first episode. In our study, the mean latent time between the initial signs/symptoms and the onset of delayed leukoencephalopathy was 24 days, which is similar to previous reports [2, 7–10]. The initial signs/symptoms are presumably related to acute myelin sheath injury, followed by secondary injury due to cell necrosis after 10 to 14 days, with a slow recovery by long-term remyelination [39]. The delay is thought to be related to the half-life of myelin turnover, toxins inducing metabolic changes related to the turnover of myelin, or toxins residing in lipid-rich myelin resulting in continuous tissue damage and leading

to progressive clinical deterioration [9, 39–41]. The definite mechanisms of the latent period preferentially occurring in heroin-induced leukoencephalopathy in IV abusers remain uncertain. The possible mechanisms may be the C_{max} of heroin, its bioavailability and metabolites (6-monoacetylmorphine, morphine and morphine-glucuronides) have been shown to be much higher following IV injection [42]. IV injection heroin abusers tend to have greater risks of overdose and blood-borne infections than abusers using non-IV injection routes [43]. In addition, morphine-induced inflammatory responses and cytokine release, which are related to hypoxic-ischemic changes, have been observed in brain samples from IV heroin abusers [44].

On the other hand, water restriction was more frequently observed in the heroin abusers using non-inhalation routes, while the T2 shine-through effect (a high T2 signal that 'shines through' to the DWI) was more frequently observed in the heroin abusers using the inhalation route [34]. In addition, water restriction was more prone to be found during the early stage [18], and the ADC values might elevate over time [2]. The occurrence of water restriction is indicative of irreversible white matter damage that prompts more remyelination and delayed leukoencephalopathy, while the absence of water restriction represents a temporary white matter injury with less remyelination. In our study, however, water restriction was not significantly associated with the routes of heroin intake or the clinical stage. The discrepancy between our study and previous cases might be due to the retrospective analysis, selection biases, inability to exclude other toxin exposures beyond heroin and other limitations of assessing disease states by collections of case reports.

The severity and outcome of heroin-induced leukoencephalopathy are thought to be dose related [3]. In previous publications, the mortality rate ranged from 23 to 48%, which is much higher than that (12%) observed in our study [1, 3, 5, 45]. The significant decline in the mortality rate might be related to an increased awareness and improved quality of health care by prompt diagnoses and appropriate management, such as antioxidative or symptomatic treatments. In our study, the mortality and non-improvement rates were both affected by the routes of heroin intake and were slightly higher in the heroin abusers using the inhalation route than in the heroin abusers using the IV injection or snorting routes (mortality rate: 16.7% versus 6.7% versus 0%; non-improvement rate: 31.8% versus 27.3% versus 0%). Although the pathophysiology remains unknown, the formulation of heroin and the greater involvement of the infratentorial regions (especially the brainstem) are assumed to be related to the high mortality rate and lower improvement rate in patients who inhale heroin. Although there is no standard treatment for patients with heroin-induced leukoencephalopathy, we found that patients who received treatments, including antioxidative or symptomatic treatments, tended to have better outcomes and a lower mortality. However, it is still difficult to conclude that the treatment was effective in these patients because of the limitations of a small size and a retrospective design, and the recovery of the disease could have been the natural course, which should also be considered.

Conclusion

The clinical symptoms, outcomes and imaging findings of heroin-induced leukoencephalopathy can be categorized in terms of the different intake routes. Our findings are likely useful for early diagnosis and treatment. Further research into the roles of antioxidants and neuroprotective agents in the treatment of heroin-induced encephalopathy might guide better clinical practice of physicians and improve the outcome of heroin abusers.

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Author contributions M-YC collected the clinical data, reviewed the literature and contributed to the manuscript preparation. S-CC reviewed and analyzed the brain MRI data. TW and S-NL both reviewed the EEG data. Y-CC, H-YH, J-LH, C-WC, W-EJT, H-TL, H-IC, B-LC and M-HT collected the clinical data and reviewed the literature. L-SR contributed to the manuscript preparation and final approval of the version to be published.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards This study was approved by the Chang Gung Memorial Hospital Institutional Review Board (No: 201800826B0) and, therefore, was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki and its later amendments, and informed consent was unnecessary.

Informed consent Informed consent is not mandatory for retrospective medical chart reviews. Details that might disclose the identity of the subjects under study should be omitted.

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