Rare disease

Delayed hypoxic-ischemic leukoencephalopathy

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Summary

A 55-year-old female was found unconscious in a ventilated room. She recovered consciousness on the way to the emergency room. Her vital signs were stable. She presented with negativism and poor communication. Physical examination, routine tests, brain CT and electroencephalogram were normal. Urine toxicology was positive for benzodiazepines. Twelve days after, she presented with catatonia and immobility. Additional examinations, including cerebrospinal fluid (CSF) testing and brain CT, were again normal. Risperidone was administered, and psychotherapy intensified. In the third week, the condition worsened, with intense pyramidal signs and decerebration that led to a vegetative state. Brain MRI revealed diffuse leukoencephalopathy. Extensive metabolic and CSF studies were persistently negative. Brain biopsy was compatible with chronic cerebral hypoxia/anoxia. A diagnosis of delayed hypoxic-ischemic leukoencephalopathy was made. Supportive measures were intensified. She was discharged from the hospital after 4 months in a minimally conscious state and was capable of elementary communication and recognising faces.

BACKGROUND

Delayed hypoxic-ischemic leukoencephalopathy (DHIL) is very rarely diagnosed in clinical practice. DHIL is characterised by acute neurologic deterioration and cerebral demyelination that occur days to weeks after the clinical recovery from a hypoxic-ischemic insult in the brain.^{1 2} Middle-aged and older people have been reported to be affected by this disease more often than other groups.¹ Delayed onset leukoencephalopathy may also be secondary to carbon monoxide poisoning or to the administration of heroin or cocaine.^{3 4} No specific therapies exist for DHIL, but the majority of affected individuals recover spontaneously.^{1 2}

CASE PRESENTATION

A 55-year-old female was found unconscious in a ventilated living room. She had a history of depression and was taking alprazolam for insomnia. She remained unreachable

for the last 4 days with her son, known to be addicted to heroin. She recovered consciousness spontaneously on the way to the emergency room, and her vital signs were stable. The patient was diagnosed with aspiration pneumonia and was treated with antibiotics. With the exception of fluctuating negativism and poor communication, the results of the patient's general physical and neurological examinations were normal. The results of the tests that were conducted at admission to the hospital (complete blood count, electrolyte tests, arterial blood gas test, CT of the brain and electroencephalogram (EEG)) were normal. The urine toxicology test was positive for benzodiazepines and negative for other drugs of abuse (opioids including heroin, amphetamines, marijuana, cocaine, tricyclic antidepressants and alcohol).

The patient was sent home 4 days after admission to the hospital with a presumptive diagnosis of psychological trauma and was medicated with sertraline and

Figure 1 T2 Flair-extensive signal abnormalities in the subcortical white matter, with areas of cystic necrosis.

Figure 2 (H&E) Diffuse loss of brain white matter fibers and infiltration by histiocytes (arrows).

bromazepine. Twelve days after the patient was sent home, after an initial period of improvement, she became catatonic and exhibited an expressionless face, negativism and immobility. The patient was hospitalised in a psychiatric infirmary. The results of several additional examinations, including an examination of the cerebrospinal fluid (CSF) and a CT of the brain, were normal. The patient's clinical phenomenology was attributed to post-traumatic stress disorder. Risperidone was administered, and the patient's psychotherapy was intensified. During the following 3 weeks, the patient's condition remained stable, with occasional periods of urinary and faecal incontinence. Suddenly, without any recognised precipitating factors, the patient's condition worsened. At that time, the patient exhibited akinetic mutism, decerebration, spastic quadriplegia, generalised symmetric hyperreflexia and the presence of bilateral Babinski's sign. She was haemodynamically stable, and the results of the general examination were normal.

The EEG revealed diffuse slowing activity of grades 4 and 5 with bilateral, symmetrical moderate-voltage θ and δ activity, without the presence of lateralising signs or epileptiform abnormalities. The MRI of the brain revealed diffuse leukoencephalopathy (figure 1). The results of an additional investigation with a comprehensive battery of tests (table 1) were normal. A sample of the CSF was sent to the National Reference Institute (Instituto 'Ricardo Jorge') for an extensive viral, fungal and bacterial analysis, and the results were negative.

The presence of subcortical demyelination and persistent negative findings on an analysis of the CSF led to the diagnosis of DHIL; however, the possibility of exposure to heroin through the patient's son suggested a delayed toxic effect of heroin, which is known as 'chasing the dragon syndrome'. Carbon monoxide poisoning was not considered due to the absence of any source of carbon monoxide and the presence of good ventilation in the place where the patient was found.

Supportive measures, including baclofen for spasticity, antioxidant ubiquinone and prednisolone were implemented; however, despite these measures, the patient progressed to a vegetative state. Intense paroxysms of dysautonomia that were characterised by diaphoresis, tachypnea, pupillary dilatation and trismus were observed frequently.

A brain biopsy during the second month of hospitalisation revealed non-specific findings; however, these findings were compatible with chronic cerebral hypoxia/anoxia (figure 2).

At the third month of hospitalisation, the patient slowly began to recover consciousness. Upon discharge from the hospital, approximately 120 days after the patient's initial evaluation (table 2), she was in a minimally conscious state and was capable of elementary communication, was able to pursue visual stimuli and was beginning to recognise her family. A physical examination revealed generalised amyotrophy, tetraparesis and the presence of a bilateral Babinski's sign. An MRI of the brain revealed that the lesion was stable.

INVESTIGATIONS

Table 1 Extensive blood and CSF investigation.

Table 2 Timeline of the clinical evolution.

DISCUSSION

Because of the environment in which the patient was found and the clinical evolution of the persistently normal CSF and metabolic status, we diagnosed the patient with DHIL. 'Chasing the dragon syndrome' was also considered as a diagnosis because of the possibility of heroin vapour exposure. This syndrome is a rare complication from the inhalation of heated heroin vapour, which rises like the tail of a dragon. In this method of heroin administration, the drug is rapidly delivered in high doses. Like DHIL, the clinical course of 'chasing the dragon syndrome' is characterised by an initial period of predominantly psychiatric manifestations. This period is followed by an asymptomatic interval of clinical improvement that precedes a late phase of neurological deterioration, which is mainly characterised by a decreased level of consciousness and pyramidal dysfunction.^{1-2 4} Unfortunately, it is impossible to distinguish these syndromes clinically.

The patient in the present study was not a heroin user, and to date, no cases of 'chasing the dragon syndrome' have ever been reported to be due to passive exposure to the drug, and the brain imaging findings in the present study were not in favour of this hypothesis, because in this syndrome there is a clear predilection and predominant involvement of cerebellum, posterior limb of the internal capsule and brainstem.^{5 6}

The patient's MRI findings were similar to those that have been reported to be typical of DHIL and consisted of diffuse hyperintensity of the cerebral white matter on T2-based sequences, particularly in the region of the dorsal frontal and parietal lobes.⁷ The histological alterations in the present study were also compatible to what is found in DHIL, different degrees of myelin loss, presence of lipid-laden macrophages.^{1-2 7} The same findings can be described in Chasing the Dragon, but in this syndrome, there is concurrent loss of oligodendrocytes, severe damage to myelin sheaths, with oedema, vacuolation and destruction which is named spongiform leukoencephalopathy.^{8 9}

It seems reasonable to assume that the patient suffered hypoxia that was secondary to alprazolam-induced respiratory depression and to speculate on whether the administration of alprazolam was a suicide attempt. Alprazolam has an average terminal elimination half-life of 12 h¹⁰; therefore, it is plausible that after a certain period of time, spontaneous recovery would eventually occur as a result of the decreasing drug concentration.

It is believed that DHIL occurs as a result of the disruption of ATP-dependent enzymatic pathways that are involved in myelin turnover, which leads to prolonged moderate hypoxia.¹ To date, it is impossible to identify patients who are at risk of developing this syndrome.

A pseudodeficiency of arylsulfatase A is considered to be a predisposing factor of DHIL^{11 12}; however, in our case, which is in agreement with the majority of previous reports, the patient exhibited normal levels of arylsulfatase A.

Because of the possibility of recovery for many patients with DHIL,^{1-2 7} it is extremely important to consider this diagnosis in non-clarified subacute neuropsychiatric

Table 1 Extensive blood and CSF investigation

Investigation panel	
Haematology	Blood count, blood times
Biochemistry	Renal function, hepatic function, Ca, Mg, Na, K, pH, lactate, pyruvate, arylsulfatase A
Endocrinology	Thyroid function, adrenal function
Autoimmunity	ANCA/ANA/FR, complements
CSF	Toxoplasma, Koch bacillus, Borrelia, Mycoplasma, Adenoviruses, CMV, EBV, HSV, VRDL, HBV, HCV, VRDL/RPR, Enterovirus, West Nile virus, JC, Prion disease
Others	Haemosedimentation rate, HIV, antiphospholipid antibodies

ANCA, antineutrophilic cytoplasmic antibodies; ANA, antinuclear antibody; CSF, cerebrospinal fluid; CMV, cytomegalovirus; EBV, Epstein-Barr virus; FR, factor rheumatoid; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; JC, John Cunningham; RPR, rapid plasma reagin; VDRL, venereal disease research laboratory.

Table 2 Timeline of the clinical evolution

Timeline	
Day 0	Found unconscious; recovered consciousness spontaneously; Aspiration pneumonia; negativism and poor communication; Normal Brain CT
Day 12	Catatonic, expressionless face and immobility
Day 31	Akinetic mutism, decerebration, spastic quadriplegia, generalised symmetric hyperreflexia and bilateral Babinski's sign. EEG: Diffuse slowing activity grade 4 and 5. Brain MRI: Diffuse leukoencephalopathy.
Day 40–50	Vegetative state; intense paroxysms of dysautonomia.
Day 80–90	Slow improvement, occasional words.
Day 120	Minimally conscious state, generalised amyotrophy, tetraparesis, bilateral Babinski's sign, discharge from the hospital.

EEG, electroencephalogram.

conditions and to optimise supportive treatment to increase the probability of a good functional recovery.

Learning points

- Delayed hypoxic-ischemic leukoencephalopathy can be easily misdiagnosed because of this disorder's biphasic pattern of evolution.
- It is extremely important to consider the diagnosis of delayed hypoxic-ischemic leukoencephalopathy in non-clarified subacute neuropsychiatric conditions because of the likelihood of recovery, even in very severe cases.
- An MRI of the brain is crucial when determining the diagnosis of delayed hypoxic-ischemic leukoencephalopathy.

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Competing interests None.

Patient consent Obtained.

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