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The clinical and pathological features of toxic encephalopathy caused by occupational 1,2-dichloroethane exposure

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Abstract

To understand the clinical and pathological features of 1,2-dichloroethane (DCE) toxic encephalopathy.

The cases of 4 patients who were admitted to Xiangya hospital between January 8, 2008 and November 8, 2012 with diagnoses of DCE toxic encephalopathy were examined. We recorded data on gender, age of onset, exposure time to DCE, symptom onset to admission interval, symptom onset to worst symptom experience interval, and clinical manifestations, as well as cranial magnetic resonance imaging (MRI) and brain biopsy pathology results.

All 4 patients had a history of DCE exposure and presented with symptoms of intracranial hypertension. Cranial MRI revealed extensive brain edema throughout the subcortical white matter, the bilateral globus pallidus, and the cerebellar dentate nuclei. The brain biopsy confirmed severe cerebral edema, including peripherovascular edema, with swelling of various cell types, with extensive glial cell necrosis. After treatment with steroids and mannitol (3–10 weeks), all 4 patients recovered, partially or completely.

Severe brain edema and extensive glial cell necrosis were the main pathological features observed in the present cases, with a likely etiology of DCE toxicity. Early, prompt, and long-term treatment with dehydrating agents and glucocorticoids was an effective treatment for this condition.

Abbreviations: ADC = apparent diffusion coefficient, CNS = central nervous system, DCE = 1,2-dichloroethane, DWI = diffusion weighted MR imaging, MRI = magnetic resonance imaging, T1WI = T1 weighted imaging, T2WI = T2 weighted imaging.

Keywords: astrocyte, brain edema, histopathology

1. Introduction

1,2-Dichloroethane (DCE) is a high lipid-soluble solvent used widely in manufacturing industries, such as shoe-making, tanneries, and toy-making, among others.[1] It can be absorbed through the respiratory tract, gastrointestinal tract, and skin and it accumulates in lipophilic tissues.[2] Low-concentration DCE exposure can cause nausea, vomiting, weakness, tremor, and vertigo, and at high concentrations, DCE exposure depresses the central nervous system (CNS). The CNS syndrome caused by acute DCE poisoning is called DCE toxic encephalopathy.[3–6] Long-term exposure to DCE can result in CNS disorders and/or liver and kidney dysfunction.[7] The broad use of DCE is likely linked to the increasing incidence of DCE toxic encephalopathy.

Although the clinical and neuroimaging features of DCE toxic encephalopathy have been described,[8,9] the pathological features of the disease are unclear. Xiangya hospital (the First Affiliated Hospital, College of Medicine, Central South University) is a major medical center in southern China where there are many manufacturing factories. Here, we report a retrospective study aimed at reviewing the clinical and pathological features of DCE toxic encephalopathy in four patients admitted to our hospital.

2. Methods

Four patients were admitted to Xiangya hospital and diagnosed subsequently with DCE toxic encephalopathy. They were employed in shoe-making (N=1) and toy-making (N=1) in Guangdong province and electronics production factories (N=2) in Zhejiang province. We recorded data on gender, age of onset, exposure time to DCE, time from onset of symptoms to hospital admission, time from symptom onset to development of the worst symptoms experienced, and clinical manifestations. All 4 patients underwent lumbar puncture and cranial magnetic resonance imaging (MRI) examinations. Two underwent pathological examination of brain biopsy samples (Table 1).

Our study plan received *a priori* approval by the local ethics committee and was completed in accordance with the principles of the Helsinki Declaration. Informed consent was obtained from each subject.

The data were analyzed with descriptive statistics and Student's t tests. All analyses were carried with the Statistical Package for Social Science, version 13.0. $P < .05$ was considered statistically significant.

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Table 1

Features of each patient (P).

P	Sex/age	Occupation/exposure time	Symptom (s)	MRI findings	ICP, mm H_2O	Pathology	Follow-up time
1	F/20 y	Shoemaker/5 mos.	Headache	Extensive edema in WM, GP, ND, and bilateral cortex.	440	Extensive severe neural edema, extensive glial cell necrosis.	8 mos.
2	M/38 y	Toymaker/1 y	Headache, blurred vision.	Extensive edema in WM and ND.	360		1 y
3	M/22 y	Electronics worker/8 mos.	Seizure	Extensive edema in WM, GP, and bilateral cortex.	410	Extensive edema in glial cytoplasm and neurites. Minor glial necrosis and pyknosis.	2 y
4	F/24 y	Electronics worker/3 mos.	Dizziness, limb weakness	Extensive edema in WM and GP.	250		6 mos.

GP = globus pallidus, ICP = intracranial pressure, mos. = months, MRI = magnetic resonance imaging, ND = nucleus dentatus, WM = white matter, y = years.

3. Results

All 4 patients had a history of DCE exposure with a subacute onset of symptoms, including headache (2/4; 50%), dizziness (1/4; 25%), seizures (1/4; 25%), limb weakness (1/4; 25%), and blurred vision (1/4; 25%). Their mean intracranial pressure (±SD) was 365 ± 72.3 (range, 250–440) mm H_2O. All

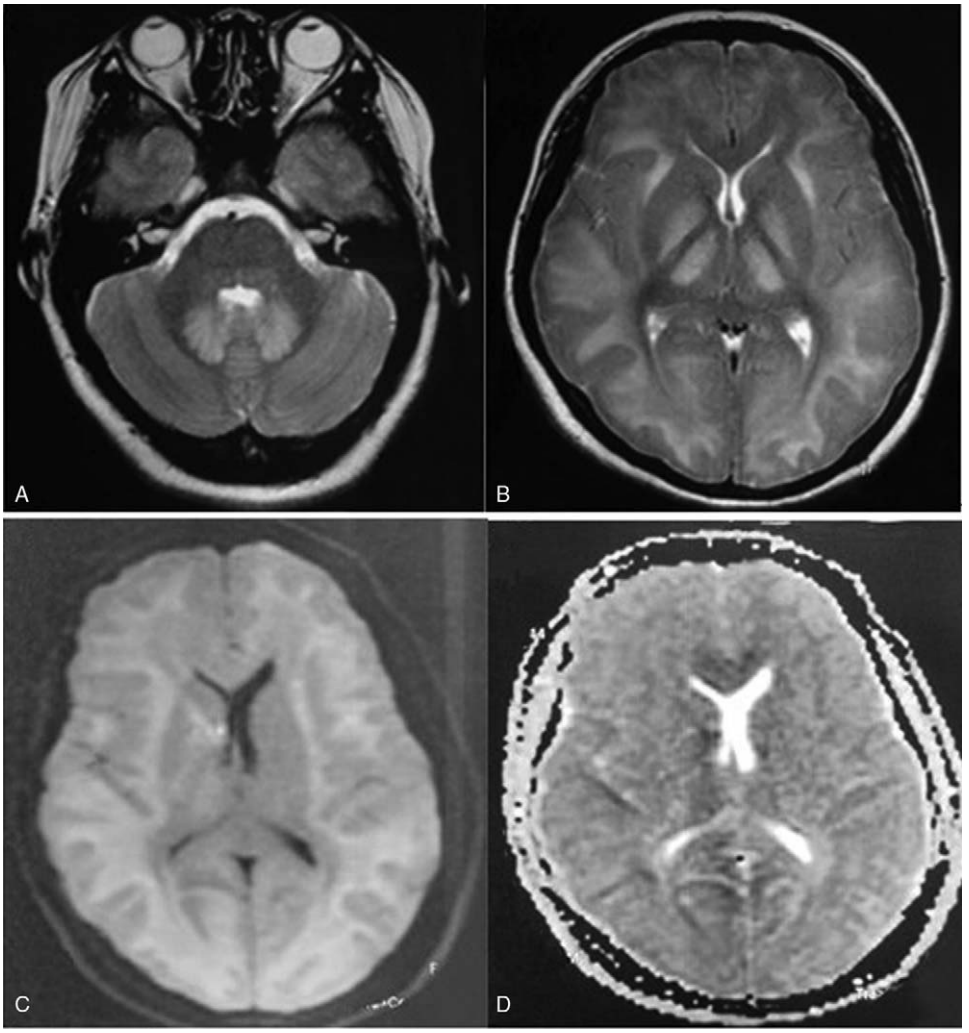

Figure 1. A 20-year-old female had worked in a shoe-making factory for 5 months. She was admitted to our hospital complaining of a headache. Her cranial MRI on T2WI showed symmetrical hyperintensity in the subcortical white matter, bilateral globus pallidus (B), and cerebellar dentate nuclei (A), as well as a swollen gyrus, a shallow/disappearing sulcus, and a reduced ventricle. DWI (TR 2400/TE 74) (C) and ADC (D) mapping showed hyperintensity and hypointensity, respectively, in the niduses above. After treatment with sufficient steroids and mannitol, she recovered, as seen by disappearance of clinical symptoms and reduced lesions on a follow-up cranial MRI (not shown).

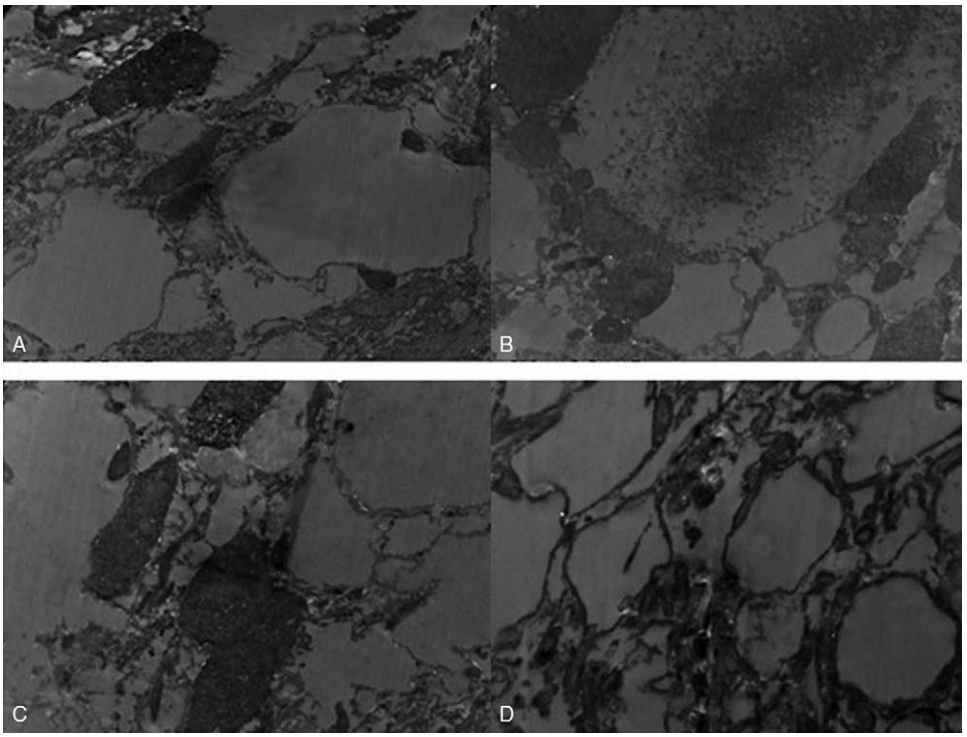

Figure 2. Electron micrographs of brain biopsy samples. A: Peripherovascular edema and neurite edema. Magnification: 3500×. B: Glial neurite (axons or dendrites) edema and neuronal necrosis. Magnification: 5000×. C: Serious edema and glial pyknosis. Magnification: 5000×. D: Reticulated neurites because of serious edema. Magnification: 10,000×.

cerebrospinal fluid samples tested had normal cell counts and biochemistry.

Cranial MRI (1.5-T) showed extensive and symmetrical abnormal signals in subcortical white matter, bilateral globus pallidus, and cerebellar dentate nuclei in both T1- and T2-weighted images (Fig. 1). Moreover, diffusion weighted MRI (DWI) and apparent diffusion coefficient (ADC) mapping showed vasogenic brain edema (hyperintensity on ADC mapping) in 1 patient (25%), cytotoxic edema (hyperintensity and hypointensity in DWI and ADC mapping, respectively), in 1 patient (25%), and mixed edema in 2 patients (50%) in the niduses above. The images also revealed swollen gyri, shallow (or disappearing) sulcus, and reduced brain ventricles (Fig. 1).

There was extensive and serious edema in glial cytoplasm and neurites, associated with pyknosis and extensive glial cell necrosis. Finally, there was swelling and expansion of neuronal endoplasmic reticulum and mitochondria, followed by a small amount of neuronal necrosis and pyknosis (Fig. 2).

After long-term (3–10 weeks) treatment with steroids and/or mannitol, all patients recovered well, as indicated by the lessening or disappearance of clinical symptoms, normal intracranial pressure in a follow-up lumbar puncture, and resolved lesions on follow-up cranial MRI examinations.

4. Discussion

Our hospital admitted 4 patients with DCE toxic encephalopathy in the last 5 years, all of whom had a history of DCE exposure and complained of symptoms such as headache, dizziness, and seizures. Cranial MRI demonstrated extensive brain edema, including vasogenic (N = 1), cytotoxic (N = 1), and mixed (N = 2) edema in the subcortical white matter, the bilateral globus pallidus, and the cerebellar dentate nuclei. The main neuroimaging manifestation was severe mixed edema.

Our neuroimaging findings differ from those of Liu and coworkers,[5] who reported vasogenic edema as the main form of brain edema in DCE toxic encephalopathy. We suspect this difference may be attributable to differences in DCE exposure in terms of duration and concentration. Two of the four patients whose conditions worsened after admittance underwent biopsy pathology, which revealed severe brain edema in one case and extensive glial necrosis in the other (Fig. 2).

Research in animals has shown that DCE-related injury to glial cells is more severe and occurs earlier than that to brain microvascular endothelial cells.[6] Our human brain pathology study provides additional supporting evidence for the glial toxicity of DCE. Astrocytes are a type of glial cells that are important for the repair of brain microvascular endothelial cells and restoration of the blood-brain barrier.[7] Thus, long-term brain edema (e.g., 10 weeks) could be associated with slowed blood-brain barrier restoration due to reduced astrocyte function. After long-term (3–10 weeks) treatment with steroids and/or mannitol, all 4 patients described in this report recovered well.

It should be noted that this study has a couple of major limitations. First, the number of cases was small and the pathological data were quite limited. Second, this was not a randomized clinical trial, which would not be ethically acceptable. Despite these limitations, we consider the pathology of DCE toxic encephalopathy to be an important strength of this study. Future investigations with larger patient samples are needed.

In conclusion, brain edema is considered to be the pathological basis of DCE toxic encephalopathy (Fig. 2), and this edema

persists for a long duration. Control of brain edema is critical to providing a curative treatment for DCE toxic encephalopathy. For a good prognosis, therapeutic drugs, generally a dehydrating agent and a glucocorticoid, should be given as soon as possible, for an extended period of time (3–10 weeks).[8] During the treatment period, clinicians should watch for possible development of a hernia resulting from long-term brain edema.

Author contributions

Conceptualization: Fafa Tian.
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Formal analysis: Jing Dang.
Funding acquisition: Jing Dang, Fangfang Bi.
Investigation: Jing Dang, Fangfang Bi.
Methodology: Fangfang Bi.
Project administration: Fangfang Bi, Fafa Tian.

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