Case Report

Propensity for seizure-related cortical laminar necrosis in hepatic encephalopathy

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1. Introduction

Cortical laminar necrosis (CLN) can result from sustained epileptic discharges[1]. Hepatic encephalopathy may also predispose to it[2]. We present three patients with liver disease who developed CLN after prolonged focal seizures. Clinical details are summarised in Table 1. All three patients suffered from hepatic encephalopathy, caused in two by cirrhosis. Peak blood ammonia levels ranged from 82 to 140 μmol/L (normal 12–47 μmol/L). Patient 1 developed focal motor status epilepticus (SE). Patient 2, who presented with frequent focal motor seizures, also had 2 focal to bilateral tonic–clonic seizures. Patient 3, in whom a left subdural haematoma was surgically drained 3 weeks beforehand, had recurrent focal impaired awareness seizures. Focal seizures were evident on electroencephalography (EEG) in all cases, with periods of non-convulsive SE in Patients 1 and 3. Sequential MR imaging in each case revealed progression to CLN (Fig. 1). All patients became permanently

disabled with increased modified Rankin Scale scores over a 6-month interval. Hypotension or hypoxia was not documented in any of the cases.

2. Discussion

[3]Epileptiform EEG abnormalities may be present in up to 15% of patients with hepatic encephalopathy [1]. The prevalence of SE in the disorder has been estimated at 0.7%, and predicts unfavorable prognosis [2]. Our observations suggest that patients with hepatic failure are at increased risk of CLN from prolonged focal seizures. Furthermore, some of the causative epileptic activity here was non-convulsive, manifesting as electrographic seizures, and not easily distinguished from metabolic encephalopathy.

CLN commences with gyral cortical T2 signal abnormality. This evolves within weeks to a high intensity T1 signal, leading on to permanent loss of volume of the cerebral cortex. Prolonged seizures are a well-established cause of CLN[4]. Hypermetabolic and excitotoxic processes associated with SE, compounded by hypoxic-ischaemic injury [3], are likely mechanisms. Areas on EEG involved in the greatest extent of epileptiform activity affect the brain preferentially [4]. However, it is important to note that focal epilepsy is much more commonly associated with transient cortical change. Although only one of our cases had MR imaging prior to the development of CLN, each showed a transition from acute T2 weighted abnormality to chronic T1 cortical signal changes and atrophy, supporting the temporal relationship from sustained epileptiform activity.

[5]MRI features of liver failure include bilateral symmetric hyperintensities of the globus pallidus on T1-weighted imaging, and involvement of the thalami and cerebral white matter on FLAIR and T2 sequences. Cerebral cortical changes, either diffuse or localized to insular and cingulate cortical regions, may occur. While some of these abnormalities are reversible, CLN has been described previously in patients with hepatic encephalopathy[6]. Neuropathological studies on two autopsy cases,

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[1] Authors: please reference the first sentence of the Introduction since you are using it as a statement of fact.

[2] The 2nd sentence in the Introduction also needs to be referenced as a statement of fact.

[3] The first two sentences in the Discussion should be moved to the first two sentences in the Introduction.

[4] The first three sentences in the second paragraph of the Discussion need to be referenced as statements of fact.

[5] The first sentence of the third paragraph in the Discussion should be referenced as a statement of fact.

[6] The third sentence in the third paragraph of the Discussion needs to be referenced.

Table 1
Clinical details.

Patient	1	2	3
Age (yrs), gender	58, male	58, female	54, male
Liver disease	Acute alcoholic hepatitis	Cryptogenic cirrhosis with portal hypertension	Alcoholic cirrhosis with portal hypertension
Peak bilirubin level (normal range < 20 μmol/L)	120	66	41
Peak ammonia level (normal range 12–47 μmol/L)	88	140	82
Premorbid modified Rankin Scale	2	3	2
6-month modified Rankin Scale	3	4	3
Location in the brain of cortical laminar necrosis	Right parietal cortex	Left parietal cortex	Left parieto-occipital cortex
Clinical features[a] seizure localization on EEG	Left hand twitching. Right temporo-parietal lateralized periodic discharges	Right facial twitching. Left frontal epileptiform discharges; focal slowing in the left temporo-occipital area. One right-fronto-temporal epilpetiform discharge also recorded.	Impaired cognitive function. Left posterior quadrant lateralized periodic discharges evolving to generalized periodic discharges.

[a] Please break this last row into two rows separated by 1. Clinical features of seizures and 2. EEG localization. For the first column "left hand twitching"; the second column is "right facial twitching"; the third column is "Impaired cognition" for the Clinical Features. For EEG localization the remainder of the text should be move.

one of whom had several convulsive seizures prior to death, revealed extensive CLN [5]. Choi et al. reported the case of a 55-year-old-male with convulsive SE and hepatic encephalopathy from alcoholic cirrhosis [6].
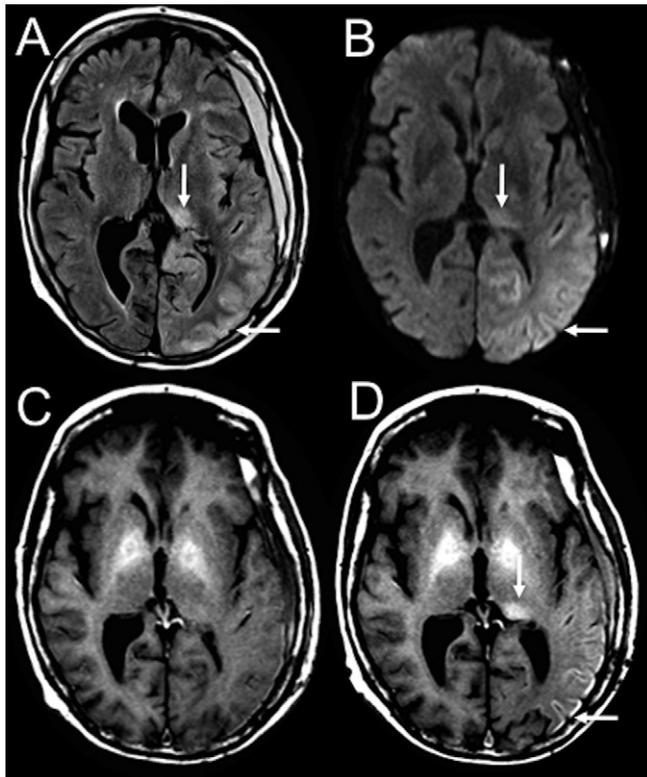
Fig. 1. Development of CLN in Patient 3. (A) Fluid attenuation inversion recovery (FLAIR) axial brain MRI shows extensive left cortical and left thalamic hyperintensity (arrows) localised to the areas of epileptiform activity. Left subdural fluid after recent evacuation of subdural haematoma is also noted. (B) Diffusion weighted axial brain MRI demonstrates concordant areas of cortical and thalamic hyperintensity (arrows). (C) Non-contrast T1 weighted axial brain MRI shows symmetric globus pallidus T1 hyperintensity. (D) Non-contrast T1 weighted axial brain MRI 11 days later demonstrating new T1 hyper intensity, localised to areas of epileptiform activity, compatible with laminar necrosis.

Bilateral temporal CLN and diffuse cerebral cortical atrophy was evident on MR imaging one month after presentation. Electrographic seizures could not be correlated with the areas of necrosis because of a delay in obtaining an EEG. The peak blood ammonia level of 1002 μmol/L, considerably greater than in our cases, was speculated to be the primary cause. The correlation between venous ammonia level and severity of encephalopathy in chronic liver disease is not particularly strong [7].

In our 3 cases, typical MR findings of hepatic encephalopathy (increased T1 in deep grey matter structures) were accompanied by CLN, which was localized to areas of maximal epileptiform activity. In hepatic encephalopathy, the excitotoxic processes of focal epileptiform discharges may be exaggerated by the metabolic consequences of hyperammonemia. Ammonia in the brain is exclusively metabolized by astrocytes, which employ the glutamine synthetase pathway. Elevated ammonia levels disrupt the normal glutamate-glutamine cycle, reducing the synaptic clearance of neuronally-released glutamate by downregulation of astrocytic glutamate molecular transport [8]. Epileptogenic and excitotoxic effects of extracellular glutamate, as seen in epileptic disorders, may therefore be magnified by hyperammonemia. Furthermore, intraneuronal glutamine is increased in hepatic encephalopathy, possibly contributing to neuronal swelling and oxidative damage [8].

Individuals with liver failure appear to have a previously under-recognized risk of developing seizure-related CLN with residual cognitive impairment and focal neurological deficits. Irrespective of venous ammonia level, it is important to detect subclinical seizures on EEG and to treat people with epileptic seizures/status epilepticus aggressively in the presence of hepatic encephalopathy. Concurrent ammonia-lowering therapies such as lactulose or rifaximin will theoretically minimize the toxic and neuronal excitatory metabolic effects associated with ongoing seizures. Conversely, valproic acid, with its propensity to increase ammonia levels even when liver function is normal, is a suboptimal anti-seizure drug for use in hepatic encephalopathy.

Study funding

Declaration of competing interest

All authors report no competing interests.

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