Delayed Cerebral Abnormalities in Acute Hyperammonemic Encephalopathy

Hiroshi Ito 1, Yasuhiro Ogawa 1, Nobutake Shimojo 1, Satoru Kawano 1

1. Division of Hospital Medicine, University of Tsukuba Hospital, Tsukuba, JPN

Corresponding author: Hiroshi Ito, itohirokan@yahoo.co.jp

Abstract

Acute hyperammonemic encephalopathy (AHE) is a rare but life-threatening condition. We present a case of an 81-year-old woman with cirrhotic AHE who presented with prolonged disorientation. Her magnetic resonance (MR) images were normal on the third hospital day, which showed bilateral abnormalities in the insular and cingulate cortices on day 13. The imaging abnormalities were slightly improved but remained on day 24. The imaging abnormalities seemed correlated with her persistent disorientation. AHE can present as delayed cerebral abnormalities, and follow-up imaging tests are useful in detecting such conditions. Further reports are needed to investigate the correlation between imaging abnormalities and clinical outcomes in patients with AHE.

Categories: Endocrinology/Diabetes/Metabolism, Emergency Medicine, Gastroenterology

Keywords: acute hyperammonemic encephalopathy, cirrhosis

Introduction

Patients with acute hyperammonemic encephalopathy (AHE) present with impaired consciousness, seizures, and death due to the toxic effect of ammonia on the brain [1]. AHE can be caused by hepatic disorders, urea cycle disorders, and drugs, including antiepileptics [2].

The typical radiologic findings of AHE have been known as four different types: diffuse cerebral edema, extensive infarct-like abnormalities, ischemic lesions, and symmetric cortical involvement [3]. However, little is known about the time course of changes in imaging findings of AHE.

Here we describe a patient with cirrhotic AHE who presented with persistent disorientation. Her magnetic resonance (MR) images of the brain were normal on admission, which later showed bilateral cortical abnormalities.

Case Presentation

An 81-year-old Japanese woman with hepatitis B virus-related cirrhosis admitted to our hospital because of impaired consciousness. Her heart rate was 103 beats per minute, blood pressure 154/72 mmHg, temperature 98°F, and respiratory rate 16 per minute. Neurological examination did not reveal neck rigidity and abnormal deep tendon reflexes. She was suspected of having hepatic encephalopathy because of asterixis and received branched-chain amino acids and lactulose. The plasma ammonia level was 322 μg/dL as seen in Table 1, and cerebrospinal fluid polymerase chain reaction for herpes simplex virus was negative.
TABLE 1: Laboratory data of the blood samples

|                      | Day 1   | Day 2   | Day 3   | Day 4   | Day 5   | Day 10  | Day 15  | Day 23  | Day 41   | Day 51   |
|----------------------|---------|---------|---------|---------|---------|---------|---------|---------|----------|----------|
| White blood cell (/μL) | 11,100  | 17,000  | 20,500  | 17,300  | 16,800  | 7,700   | 8,600   | 7,800   | 8,000    | 6,600    |
| Hemoglobin (g/dL)     | 7.2     | 6.6     | 9.7     | 8.6     | 8       | 8.3     | 8.8     | 8.7     | 7.8      | 8.4      |
| Platelet (×10⁴ /μL)  | 21.6    | 24.4    | 23.6    | 18.8    | 11.7    | 9.9     | 12.9    | 9.1     | 10.4     | 10.7     |
| Aspartate aminotransferase (U/L) | 22 | 30 | 29 | 73 | 95 | 132 | 70 | 38 | 28 | 37 |
| Alanine aminotransferase (U/L) | 12 | 12 | 13 | 26 | 81 | 133 | 102 | 41 | 17 | 15 |
| Lactate dehydrogenase (U/L) | 302 | 383 | 494 | 622 | 456 | 468 | 553 | 632 | 411 | 446 |
| Alkaline phosphatase (U/L) | 189 | 185 | 152 | 174 | 741 | 739 | 595 |
| γ-glutamyl transferase (U/L) | 40 | 37 | 35 | 41 | 60 | 378 | 321 | 226 | 122 |
| Sodium (mEq/L)        | 140     | 142     | 148     | 150     | 161     | 146     | 153     | 155     | 147      | 150      |
| Chlorine (mEq/L)      | 98      | 101     | 106     | 114     | 129     | 115     | 118     | 121     | 110      | 112      |
| Potassium (mEq/L)     | 2.8     | 3.1     | 3       | 4       | 3.6     | 3.8     | 3.1     | 4       | 4.2      | 4.9      |
| Urea nitrogen (mg/dL) | 80.1    | 93.3    | 131.1   | 153.1   | 125.6   | 32.3    | 42.2    | 31.5    | 40       | 30.5     |
| Creatinine (mg/dL)    | 0.95    | 1.22    | 1.92    | 1.81    | 1.15    | 0.94    | 0.81    | 0.81    | 0.73     | 0.66     |
| Ammonia (μg/dL)       | 322     | 417     | 214     | 115     | 54      | 42      | 57      |
| C-reactive protein (mg/dL) | 2.2 | 2.24 | 3.32 | 4.63 | 3.94 | 1.8 | 2.91 | 0.97 | 3.21 | 1.84 |

Serum ammonia reached its peak on the third hospital day, and decreased gradually.

She developed status epilepticus and was intubated on the third hospital day. MR images on day 11 showed symmetric abnormal signal intensity in the insular and cingulate cortices bilaterally, which suggested the toxic effect of accumulated ammonia (Figure 1A).

Her consciousness improved slightly after extubation on day 13, when the plasma ammonia level was 32 μg/dL. The abnormal signal intensity on the brain MR images partially improved on day 24, but her disorientation remained (Figure 1C). She was transferred to a long-stay hospital to continue rehabilitation on day 52.
FIGURE 1: MR images of the brain

(A) Initial MR images of the brain showing no remarkable changes. (B) MR images on day 11 showing symmetric abnormal signal intensity in the insular (arrows) and cingulate cortices (arrowheads) on diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) imaging sequences. (C) MR images on day 24 showing improvement of the abnormal signal intensity.

Discussion

We found out two important clinical issues. AHE can present as delayed cerebral abnormalities. Follow-up MR imaging is useful for the diagnosis of this condition.

First, AHE can present as late-onset abnormalities of the brain. Previous reports have described various radiographic findings of AHE (Table 2).

| Author          | Case | Age | Gender | Etiology                        | Plasma ammonia | MR imaging finding                          |
|-----------------|------|-----|--------|---------------------------------|----------------|---------------------------------------------|
| Gomceli YB, et al. (2007) [4] | 1    | 20  | female | drug-induced liver injury (valproic acid) | 133 mg/dL | right mesial temporal sclerosis            |
|                 | 2    | 23  | female | drug-induced liver injury (valproic acid) | 132 mg/dL | cerebellar agenesis                         |
|                 | 3    | 28  | male   | drug-induced liver injury (valproic acid) | 130 mg/dL | postoperative changes (related to the brain surgery) |
|                 | 4    | 56  | male   | drug-induced liver injury         | 115 mg/dL | lacunar infarcts                            |
| No. | Age | Gender | Diagnosis                        | Serum Level | Test Result       |
|-----|------|--------|----------------------------------|-------------|-------------------|
| 5   | 55   | female | Drug-induced liver injury (valproic acid) | 124 mg/dL   | normal            |
| 6   | 64   | female | Drug-induced liver injury (valproic acid) | 142 mg/dL   | normal            |
| 7   | 39   | male   | Drug-induced liver injury (valproic acid) | 122 mg/dL   | normal            |
| 8   | 19   | male   | Drug-induced liver injury (valproic acid) | 119 µg/dL   | not available     |
| 9   | 24   | female | Post-heart-lung transplant         | 286 µg/dL   | Bilateral changes in the insular and cingulate cortices |
| 10  | 48   | male   | Drug-induced liver injury (acetaminophen) | 173 µg/dL   | Bilateral changes in the insular and cingulate cortices, and thalami |
| 11  | 55   | male   | HCV-related cirrhosis             | 139 µg/dL   | Bilateral changes in the insular and cingulate cortices |
| 12  | 42   | female | Post-liver transplant graft rejection | 94 µg/dL    | Bilateral changes in the insular and cingulate cortices |
| 13  | 36   | male   | Drug-induced liver injury (valproic acid) | 483 µg/dL   | not available     |
| 14  | 59   | female | Primary biliary cirrhosis         | 374 mg/dL   | An oval-shaped change in the white matter |
| 15  | 49   | female | Alcoholic cirrhosis               | 723 µg/dL   | Bilateral changes in the insular and cingulate cortices, and thalami |
| 16  | 49   | male   | Alcoholic cirrhosis               | 396 µg/dL   | Bilateral changes in the insular and cingulate cortices, and thalami |
| 17  | 40   | female | Drug-induced liver injury (acetaminophen) | 369 µg/dL   | Bilateral changes in the insular and cingulate cortices, and thalami |
| 18  | 21   | male   | Hepatocellular carcinoma         | 1,032 mg/dL | Not available     |
| 19  | 35   | female | OTC deficiency                    | 593 µg/dL   | Normal            |
| 20  | 26   | female | OTC deficiency                    | 466 µg/dL   | Oval-shaped changes in the white matter, bilateral changes in the insular cortices |
| 21  | 56   | male   | Ureaplasma infection              | 661 µg/dL   | Bilateral changes in the insular and cingulate cortices, and thalami |
| 22  | 45   | male   | Drug-induced liver injury (acetaminophen) | >400 µg/dL  | Bilateral changes in the insular and cingulate cortices, and thalami |
| 23  | 49   | male   | Cirrhosis (unknown cause)         | 745 µg/dL   | Bilateral changes in the insular and cingulate cortices |
The mechanism of these findings has not been fully elucidated, but a major hypothesis is that glutamine produced from ammonia causes swelling of astrocytes, resulting in brain edema. Other hypotheses include the production of the neurotoxin alpha-ketoglutaramate [14]. However, several reports have described AHE patients whose radiographic findings of the brain were within normal limits. These patients might have presented with delayed cerebral edema if they had undergone follow-up imaging tests.

Second, follow-up MR imaging is useful in detecting late-onset cerebral abnormalities. Our patient showed prolonged MR imaging abnormalities, which seemed correlated with her persistent disorientation. Treusch and colleagues described a woman with HAE who became asymptomatic two weeks after onset when her MR images also became normal [8]. Although the relationship between abnormalities on MR images and neurological prognosis has not been investigated, follow-up MR imaging may be useful in predicting neurological recovery of HAE patients. The differential diagnosis of symmetric abnormal signal intensity in MR images includes posterior reversible encephalopathy syndrome, seizure activity, and diffuse hypoxic-ischemic injury [6].

The delayed imaging findings of diseases have well been described in other fields, which can be detected by follow-up imaging tests. For example, it has been known that patients with early pneumonia may not present with significant findings on chest radiographs [15]. Follow-up chest radiography is useful in diagnosing pneumonia in some of these patients [16]. Imaging tests should, if possible, be evaluated more than once to assess the state of diseases over time.

Conclusions
AHE can present as delayed cerebral abnormalities, and follow-up MR imaging is useful for the diagnosis of this condition. These abnormalities can be revealed in MR images several days after the serum ammonia level reaches its peak, and can be missed without follow-up imaging tests. Further reports should be accumulated to determine whether “hidden” AHE may be much more frequently present and whether follow-up imaging tests may contribute to picking up AHE patients with poor clinical outcomes.

Additional Information
Disclosures
Human subjects: Consent was obtained by all participants in this study. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following:
Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any
organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

**References**

1. Clay AS, Hainline BE: Hyperammonemia in the ICU. Chest. 2007, 132:1368-1378. 10.1378/chest.06-2940
2. Pendela VS, Kudaravalli P, Munoz A, Razzouk G: A mysterious case of recurrent acute hyperammonemic encephalopathy. Cureus. 2020, 12:e7484. 10.7759/cureus.7484
3. Takanashi J, Barkovich AJ, Cheng SF, Kostiner D, Baker JC, Packman S: Brain MR imaging in acute hyperammonemic encephalopathy arising from late-onset ornithine transcarbamylase deficiency. AJNR Am J Neuroradiol. 2005, 24:390-393.
4. Gomceli YB, Kutlu G, Cavdar L, Sanivar F, Inan LE: Different clinical manifestations of hyperammonemic encephalopathy. Epilepsy Behav. 2007, 10:585-587. 10.1016/j.yebeh.2007.02.013
5. Velioglu SK, Gazioglu S: Non-convulsive status epilepticus secondary to valproic acid-induced hyperammonemic encephalopathy. Acta Neurol Scand. 2007, 116:128-152. 10.1111/j.1600-0404.2006.00795.x
6. U-King-Im JM, Yu E, Bartlett E, Soobrah R, Kucharzyk W: Acute hyperammonmic encephalopathy in adults: imaging findings. AJNR Am J Neuroradiol. 2011, 32:413-418. 10.3174/ajnr.A2290
7. Tarafdar S, Slee M, Ameer F, Doogue M: A case of valproate induced hyperammonemic encephalopathy. Case Rep Med. 2011, 969505. 10.1155/2011/969505
8. Treusch NA, van de Loo S, Hattingen E: Reversible laminar signal intensity in deep cortical gray matter in T1-weighted images and FLAIR after mild acute hyperammonemic hepatic encephalopathy. J Neuroradiol. 2012, 39:350-353. 10.1016/j.neurad.2012.03.002
9. Rosario M, McMahon K, Finelli PF: Diffusion-weighted imaging in acute hyperammonmic encephalopathy. Neurohospitalist. 2013, 3:125-130. 10.1177/1941874412467806
10. Shinde SS, Sharma P, Davis MP: Acute hyperammonmic encephalopathy in a non-cirrhotic patient with hepatocellular carcinoma reversed by arginine therapy. J Pain Symptom Manage. 2014, 47:E5-E7. 10.1016/j.jpainsymman.2014.01.002
11. Mahmood T, Nugent K: Nonhepatic hyperammonmic encephalopathy due to undiagnosed urea cycle disorder. Proc (Bayl Univ Med Cent). 2015, 28:357-377. 10.1080/089998280.2015.11929281
12. Algahtani H, Alameer S, Marzouk Y, Shirah B: Urea cycle disorder misdiagnosed as multiple sclerosis: a case report and review of the literature. Neuroradiol J. 2018, 31:213-217. 10.1177/1971400917715880
13. Reis E, Coolen T, Lolli V: MRI findings in acute hyperammonmic encephalopathy: three cases of different etiologies. J Belg Soc Radiol. 2020, 104:9. 10.5334/jbsr.2017
14. Butterworth RF: Pathophysiology of brain dysfunction in hyperammonmic syndromes: the many faces of glutamine. Mol Genet Metab. 2014, 113:113-117. 10.1016/j.ymgme.2014.06.003
15. Basi SK, Marrie TJ, Huang IQ, Majumdar SR: Patients admitted to hospital with suspected pneumonia and normal chest radiographs: epidemiology, microbiology, and outcomes. Am J Med. 2004, 117:305-311. 10.1016/j.amjmed.2004.03.029
16. Hagaman JT, Rouan GW, Shipley RT, Panos RJ: Admission chest radiograph lacks sensitivity in the diagnosis of community-acquired pneumonia. Am J Med Sci. 2009, 337:236-240. 10.1097/MJA.0b013e51818ad805