Valproate-induced Encephalopathy: Assessment with MR Imaging and $^1$H MR Spectroscopy

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Summary: The anticonvulsant agent valproate (VPA) may cause hyperammonemic encephalopathy. Magnetic resonance imaging (MRI) and proton MR spectroscopic (MRS) findings in a patient with VPA-induced hyperammonemic encephalopathy are described. MRI showed a metabolic-toxic lesion pattern with bilateral $T_2$-hyperintense lesions in the cerebellar white matter and in the globus pallidus. MR spectroscopic findings were indistinguishable from hepatic encephalopathy with severe depletion of myo-inositol and choline and with glutamine excess. N-Acetylaspartate levels were moderately decreased. Quantitative MRS gave detailed insight into alterations of brain metabolism in VPA-induced encephalopathy. Key Words: Magnetic resonance imaging—Magnetic resonance spectroscopy—Valproate—Encephalopathy—Hyperammonemia.

Valproate (VPA) is an antiepileptic drug (AED) for the treatment of both generalized and partial seizures in children and adults. Besides this classic indication, the drug is increasingly used for therapy for bipolar and chizoaffective psychiatric disorders, neuropathic pain, and prophylactic treatment of migraine (1). Possible adverse effects are idiosyncratic fatal hepatotoxicity, teratogenicity, inhibited catabolism of other AEDs, such as phenobarbital (PB), and hyperammonemic encephalopathy without hepatic dysfunction (2,3).

We describe MR imaging (MRI) and proton MR spectroscopic ($^1$H-MRS) findings in a patient with VPA-induced hyperammonemia and encephalopathy without hepatic dysfunction. There is only one report on MRI findings in VPA encephalopathy in the literature (4).

CASE REPORT

A 32-year-old patient had been treated with $3 \times 500$-mg VPA daily because of epileptic seizures since traumatic brain injury 6 years ago. The patient was admitted with vertigo, disturbance of concentration, slight gait ataxia, and asterixis. Laboratory findings and sonography excluded liver disease. Serum VPA level was within the therapeutic range ($68 \text{ mg/L}$). Ammonia serum level was markedly elevated, with $152 \mu\text{M}$ (normal range, 11–35), and gradually normalized after discontinuation of VPA. EEG showed generalized slowing of background activity characterized by slow alpha and theta activity. In addition, continuous theta and rare delta waves were visible bilaterally over frontal and fronto-basal regions. Within 1 month, these findings resolved, with improvement of clinical symptoms and decreasing NH$_3$ serum levels.

MRI and $^1$H-MRS were performed on a 2-T whole body system (Bruker MEDSPEC S200) by using a quadrature head coil. Transversal $T_{1w}$ spin-echo and transverse and coronal $T_{2w}$ RARE sequences of the whole brain were acquired. For $^1$H-MRS we used a short echo time PRESS sequence (TR 1,500, TE 30, 256 averages). Eight-milliliter voxels were placed in the occipital lobe covering predominantly gray matter and in the left parietal lobe including mainly white matter.

For quantification of the metabolite concentrations, the signal from an external water reference was measured, omitting the water suppression with otherwise identical acquisition parameters (eight averages). Spectral analysis was performed with the LCMModel algorithm (5). The program uses in vitro spectra of the expected metabolites as model functions. The concentrations were compared with results from a group of 25 normal control subjects.

RESULTS

MRI depicted old contusion defects in the basal frontal lobes. $T_{2w}$ images showed prominent bilateral symmetric
hyperintense signal of the cerebellar white matter. These changes abutted the dentate nucleus from laterally (Fig. 1). Bilateral T₂ hyperintense lesions in the globus pallidus were shown in addition (Fig. 2). ¹H-MRS showed marked abnormalities of the choline (Cho), myoinositol (Myl), and glutamate/glutamine (Glu/Gln) resonances (Fig. 3; Table 1).

Cho signal was diminished by -50%. Absolute concentrations were 0.6 mmol/kg wet weight (mmol/kg ww) in both locations (normal value, 1.4). Myl was markedly depleted, with a concentration of 0.9 mmol/kg ww in occipital gray matter (normal value, 4.4). Myl was undetectable in the parietal mainly white-matter voxel.

¹H-MRS showed prominent signal amplitudes at 3.75 and between 2.1 and 2.5 ppm, corresponding to the α- and the β/γ protons of Glu and Gln, respectively (6).

At the time the patient was examined, we were not able to establish normal values for Glu and Gln for technical reasons. In comparison with results from the literature (7), Gln concentrations were elevated about fourfold (occipital) to sevenfold (parietal) above the mean normal value. Glu concentrations were decreased by -30% in

FIG. 1. Coronal T₂ weighted magnetic resonance image showing prominent cerebellar white matter hyperintensities.
Valproate-induced encephalopathy

Patients with genetic defects of urea cycle enzymes are prone to VPA-induced hyperammonemia with encephalopathy. Undetected heterozygote and atypical late-onset cases may develop severe hyperammonemia with VPA administration (9,10).

However, in the majority of patients with VPA encephalopathy, enzymatic abnormalities are absent. In these patients, VPA-mediated inhibition of ammonia elimination through the hepatic urea cycle seems to become relevant with high nutritional amino acid load.

Patients with VPA-induced hyperammonemia are seen with confusion, lethargy, coma, ataxia, and asterixis. Se-
Serum ammonia peaked to a value 15-fold above the upper normal limit, and in our patient, only sixfold.

Bilateral basal ganglia lesions are common in toxic–metabolic encephalopathies. In addition, cerebellar white matter may be involved in several metabolic disorders (11). The MRI pattern in our patient was consequently compatible with a toxic–metabolic encephalopathy.

To our knowledge this is the first report on $^1$H-MRS findings in VPA encephalopathy in the literature. Pathologic MRS features of VPA encephalopathy were a significant decrease of Cho and MyI resonances and Glu excess. This MRS pattern has been described in other hyperammonemic encephalopathies like acute (12) and chronic (13) hepatic encephalopathy.

Because of the strong overlap of the resonances of Glu and Glu in the spectral domain, contributions from the two metabolites are difficult to differentiate at a magnetic field strength of 2 T. The corresponding peak areas are therefore commonly assigned as the sum of both components, "Glx." The time domain fitting algorithm LCMelodel is able to separate the signals of Glu and Glu with a high level of significance, and their concentrations can be determined quantitatively (7).

Our MRS results reflect pathobiochemical considerations of Glu/Glu metabolism during hyperammonemia. The excitatory neurotransmitter Glu, once released to synaptic space, undergoes astrocytic uptake and metabolism to Glu through glutamine synthetase (GS). This step consumes equimolar ammonia. Glu is transported into neurons and converted to Glu by the neuronal enzyme glutaminase. Hyperammonemia has been shown to stimulate GS and to inhibit glutaminase. This leads to an accumulation of Glu and a moderate but significant depletion of Glu, as alternative sources of Glu synthesis fail to replenish the Glu pool (14). However, the total amount of Glu + Glu increases in hyperammonemic encephalopathies, producing elevated "Glx" in MRS.

VPA encephalopathy simulates MRS findings of hepatic encephalopathy with regard to Cho and MyI depletion. Reduction of MyI reflects its role as an organic cerebral osmolyte compensating for osmotically active Glu excess (14). The mechanisms of Cho depletion are still to be elucidated (14).

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**TABLE 1. Results of $^1$H-MRS in patient with VPA encephalopathy compared with normal controls**

<table>
<thead>
<tr>
<th>Brain metabolite concentration in mmol/kg wet weight</th>
<th>NAA</th>
<th>Cho</th>
<th>Glu</th>
<th>Glu</th>
<th>Glu + Glu</th>
<th>Crea</th>
<th>MyI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient, occipital gray matter (GM)</td>
<td>7.3</td>
<td>0.74</td>
<td>16.2</td>
<td>6.5</td>
<td>22.7</td>
<td>5.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Patient, parietal white matter (WM)</td>
<td>7.1</td>
<td>0.74</td>
<td>13.3</td>
<td>4.1</td>
<td>17.4</td>
<td>3.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Normal controls, occipital GM (n = 25)</td>
<td>11.8 ± 1.1</td>
<td>1.6 ± 0.2</td>
<td>4.1 ± 1.3 $^a$</td>
<td>8.8 ± 1.1 $^a$</td>
<td>12.9 $^a$</td>
<td>6.9 ± 0.8</td>
<td>4.4 ± 0.7 $^a$</td>
</tr>
<tr>
<td>Normal controls, parietal WM (n = 24)</td>
<td>10.7 ± 0.7</td>
<td>2.05 ± 0.21</td>
<td>1.8 ± 1.2 $^a$</td>
<td>5.8 ± 1.2 $^a$</td>
<td>7.6 $^a$</td>
<td>5.4 ± 0.5</td>
<td>5.1 ± 0.7 $^a$</td>
</tr>
</tbody>
</table>

MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; Cho, choline; Glu, glutamine; Glu, glutamate; Crea, creatinine; MyI, myoinositol.

$^a$ Values from Pauwels P, et al. 1999 (7).

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We found a 30% reduction of cerebral NAA concentrations in VPA encephalopathy. In the spectroscopic literature, NAA is assigned as a neuronal marker indicating viability and density of neuronal tissue. However, in our patient, MRI did not depict cerebral morphologic changes suggestive of neuronal loss. There is accumulating evidence for a role of NAA as a neuronal molecular water pump (15). We speculate that reduction of NAA resonances in VPA encephalopathy could indicate disturbance of osmotic homeostasis on a cellular level.

In conclusion, MRI findings of our patient with VPA-induced hyperammonemia are compatible with a toxic–metabolic encephalopathy. The results of 1H-MRS reflect the effects of hyperammonemia on Glu/Gln metabolism and cerebral osmoregulation. 1H-MRS offers the opportunity to monitor cerebral metabolic alterations related to VPA therapy.

REFERENCES