Case Report

Proton Magnetic Resonance Spectroscopy Findings Of Wilson’s Disease: Case Report

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Abstract
Magnetic Resonance Spectroscopy (single voxel) was applied in both the left and right basal ganglia of a patient clinically proven Wilson's disease. Decreased in NAA/Cr and Cho/Cr ratios was found and inverted lactate peak was observed. These findings reveal neuronal tissue degeneration and anaerobic metabolism (glycolysis) at basal ganglia in Wilson's disease.

Keywords: Wilson’s disease, Magnetic Resonance Spectroscopy, Basal Ganglia

Introduction
Wilson's disease (WD) is an inherited autosomal recessive disorder of copper metabolism with an incidence one in 30,000. Hepatolenticular degeneration first described by Kinnier Wilson in 1912, is a genetically determined autosomal recessive disease with deficient biliary excretion of copper, leading to excessive copper deposition in many tissues particularly the liver, brain, cornea and kidney. Hepatic and neuro-psychiatric features predominate clinically.¹⁴,¹⁶,¹⁸ Because the disease is progressive and fatal when untreated, accurate diagnosis is important. Magnetic resonance imaging (MRI) shows nonspecific changes in the brain such as brain atrophy and focal abnormalities in lenticular, thalamic and caudate nuclei as well as in the brain stem and white matter.¹ Furthermore, the lesions may usually be bilateral and appear hypointense on T1 weighted (T1W), and hyperintense on T2 weighted (T2W) images.¹⁴
With increasing use and application in different diseases of central nervous system, magnetic resonance spectroscopy (MRS) would aid in the diagnosis and clinical management of various pathologic processes and could provide clinically useful pathophysiological information. MRS reports on WD are limited. This article focuses on bilateral changes in the spectra of bilateral basal ganglia in a patient, who had clinically proven WD.

**Case Report**

A 23 year-old male, was admitted with progressively worsening unconsciousness with slurred speech and cognitive impairment for last two weeks. Neurological examination showed emotional lability, motor impersistance, hypokinetic dysartria, postural and intention tremor affecting the upper extremities and generalized rigidity. In the past, he had jaundice for about two months. His younger sister had died with a story suggesting hepatic encephalopathy. Examination of the eyes showed bilateral Kayser Fleischer ring on slit lamp examination. He had low serum ceruloplasmin (9 mg/dL) (normal values: 20-40 mg/dL) and increased urine copper excretion (229 µg/dL) (normal values 10-60 µg/dL). Nonenhanced abdominal computed tomography (CT) showed multiple hyperdense areas (52–70 HU) in both lobes of the liver. Ultrasound guided liver biopsy confirmed increased copper content in the liver parenchyma. He was started on D-penicillamine, pyridoxine and zinc treatment on slowly and gradually increasing doses. He was almost stable without any improvement.

![Image of brain MRI](image)

**Figure 1:** Axial T2-weighted magnetic resonance image obtained the time of diagnosis from patient with Wilson's disease shows hyperintensity in caudate nucleus, putamen and the posterior limb of internal capsule bilaterally.
The cranial MRI and MRS studies were performed with a 1.5 T system (Philips Gyroscan Intera, Best, Holland). Standard head coil was used. First, the diagnostic MRI was carried out. Images were acquired in three orthogonal orientations using the spine echo (SE) T1 weighted (T1W) (TR/TE: 582/15 msec) and turbo spine echo (TSE) T2 weighted (T2W) (TR/TE: 4464/100 msec) sequences and the PRESS (Point resolved surface coil spectroscopy). MRI showed symmetrical high signal intensity in the putamen, caudate nucleus, the posterior limb of internal capsule and parietal white matter on T2W images with no atrophic changes (Figure 1). MRS was done before and one month after starting treatment. An echo time of 136 msec was used to acquire water-suppressed proton spectra from the volume of interest (VOI). The 2x2x2 cm^3 voxel size was used and both basal ganglia were sampled. The spectra were acquired from the voxels in the globus pallidus, putamen, caudate nucleus and internal capsule (Figures 2 and 3). Resonances were assigned as follows: N-acetyl aspartate (NAA) at 2.02 ppm, creatine (Cr) at 3.0 ppm and choline (Cho) containing compounds at 3.2 ppm. Peak area metabolite ratios (NAA/Cr, Cho/Cr and NAA/Cho) were calculated. Three age- and sex-matched healthy volunteers were used as controls. Metabolite ratios obtained from bilateral basal ganglia of the patient and controls are presented in Table 1. A markedly reduced NAA peak was observed in our case compared to control subjects. The inverted lactate peak was established at 1.4 ppm. The ratios of NAA/Cr, Cho/Cr and NAA/Cho were found reduced in left and right basal ganglia compared to control subjects. After one-month treatment of patient, similar MRS findings sustained.

**Figure 2:** Proton magnetic resonance spectra from the right basal ganglia shows markedly reduced NAA and an inverted lactate peak at 1.4 ppm. NAA: N-acetyl aspartate, Cr: Creatine, Cho: Choline.
Discussion

In WD, neurological symptoms are usually secondary to cerebral copper accumulation, which is sufficient to destroy the nerve cells. Predominant presentation includes dystonia, tremor, dysphasia, dysarthria, gait and limb ataxia, and neuropsychiatric manifestations. Histopathologic studies in WD have shown atrophy, spongy softening, cavitations, general reduction in neurons and increased cellularity in basal ganglia.

MRI has proved to be more sensitive than CT for demonstrating brain tissue changes caused by WD. High signal intensity of gray matter nuclei in T2 weighted images may be due to edema, gliosis, necrosis and cystic degeneration. High signal intensity of white matter on T2 weighted images may be explained as demyelination, softening, spongy formation or cavitary disintegration. In Kozic’s study, bilateral and symmetric T2W and/or PDW hyperintensities were found in eight patients (50%). Hypointensities on T2-weighted MRI can most likely be explained by the paramagnetic effects of accumulated copper and iron. In our case, T2W images showed high signal hyperintensity in caudate nucleus and putamen.

In contrast to conventional MRI, MRS could provide information on neuronal/axonal viability, cellular energetics, and cellular membrane status. The prominent resonances detected on MRS in normal brains include NAA, Cho, and Cr. NAA is the most sensitive central nervous system metabolite. Since it is a neuroaxonal marker, abnormalities of neuronal structures, like reduced neuronal density or viability, lead to the reductions in NAA. Therefore, it is an important predictor of neuronal dysfunction. Major components of the Cho resonance are choline-containing compounds with small molecular weight, such as phosphocholine and glycerophosphocholine that form a pool involved in membrane synthesis and degradation.

Figure 3: Proton magnetic resonance spectra from the left basal ganglia shows markedly reduced NAA and an inverted lactate peak at 1.4 ppm similarly right basal ganglia. NAA: N-acetyl aspartate, Cr: Creatine, Cho: Choline.
We observed evident reduction in the NAA/Cr and Cho/Cr ratios. The reduction in NAA/Cr could reflect either a reduction in NAA or an increase in Cr. Creatine plays an important role in the cellular energy metabolism. It is more concentrated in glia than neurons. Except from trauma, stroke, tumor, and Cr deficiency syndromes, Cr levels tend to remain relatively unchanged. Therefore, we speculated that NAA is reduced rather than Cr increase in our patient. Furthermore, the reduction in NAA/Cr, which in turn is likely to indicate neuronal loss. In a study with 22 WD patients, authors observed a reduction in the NAA/Cr and Cho/Cr ratios compared to the controls. In Jayasundar et al.'s study, both NAA and Cho were found reduced in the basal ganglia of untreated patients. The reduction in Cho/Cr ratio can be taken as a result of Cho reduction. Cho resonance with contributions from several Cho containing compounds is thought to reflect biosynthesis of phospholipids and acetylcholine in cholinergic neurons. Cho is a constituent of the phospholipids metabolism of cell membranes and reflects membrane turnover. Therefore, decreased Cho probably reflects decreased membrane synthesis and/or a decreased number of cells. On the other hand, one cannot rule out the possibility of the paramagnetic effects of copper or iron being the cause of reduction in the Cho signals. A combination of the two, i.e., a reduction in NAA and a reduction in Cho, if it is weighed more with the reduction in NAA, could lead to a reduction in the ratio NAA/Cho.

Table 1: NAA/Cho, Naa/Cr and Cho/Cr ratios of the bilateral basal ganglia for patient with Wilson’s disease and age and sex matched control subjects.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment</th>
<th>Under treatment</th>
<th>Controls</th>
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<tbody>
<tr>
<td><strong>Right Basal Ganglia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>0.93</td>
<td>0.94</td>
<td>1.29 ± 0.15</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>0.99</td>
<td>1.02</td>
<td>1.44 ± 0.07</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>0.92</td>
<td>0.90</td>
<td>1.87 ± 0.28</td>
</tr>
<tr>
<td><strong>Left Basal Ganglia</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAA/Cho</td>
<td>0.84</td>
<td>0.85</td>
<td>1.07 ± 0.14</td>
</tr>
<tr>
<td>NAA/Cr</td>
<td>0.95</td>
<td>0.99</td>
<td>1.45 ± 0.21</td>
</tr>
<tr>
<td>Cho/Cr</td>
<td>0.80</td>
<td>0.83</td>
<td>1.55 ± 0.08</td>
</tr>
</tbody>
</table>

Normally quantifiable amounts of lactate are not present in brain. Lactate peak reveals cellular energy being supplied by anaerobic glycolysis and indicates that longer functioning properly. It may be observed in patients with acute ischemic cerebral infarction, cardiac arrest, hypoxia or hypoglycemic brain injury and mitochondrial disorders.
The presence of lactate accumulation in the basal ganglia may suggest a failure of aerobic metabolism of the brain cells in WD.

In our case, metabolite ratio values (NAA/Cr and Cho/Cr) were not differed before and under treatment. MRS findings of 13 cirrhotic patients with WD did not reveal any reduction in the NAA/Cr and Cho/Cr ratios. In contrast, Jayasundar et al. found striking decrease in the spectra and the metabolite ratios in the untreated patients compared to the other patients who are under treatment (3 and 8 months after treatment). In our case, the reason of unchanged data in MRS before and after one month of treatment may be due to an earlier MRS evaluation.

The findings in this patient with WD suggested that MRS imaging can show neuronal tissue degeneration and anaerobic metabolism. MRS can be used in evaluation of basal ganglia involvement in WD.

References


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**Recived by:** 11.03..2005

**Accepted:** 25.05.2005