Demonstration of the Deposition of Hemosiderin in the Kidneys of Patients with Paroxysmal Nocturnal Hemoglobinuria by Magnetic Resonance Imaging

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Hemosiderinuria caused by intravascular hemolysis is a characteristic clinical feature of an acquired hemolytic disorder, paroxysmal nocturnal hemoglobinuria (PNH). We examined the deposition of hemosiderin (iron) in the kidneys of 6 patients with PNH using magnetic resonance imaging (MRI). Three patients with autoimmune hemolytic anemia (AIHA), a hemolytic disorder showing extravascular hemolysis, served as controls. In five of the six patients with PNH, a characteristic T2-weighted MRI of the kidneys, suggesting the deposition of iron (hemosiderin) predominantly in the renal cortex, was obtained. Hemosiderin-deposition was not revealed in the kidneys of any of the patients with AIHA. We conclude that MRI is a sensitive means of detecting hemosiderin deposited in the renal cortex of patients with PNH and that this feature is considerably specific for diseases showing intravascular hemolysis, as represented by PNH.

Key words: hemolysis, paroxysmal nocturnal hemoglobinuria, iron, renal dysfunction

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired hemolytic disorder characterized by red blood cells (RBC) with enhanced complement-sensitivity (1). Hemoglobinuria and hemosiderinuria due to chronic intravascular hemolysis of the complement-sensitive RBC are characteristic clinical features of the disorder and have considerable diagnostic value (2). A variety of functional and radiological abnormalities of the kidney are found in PNH, including hyposmenuria, tubular dysfunction, and declining creatinine clearance (2, 3). According to a previous case report, the amount of iron deposited in the kidneys of patients with PNH was estimated to be 80-times higher than normal (4). Furthermore, an autopsy study revealed that hemosiderin is deposited predominantly in the proximal convoluted tubules but not in the distal tubules (5). These observations suggest that proximal tubular dysfunctions often found in PNH, e.g. renal proximal tubular acidosis (3, 6), are causally related to hemosiderin deposition in the proximal tubular cells (7). The hemoglobin released to the serum by an intravascular hemolysis is captured by haptoglobin and carried to the liver. However, in a condition like chronic intravascular hemolysis in PNH, haptoglobin is intensely consumed and appears as encaptured hemoglobin in the serum. It is filtered at the glomeruli and extensively reabsorbed by the proximal tubular cells (8, 9). When the amounts of hemoglobin absorbed exceed the ability of the kidney to dispose of the iron, hemosiderin is deposited in the tubules.

Such change might be detected by computed tomography (CT) (9) but the MRI is more sensitive. Four groups of investigators have reported characteristic MRI patterns of PNH-affected kidneys (10-13). The typical feature of the MRI of PNH-affected kidneys was a low signal intensity of the cortex in T2-weighted images. We examined the kidneys of 6 patients with PNH and of 3 patients with autoimmune hemolytic anemia (AIHA) using T1- and T2-weighted MRI. Characteristic results for the T2-weighted MRIs of the kidney were obtained as previously reported in 5 of the 6 patients with PNH, whereas the pattern typical of PNH was not observed in any patients with AIHA. The specificity of the MRI pattern of PNH-affected kidneys and its relationship to the renal dysfunctions are discussed.
Iron in PNH Kidney Detected by MRI

Materials and Methods

Patients with PNH

Six patients with PNH were studied. Their diagnoses of PNH were made by the demonstration of complement-sensitive RBC and intravascular hemolysis. The patients' clinical profiles are listed in Table 1. All but one (Patient F.K.) patient showed hemosiderinuria at the time of study. In Patient F.K., there had been no clinical evidence of hemolysis for at least one year before the study, although she showed clinical features typical for PNH at her disease onset.

Patients with AIHA

Three patients with Coombs-positive autoimmune hemolytic anemia (AIHA) served as controls. Their diagnoses were made by the positive anti-globulin tests (direct Coombs' tests). Hemosiderinuria was never observed in the clinical courses of these patients.

Magnetic resonance imaging

All MRI examinations were performed with a 1.5T superconducting magnet (Signa, General Electrics, Milwaukee, WI, U.S.A.). The Spin Echo Pulse Sequence was used to construct images. T1- and T2-weighted images were obtained at repetition times (TR) of 400 msec and echo delay time (TE) of 10 msec, and 2,000 msec TR and 90 msec TE, respectively. Images were reconstructed using a two-dimensional Fourier transformation utilizing a matrix grid of 256×128 elements in the T2-weighted images. The signal intensities of the renal cortex and medulla, bone marrow, liver and spleen on each image were evaluated by at least two diagnostic radiologists. Three patients with AIHA were also examined by T1- and T2-weighted MRI as described above.

Renal dysfunction in patients with PNH

Renal functions in patients with PNH were evaluated by assessing the serum blood urea nitrogen (BUN) and creatinine levels, creatinine clearance (Ccr), phenolsulfonphthalein (PSP)-test (15 min-values), urinary protein, urinary β2-microglobulin, and urinary N-acetyl-β-D-glucosaminidase (NAG), in addition to the clinical symptoms of the patients.

Results

Characteristic MRI of PNH-affected kidneys

The MRI pattern of the kidneys in normal individuals were low and high intensity in T1- and T2-weighted images, respectively (Figs. 1A, 2A). In T1-weighted images there were no significant differences between the cases examined. On the other hand, as shown representatively in Fig. 2B, a low signal intensity in T2-weighted MRI images of the renal cortex was demonstrated in 5 of the 6 patients with PNH. In one patient with PNH (Patient F.K.), the intensity of the T2-weighted image was high, similar to that of the normal kidney (Fig. 2C). The results of T2-weighted MRI examinations of the patients with PNH are summarized in Table 2. We arbitrarily assigned those MRI results that indicated deposition of iron into one of two grades based on the extent of the MRI image, deposition: ++ (intense hemosiderosis); + (hemosiderin deposition). In 3 patients with PNH (Patients I.S., Y.A., and S.K.), the hemosiderin deposition in the renal cortex was more intense than in the other 2 patients with PNH (Patients N.K., G.K.). But, there was no significant relationship between the values of serum ferritin and the intensity of hemosiderin deposition. In another patient with PNH (Patient F.K.), no hemosiderosis was observed in the kidney. As described above, there had been no evidence of hemolysis in this patient for at least one year before the study. This clinical feature was consistent with data showing only a small percentage of complement-sensitive RBC in this individual (data not shown). It was also noted that she had the lowest value of serum ferritin among the 6 patients with PNH. None of the patients with AIHA showed any abnormal MRI findings related to hemosiderin deposition in the kidney (Fig. 2D).

Hemosiderin deposition and renal dysfunction

The results of the analysis of renal function in the patients with PNH are shown in Table 3. In the two patients with renal dysfunction (Patients Y.A. and S.K.), intense hemosiderin depositions in the renal cortex were demonstrated by MRI. The other three patients in whom renal hemosiderosis was established by MRI (Patients I.S., N.K., and G.K.) did not show any abnormal renal function data. All the patients with AIHA had normal renal function (data not shown).

Table 1. Clinical Features of Patients with Paroxysmal Nocturnal Hemoglobinuria

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Onset</th>
<th>Hb g/dL</th>
<th>WBC ×10⁹/L</th>
<th>Platelet</th>
<th>GOT IU/L</th>
<th>LDH IU/L</th>
<th>Ferritin ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 I.S.</td>
<td>45</td>
<td>M</td>
<td>1984</td>
<td>10.3</td>
<td>3,400</td>
<td>161</td>
<td>71</td>
<td>2,960</td>
<td>40.7</td>
</tr>
<tr>
<td>2 N.K.</td>
<td>46</td>
<td>M</td>
<td>1980</td>
<td>15.3</td>
<td>4,300</td>
<td>147</td>
<td>18</td>
<td>802</td>
<td>142.2</td>
</tr>
<tr>
<td>3 F.K.</td>
<td>65</td>
<td>F</td>
<td>1977</td>
<td>7.1</td>
<td>1,900</td>
<td>51</td>
<td>21</td>
<td>723</td>
<td>14.2</td>
</tr>
<tr>
<td>4 Y.A.</td>
<td>66</td>
<td>M</td>
<td>1988</td>
<td>9.5</td>
<td>3,500</td>
<td>231</td>
<td>110</td>
<td>4,422</td>
<td>29.9</td>
</tr>
<tr>
<td>5 S.K.</td>
<td>67</td>
<td>M</td>
<td>1961</td>
<td>7.3</td>
<td>6,600</td>
<td>170</td>
<td>90</td>
<td>3,592</td>
<td>142.2</td>
</tr>
<tr>
<td>6 G.K.</td>
<td>63</td>
<td>M</td>
<td>1983</td>
<td>14.9</td>
<td>4,300</td>
<td>202</td>
<td>35</td>
<td>1,514</td>
<td>86.1</td>
</tr>
</tbody>
</table>

GOT: glutamic oxaloacetic transaminase, LDH: lactic dehydrogenase.
Hemosiderin contains hemic iron (25–45%), which is recognized as a paramagnetic agent by MRI (10). MRI of the kidneys of all but one of the patients with PNH we studied resulted in characteristic T2-weighted images. These images indicated shortened T2-relaxation times of the renal cortex. This low signal intensity, observed predominantly in the cortex, is considered to be related to the hemosiderosis of the proximal convoluted tubules of the kidneys in patients with PNH (10–12). One of the patients with PNH studied here did not have the characteristic MRI images of the kidney associated with hemosiderosis. This finding was not surprising since the patient in question had no signs of hemolysis for more than a year and only a small percentage of her RBC were complement-sensitive, although apparently abnormal PNH neutrophils were still present. Intense hemosiderosis of the kidneys, predominantly in the proximal tubules as seen in PNH (5), indicates a rate of filtration of hemoglobin constantly in excess of the absorptive capacity of the proximal tubular epithelial cells.

PNH is representative of the hemolytic anemias that involve intravascular hemolysis. Sickle cell anemia is also associated with intravascular hemolysis and complicated nephropathy (2). It has been reported that the renal pathological findings in PNH bear striking similarity to those of sickle cell anemia (3). In addition, it is of interest that the results of T2-weighted MRI of the kidneys of patients with sickle cell anemia also show low signal intensities for the renal cortex (14). Although we had no opportunity to examine the kidneys of patients with sickle cell anemia by MRI, previously reported results suggest a causal relationship between hemosiderin deposition, which occurs predominantly in the renal cortex, and intravascular hemolytic events. The results of MRI examinations of the kidneys of patients with a hemolytic disease showing extravascular hemolysis, AIHA, were different from those seen in PNH, and intravascular hemolytic events. The results of MRI examinations of the kidneys of patients with a hemolytic disease showing extravascular hemolysis, AIHA, were different from those seen in PNH, supporting the speculation that hemosiderin deposition in the renal cortex is a fairly specific feature of intravascular hemolysis. The hemosiderin deposition observed in Patients 1, 2 and 6, in whom renal dysfunction was not detected by conventional examination (Table 2), may indicate that subclinical hemosiderosis can be detected by MRI.

We conclude that the characteristic results of MRI of the
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Fig. 2. T2-weighted MR image of the kidneys. The images were obtained from the patients indicated in Fig. 1. Of the patients with paroxysmal nocturnal hemoglobinuria, all but one (Patient F.K., shown in Panel C) had a characteristic low intensity pattern of the cortex in T2-weighted MRI (represented in Panel B). None of the patients with autoimmune hemolytic anemia had any abnormal MRI findings (Panel D).

Table 2. Results of T2-Weighted MRI Examination of Patients with Paroxysmal Nocturnal Hemoglobinuria

<table>
<thead>
<tr>
<th>Patient</th>
<th>Decreased signal intensity in T2-weighted images</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kidney</td>
</tr>
<tr>
<td>1 I.S.</td>
<td>++</td>
</tr>
<tr>
<td>2 N.K.</td>
<td>+</td>
</tr>
<tr>
<td>3 F.K.</td>
<td>-</td>
</tr>
<tr>
<td>4 Y.A.</td>
<td>++</td>
</tr>
<tr>
<td>5 S.K.</td>
<td></td>
</tr>
<tr>
<td>6 G.K.</td>
<td>+</td>
</tr>
</tbody>
</table>

Low signal intensity of renal cortex was graded as follows. ++: intense hemosiderosis, +: hemosiderin deposition. * The intensity was not as low as other positives of the kidney.

Table 3. Renal Functions of Patients with Paroxysmal Nocturnal Hemoglobinuria

<table>
<thead>
<tr>
<th>Patient</th>
<th>( C_{cr} ) mL/min</th>
<th>PSP %</th>
<th>Cr mg/dL</th>
<th>BUN mg/dL</th>
<th>U-Prot. mg/dL</th>
<th>NAG IU/L</th>
<th>( \beta 2 ) micro-globulin IU/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 I.S.</td>
<td>115</td>
<td>48</td>
<td>0.8</td>
<td>15.2</td>
<td>80</td>
<td>3.2</td>
<td>188</td>
</tr>
<tr>
<td>2 N.K.</td>
<td>124</td>
<td>44</td>
<td>0.6</td>
<td>12.0</td>
<td>0</td>
<td>2.0</td>
<td>140</td>
</tr>
<tr>
<td>3 F.K.</td>
<td>112</td>
<td>53</td>
<td>0.6</td>
<td>11.7</td>
<td>0</td>
<td>2.0</td>
<td>204</td>
</tr>
<tr>
<td>4 Y.A.</td>
<td>28</td>
<td>12</td>
<td>1.2</td>
<td>25.0</td>
<td>100</td>
<td>78.4</td>
<td>62,412</td>
</tr>
<tr>
<td>5 S.K.</td>
<td>44</td>
<td>4</td>
<td>2.1</td>
<td>27.2</td>
<td>152</td>
<td>19.6</td>
<td>69,804</td>
</tr>
<tr>
<td>6 G.K.</td>
<td>98</td>
<td>33</td>
<td>1.0</td>
<td>14.0</td>
<td>16</td>
<td>4.4</td>
<td>44</td>
</tr>
</tbody>
</table>


Table references:

1) Rosse WF, Parker CJ. Paroxysmal nocturnal haemoglobinuria. Clin Internal Medicine Vol. 32, No. 9 (September 1993) 689

kidneys of patients with PNH indicate preferential deposition of hemosiderin in the renal cortex and that they are considerably specific for diseases showing intravascular hemolysis, as represented by PNH. Furthermore, MRI detected hemosiderin deposition before the appearance of any renal dysfunction related to it.

References

1) Rosse WF, Parker CJ. Paroxysmal nocturnal haemoglobinuria. Clin


