Impact of Magnetic Resonance Imaging on the Diagnosis of Abdominal Complications of Paroxysmal Nocturnal Hemoglobinuria

By Didier Mathieu, Alain Rahmouni, Patricia Villeneuve, Marie Christine Anglade, Henri Rochant, and Norbert Vasile

Magnetic resonance (MR) imaging is a method of choice for assessing vascular patency and parenchymal iron overload. During the course of paroxysmal nocturnal hemoglobinuria (PNH), it is clinically relevant to differentiate abdominal vein thrombosis from hemolytic attacks. Furthermore, the study of the parenchymal MR signal intensity adds information about the iron storage in kidneys, liver, and spleen. Twelve PNH patients had 14 MR examinations of the abdomen with spin-echo T1- and T2-weighted images and flow-sensitive gradient echo images. Vessels patency and parenchymal signal abnormalities—either focal or diffuse—were assessed. MR imaging showed acute complications including hepatic vein obstruction in five patients, portal vein thrombosis in two patients, splenic infarct in one patient. In one patient treated with androgens, hepatocellular adenomas were shown. Parenchymal iron overload was present in the renal cortex of eleven patients with previous hemolytic attacks. On the first MR study of the remaining patient with an acute abdominal pain showing PNH, no iron overload was present in the renal cortices. Follow-up MR imaging showed the onset ofrenal cortex iron overload related to multiple hemolytic attacks. Despite the fact that all our patients were transfused, normal signal intensity of both liver and spleen was observed in three of them. MR imaging is particularly helpful for the diagnosis of abdominal complications of PNH.

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PAROXYSMAL nocturnal hemoglobinuria (PNH) is a rare acquired disorder of a hematopoetic stem cell caused by a mutation within the phosphatidylinositol glycan-class A (PIG-A) gene resulting in an abnormal glycosyl-phosphatidylinositol anchor that is unable to bind membrane functional proteins. Among these proteins, the inhibitors of complement play a key role in protecting the blood cells from complement cascade attack. The lack of these proteins in PNH explains the characteristic chronic hemolysis with occurrence of acute intravascular hemolytic exacerbations. However, the most serious and life-threatening complication of PNH is thrombosis of intraabdominal veins. An increased sensitivity of PNH platelets to activation by the terminal complement proteins may explain in part these thrombotic complications. Distinguishing acute hemolytic attacks from abdominal venous thrombosis may be of critical importance for therapy. Abdominal venous thrombosis can involve the hepatic veins with subsequent Budd Chiari syndrome (BCS), the portal vein, and the mesenteric and splenic veins.

Multiple imaging modalities have been used for the evaluation of these vascular thromboses including ultrasonography (US), angiography, and computed tomography (CT) during these acute complications. US examination is frequently limited by ascitis and bowel gas distension. In addition, iodinated contrast agents, used on angiography and CT, may induce acute hemolysis during PNH. Magnetic resonance (MR) imaging, on the contrary, is a safe and sensitive method for the diagnosis of abdominal venous thrombosis. Previous occasional MR case reports have emphasized the abnormal signal intensity of kidneys in PNH.

The purposes of this study including 12 patients with PNH were twofold: to assess the value of MR imaging in the diagnosis of these acute abdominal complications and to clarify the appearances and, particularly, the significance of the abnormal signal intensities observed in the kidneys, liver, and spleen. In this study, we have not formally compared MR imaging with the other radiologic methods.

MATERIALS AND METHODS

From January 1991 to June 1994, 14 MR examinations were performed in 12 patients with PNH, 6 women and 6 men aged from 18 to 60 years old (mean, 30 years). The diagnosis of PNH was confirmed by a positive Haem test (acid hemolysis test) and a positive sucrose hemolysis test. According to the clinical presentation, three groups of patients underwent MR examination: (1) in the first group, MR imaging was performed during an acute abdominal pain occurring in previously diagnosed PNH patients (6 patients, Table 1); (2) in the second group, MR imaging was performed in the follow-up of previously diagnosed PNH patients without current acute clinical symptoms (5 patients, Table 2); and (3) MR imaging was performed in a patient presenting with an acute abdominal pain showing PNH disease (Table 3).

In the first group (Table 1), the duration of PNH before the onset of the acute episode varied from 1 to 6 years. All six patients experienced previous multiple hemolytic attacks, infections, and thrombosis including episodes of hepatic vein obstructions (patients no. 1 and 2), or cerebral vein thrombosis (patients no. 4 and 6). All have been treated by blood transfusions and androgens.

In the second group (Table 2), the duration of PNH before the MR examination varied from 5 to 14 years. All five patients also experienced previous multiple hemolytic crisis, infections, and thrombosis including renal vein thrombosis (patient no. 10), cerebral vein thrombosis (patient no. 11), and episodes of hepatic vein obstructions (patient no. 8). All five patients were treated by blood transfusions and androgens.

In an 18-year-old woman (patient no. 12, Table 3) with an acute abdominal pain, a portal thrombosis was diagnosed. The course of PNH was thereafter marked by multiple acute hemolytic attacks with gross hemoglobinuria. This patient was treated by blood transfusions (10 to 12 U/mo). For evaluation of abdominal pains, follow-up MR examinations were performed at 3 and 8 months after the initial MR study.

All 12 patients were examined by MR with a 1.5-T magnet (Magnetom SP 63; Siemens, Erlangen, Germany). MR examinations were performed without intravenous injection of paramagnetic contrast agent. These successive axial transverse images were obtained:

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Table 1. Acute Abdominal Pain Occurring in Previously Diagnosed PNH Patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)/Sex</th>
<th>Duration of Disease (yrs)</th>
<th>Previous Complications</th>
<th>Acute Complications</th>
<th>Renal Cortex Signal Intensity</th>
<th>Liver Signal Intensity</th>
<th>Spleen Signal Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19/F</td>
<td>1</td>
<td>Hemolytic attacks, infections, BCS</td>
<td>Acute BCS and cavernous transformation of the portal vein</td>
<td>Decreased</td>
<td>Heterogeneous</td>
<td>Decreased</td>
</tr>
<tr>
<td>2</td>
<td>51/M</td>
<td>6</td>
<td>Hemolytic attacks, infections BCS</td>
<td>Acute BCS and portal and mesenteric thrombosis</td>
<td>Decreased</td>
<td>Heterogeneous</td>
<td>Decreased</td>
</tr>
<tr>
<td>3</td>
<td>18/F</td>
<td>1</td>
<td>Hemolytic attacks, infections</td>
<td>Portal thrombosis</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>4</td>
<td>19/M</td>
<td>2</td>
<td>Hemolytic attacks, infections, cerebral vein thrombosis</td>
<td>Splenic infarct</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>5</td>
<td>20/M</td>
<td>3</td>
<td>Hemolytic attacks, infections</td>
<td>Acute BCS</td>
<td>Decreased</td>
<td>Heterogeneous</td>
<td>Normal</td>
</tr>
<tr>
<td>6</td>
<td>36/M</td>
<td>5</td>
<td>Hemolytic attacks, infections, cerebral vein thrombosis</td>
<td>Acute BCS</td>
<td>Decreased</td>
<td>Heterogeneous</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

TI-weighted spin-echo (SE) images were obtained with a repetition time (TR) of 420 milliseconds and an echo time (TE) of 15 milliseconds (TR/TE = 420/15), a matrix of 192 × 256, three acquisitions, and an 8-mm thickness with a gap of 0.8 mm; (2) T2-weighted SE images were obtained with a TR of 2,200 milliseconds and a TE of 45 and 90 milliseconds (TR/TE = 2,200/45,90), a matrix of 160 × 256, two acquisitions, and an 8-mm thickness with a gap of 0.8 mm (additional coronal images were obtained in one patient); (3) flow-sensitive fast low angle shot (FLASH) gradient echo (GRE) images were obtained with TR of 30 milliseconds, TE of 8 milliseconds, a flip angle of 35°C during breatholding, and a matrix of 256 × 256 with contiguous 8-mm thickness sections (these axial GRE sequences were performed from the right atrium to the plane of the renal veins. Additional coronal images were obtained in six examinations).

All MR imaging studies were prospectively read by one of the authors (D.M. or A.R.) and retrospectively reviewed by both of these authors in conference. For the 14 MR examinations, different abdominal MR abnormalities were considered including (1) thrombosis of the abdominal vessels including inferior vena cava and hepatic, portal, splenic, mesenteric, and renal veins on GRE images (ie, in the absence of thrombosis, a vessel appears as a bright lumen on these images, and on the other hand, an obstructed vessel exhibits a lower signal than flowing blood); (2) presence of focal liver or splenic lesions; and (3) diffuse decreased signal intensity of the liver, the spleen, and the renal cortex for the assessment of iron overload (Fig 1); the signal intensity was considered decreased if it was less than the signal intensity of skeletal muscle—used as a reference tissue—on T2-weighted SE and, particularly, on GRE images.11-14

RESULTS

In five patients from the first group (Table 1), obstruction of the upper abdominal vessels without collateral pathways, indicating an acute episode, was shown including BCS in four patients (patients nos. 1, 2, 5 and 6), associated in one case with thrombosis of the portal and the mesenteric veins (patient no. 2) and an isolated portal vein thrombosis in one
Fig 1. Normal and abnormal appearance of kidneys in PNH disease. (A) Normal appearance of the kidneys on axial GRE image. The signal intensity of the renal cortex was equal to the signal intensity of the skeletal muscles. The patency of the different abdominal vessels is marked by a bright signal (patient no. 12). (B) Iron overload of the renal cortex on axial GRE image. Diffuse low signal intensity of the renal cortex. This signal intensity is less than the signal intensity of the skeletal muscles (patient no. 9). (C) Localized low signal intensity of the corticomedullary junction on axial GRE image in a patient with PNH disease (patient no. 7). Notice the low signal intensity of both liver and spleen corresponding to iron overload.

In the four patients with BCS, liver enlargement and hypertrophic caudate lobe were associated with a heterogeneous signal and the presence of hypointense peripheral areas on SE and GRE images (Figs 4, 5, and 6B). Venous abnormalities included comma-shaped intrahepatic collateral veins (two patients), irregular hepatic veins (one patient), nonvisualization of the hepatic veins (one patient). Thrombosis of the portal and mesenteric veins was also present in one patient with mesenteric infarction leading to a rapid fatal outcome (patient no. 2). In the four patients with acute BCS, the signal intensity of the liver was heterogeneous, as described above. In another patient, both liver and spleen had a low signal intensity on T2-SE and GRE images (patient no. 3). In the remaining patient, no iron overload could be detected in either liver or spleen (patient no. 4). In all the patients of this group (Table 1), the renal cortex had a low signal intensity on both T2-SE and GRE images (Fig 1B).

In the five patients of the second group (Table 2), no vascular abnormalities were observed. In four patients, no liver or splenic focal lesions were observed. In one patient who had been treated by androgens for 4 years, three hepatic lesions (diameter, 2 to 4 cm) were present and consistent with the diagnosis of hepatocellular adenomas, ie, hypointense on T1-SE images and slightly hyperintense on T2-SE images. Right heptectomy and pathologic examination confirmed the presence of hepatocellular adenomas (patient no. 10). In four patients, both liver and spleen had a low signal intensity on T2-SE and GRE images (patients no. 7, 8, 9, and 11). In another patient, no iron overload could be detected in the liver and the spleen (patient no. 10).

The renal cortex was abnormal in all five patients of this second group, on both T2-SE and GRE images, marked by a diffuse low signal intensity in four patients and a localized low signal intensity as a rim at the corticomedullary junction in one patient. For this latter patient, the diagnosis of PNH was made 14 years ago, and no recurrent hemolytic attacks had occurred for 8 years (patient no. 7, Fig 1C).

Finally, in patient no. 12, MR imaging showed an obstruction of the main portal vein (Table 3). On this MR examination, no parenchymal iron overload, particularly of the renal cortex, could be detected (Fig 6A). On the 3-month follow-up MR examination, decreased signal intensity of the renal cortex was obvious, associated with decreased signal intensity of both liver and spleen. This low signal intensity of the renal cortex was still present at the 8-month follow-up MR examination, which also showed a hepatic venous obstruction and a cavernous transformation of the portal vein (Fig 6B).

DISCUSSION

The PNH syndrome encompasses pancytopenia, chronic intravascular hemolysis, and recurrent thrombotic epi-
Table 3. Acute Abdominal Pain Showing PNH

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (yrs)/Sex</th>
<th>MR Examination</th>
<th>Acute Complication</th>
<th>Blood Transfusions (U/mo)</th>
<th>Renal Cortex Signal Intensity</th>
<th>Liver Signal Intensity</th>
<th>Spleen Signal Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>18/F</td>
<td>Portal vein thrombosis</td>
<td>3 mo after</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemolytic attacks</td>
<td>8 mo after</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

During the course of this disease, numerous severe hemolytic attacks may occur marked by malaise, fever, headache, abdominal, and lumbar pains. The same acute clinical symptoms may also be caused by vascular thromboses. To differentiate the etiologies of these acute symptoms, imaging studies are required for an adequate and prompt treatment. PNH is the condition associated with the highest risk of hepatic vein obstruction or BCS. Using flow-sensitive GRE sequences, without injection of contrast agent, MR imaging is a highly sensitive method of assessing vascular patency. In the five BCS patients of the present study, GRE images showed characteristic hepatic vein abnormalities, ie, irregular veins, absence of hepatic veins, intrahepatic venous collateral pathways associated with a liver enlargement, and a hypertrophic caudate lobe. A heterogeneous appearance of the liver parenchyma was also shown, ie, hypointense areas in the periphery of the liver contrasting with a normal signal intensity of the caudate lobe (Figs 4 and 5). These areas could represent different and progressive stages of the disease, ie, congestion, ischemia, necrosis, and subsequent fibrosis. In our series, it is noteworthy that these hypointense areas were peripheral supporting the theory of the progressive extension from small-sized hepatic vein involvement to obstruction of the large-sized hepatic veins, as described by Valla et al.

MR imaging is also a sensitive method for the detection of iron overload leading to magnetic field inhomogeneities and, therefore, a loss of signal, particularly on GRE images. In the absence of hepatic vein obstruction, both liver and splenic iron overload were present in five patients treated by previous blood transfusions. Reticulo-endothelial cell iron in the liver and spleen is derived from the phagocytosis of intact red blood cells, occurring during the metabolism of transfused erythrocytes. However, normal signal intensity of both liver and spleen was observed in three of our patients: one patient with a newly diagnosed PNH disorder and two other patients treated by multiple blood transfusions during the year before the MR examination, respectively 50 and 80 U/yr. In these two latter patients, the intense intravascular hemolysis with important urinary iron loss could explain the absence of parenchymal iron overload of liver and spleen. Free hemoglobin is filtered by the kidneys and is both reabsorbed and stored by the epithelial cells of the proximal tubules. Marked hemosiderin deposits in the proximal renal tubule are a common feature in all autopsy and biopsy reports dealing with PNH. As shown in occasional case reports, low signal intensity of the renal cortex can be observed in PNH because of the iron overload represented by hemosiderin. Our study confirms that this...
Fig 4. Budd-Chiari syndrome. Hypointense peripheral areas (·) in comparison to the normal signal intensity of the hypertrophic caudate lobe. Presence of multiple intrahepatic and periportal collateral veins with a patent IVC. Notice the diffuse low signal of the renal cortex of the left kidney on this axial GRE image.

Fig 5. Budd-Chiari syndrome. On this coronal GRE image, hypointense peripheral areas (·) are present within an enlarged liver. The portal vein and the mesenteric vein are patent.

Fig 6. Patient with acute portal thrombosis showing a PNH disease (patient no. 12). (A) On this initial MR examination, the signal intensity of both kidneys appears normal in comparison with the signal intensity of the skeletal muscles on this coronal GRE image. (B) 8-month follow-up MR examination. On an identical coronal GRE image, the signal intensity of renal cortex is now low. Notice the presence of hypointense areas of the inferior part of the right hepatic lobe corresponding to hepatic venous obstruction.

Finding is always present when previous hemolytic attacks have occurred during the course of PNH. This low signal intensity was diffuse within the cortex in 10 patients with previous hemolytic attacks (Fig 1B). In one patient of our series, this low signal intensity was localized at the corticomedullary junction (Fig 1C). It is tempting to speculate that this peculiar feature was a residual hemosiderin deposition in a patient who did not experience hemolytic attacks for many years. Finally, in one patient, MR appearance of the kidneys was normal (Fig 1A). This patient had no previous hemolytic attacks before the MR examination. The course of this patient was rapidly marked by multiple acute episodes of hemolysis, and then a decreased signal intensity of the renal cortex appeared on follow-up MR examinations (Fig 6, A and B). However, low signal intensity of the renal cortex is not pathognomonic of PNH because this appearance has otherwise been shown in the kidneys of patients with long-standing sickle cell anemia, treated by multiple blood transfusions, with hemosiderin deposition in glomerular epithelium. This MR finding may also be obtained in any patient with chronic hemoglobinuria.

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REFERENCES


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