The Kidneys in Paroxysmal Nocturnal Hemoglobinuria

By Douglas A. Clark, Stephen A. Butler, Victor Braren, Robert C. Hartmann, and David E. Jenkins, Jr.

Long-term study of 21 PNH patients revealed an unexpectedly high incidence of functional and anatomic renal abnormalities. Most patients demonstrated varying degrees of hematuria and proteinuria distinct from hemoglobinuria. Evaluation of renal function revealed hyposthenuria, abnormal tubular function, and declining creatinine clearance. Radiologically these patients had enlarged kidneys, cortical infarcts, cortical thinning, and papillary necrosis which were confirmed by autopsy studies. Hypertension developed in eight patients. Urinary tract infection was uncommon. The renal findings bear striking similarity to those of sickle cell anemia. Contrary to the usual opinion, our studies clearly showed evidence of widespread renal pathology in PNH most likely due to repeated microvascular thrombosis similar to the venous thrombosis involving other organs in this disorder.

This report is a review of the renal status of 21 patients followed at Vanderbilt University Hospital from 1957 until the present. Contrary to the usual opinion, our studies clearly show evidence of widespread renal pathology in PNH most likely due to repeated episodes of microvascular thrombosis, similar to the venous thromboses involving other organs in this disorder.

MATERIALS AND METHODS

The diagnosis of PNH was confirmed using the acid hemolysis test and the sucrose hemolysis test. The case numbers are the same as in previous publications. Age at the time of diagnosis ranged from 14-67 yr. Time of diagnosis was arbitrarily set at the onset of gross hemoglobinuria. (Case 12 never had gross hemoglobinuria, and onset in her was timed from the discovery of positive serologic tests for PNH.) There are 12 females (5 dead) and 9 males (5 dead). Of the patients who died, 7 were autopsied.

Renal studies were carried out in the chronic, steady state, i.e., remote from episodes of gross hemoglobinuria and usually from transfusion therapy. Renal functional abnormalities were found in the presence of little or no anemia as well as with marked anemia.

Renal evaluation consisted of the following:

1. Radiologic: intravenous pyelograms (IVP) and renal arteriograms.
2. Renal function studies: urinalysis; bacteriology; concentration test (Fishberg) and urine osmolalities; phenolsulfonphthalein (PSP) excretion; glomerular filtration rates (GFR)—creatinine clearance; renograms.
3. Autopsy findings.

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Table 1. Renal Studies in Paroxysmal Nocturnal Hemoglobinuria

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Onset</th>
<th>Fishberg PSP</th>
<th>Renogram</th>
<th>Onset of Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>2*</td>
<td>1952</td>
<td>1.018 (1978)</td>
<td>40% (1968)</td>
<td>1976</td>
</tr>
<tr>
<td>3‡‡</td>
<td>1956</td>
<td>1.017 (1962)</td>
<td>24% (1961)</td>
<td>—</td>
</tr>
<tr>
<td>4‡</td>
<td>1957</td>
<td>1.030 (1962)</td>
<td>20% (1962)</td>
<td>—</td>
</tr>
<tr>
<td>5</td>
<td>1957</td>
<td>1.016 (1964)</td>
<td>10% (1962)</td>
<td>1968</td>
</tr>
<tr>
<td>6‡</td>
<td>1957</td>
<td>1.014 (1958)</td>
<td>35% (1958)</td>
<td>—</td>
</tr>
<tr>
<td>7‡</td>
<td>1959</td>
<td>1.014 (1964)</td>
<td>21% (1963)</td>
<td>1965</td>
</tr>
<tr>
<td>8</td>
<td>1960</td>
<td>1.017 (1962)</td>
<td>25% (1962)</td>
<td>—</td>
</tr>
<tr>
<td>9</td>
<td>1965</td>
<td>1.014 (1965)</td>
<td>25% (1966)</td>
<td>—</td>
</tr>
<tr>
<td>11‡</td>
<td>1961</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>12</td>
<td>1967</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>13</td>
<td>1968</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>14</td>
<td>1963</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>15</td>
<td>1965</td>
<td>1.019 (1972)</td>
<td>(30 hours)</td>
<td>—</td>
</tr>
<tr>
<td>16‡‡</td>
<td>1962</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>1967</td>
<td>1.023 (1976)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>18</td>
<td>1966</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>19</td>
<td>1975</td>
<td>1.021 (1975)</td>
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<tr>
<td>20</td>
<td>1976</td>
<td>—</td>
<td>—</td>
<td>1976</td>
</tr>
<tr>
<td>21</td>
<td>1977</td>
<td>1.014 (1978)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>22</td>
<td>1977</td>
<td>1.014 (1977)</td>
<td>—</td>
<td>1977</td>
</tr>
</tbody>
</table>

*Case 1 died in 1958 prior to initiation of studies.
†Autopsied patients.
‡Case 3 developed acute tubular necrosis (ATN) secondary to a transfusion reaction; case 16 developed ATN secondary to urokinase.
§Uretero pelvic junction.
Renal Function Studies

Urinalysis. During the many years of observation all patients, except case 12, had episodes of mild to severe gross hemoglobinuria. When diligently sought and carefully delineated from hemoglobinuria, all patients had microscopic hematuria on most occasions and three initially presented with gross hematuria. Microscopic hematuria was seen remote from episodes of gross hemoglobinuria. Intermittent proteinuria and granular casts were seen at some time in most patients. Case 5 had persistent heavy proteinuria (3–4 g per day) with a nonselective pattern. Although a renal biopsy has not been performed he is believed to have a glomerulonephritis; this is a unique finding in our series.

Bacteriology. Urinary tract infections were not a prominent feature in most of our PNH patients. Nine had evidence of infection at some time, but none had chronic pyelonephritis. Cases 3 and 18 developed gram negative urinary tract infection in association with instrumentation, and Case 4 had an *E. coli* urinary tract infection associated with prostatic hypertrophy. Case 17 had a staphylococcal UTI in association with a neurogenic bladder produced by a herniated nucleus pulposus. Cases 7, 15, and 16 all had acute urinary tract infections without clear predisposing factors, which cleared with antibiotic therapy, and case 8 gave a history of trichomonas prostatis. At autopsy cases 3, 4, and 7 were all found to have evidence of acute pyelonephritis, but in each case this seemed to be related to the patient’s terminal illness and debilitation, rather than his chronic progressive renal dysfunction.

Only in case 5 did urinary tract infection play a major role in the course of his illness and the deterioration of his renal function. In 1975 this patient presented with sepsis and shock arising from an *E. coli* urinary tract infection. He required an indwelling foley catheter for some time and ultimately underwent drainage of a prostatic abscess and transurethral resection of the prostate. His creatinine clearance declined from 130 ml/min in 1974 to 32 ml/min in 1975 after this illness.

Concentration tests. Fishberg concentration tests were done repeatedly in 11 patients and all, except case 4, demonstrated inability to concentrate the urine to a specific gravity greater than 1.016 (Table 1). Normally one urine specimen should have reached a specific gravity of 1.025 (800 milliosmols/liter). Case 15 had a urine osmolality of only 480 milliosmols/liter.
after 24 hr dehydration and after 30 hr of dehydration had a specific gravity of only 1.019. Most of these patients developed their abnormal Fishberg tests within 5 yr of the onset of PNH. Some of the higher numbered PNH patients did not have concentration tests because of our increasing concern regarding the association of thrombosis with dehydration. Such tests cannot be undertaken lightly in PNH. None of our patients suffered ill effects from the dehydration accompanying the Fishberg test and prompt rehydration was instituted once the test was completed.

**PSP excretion.** Excretion during the first 15 min is the most sensitive indicator of abnormal tubular function with this procedure. Normally an average of 35% of the injected dye is excreted during this period with a minimum excretion of 28%. Six of nine patients studied had defective tubular function as measured by a low excretion of PSP (less than 25%) within the first 15 min (Table 1). Again, most of these patients developed their abnormal PSP excretion rates within 5 yr after the onset of PNH.

**Glomerular filtration rates (GFR).** Thirteen of 19 patients tested had reduced creatinine clearance rates (Table 1). Eleven had creatinine clearances of less than 70 ml per minute and six of less than 60. Two patients (cases 3 and 16) developed reduced creatinine clearance rates after episodes of acute tubular necrosis (ATN). One of these episodes was thought to be secondary to a transfusion reaction and the other to urokinase infusion.

**Renograms.** Renograms were done on nine patients (cases 2, 5, 12, 17, 18, 19, 20, 21, and 22). Five (cases 2, 5, 12, 17, and 19) demonstrated delayed time to peak. The absence of urinary outflow obstruction, which these patients did not have, suggests vascular lesions as the cause. Case 18 demonstrated

| PNH Case | Cause of Death | Age at Death | Renal Pathology | Renal Weight in Grams*
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Subdural hematoma</td>
<td>55</td>
<td>Hemosiderin deposition in tubules, Papillary necrosis, Marked hyalinization with scarring, Vascular sclerosis, Acute pyelonephritis of (R) kidney</td>
<td>170 (R), 280 (L)</td>
</tr>
<tr>
<td>4</td>
<td>Hepatic venous thrombosis (HVT)</td>
<td>67</td>
<td>Infarct; acute pyelonephritis (? cryptococcal), Interstitial scarring, Nephrosclerosis; hemosiderin deposition in tubules</td>
<td>200 (R), 150 (L)</td>
</tr>
<tr>
<td>6</td>
<td>HVT</td>
<td>50</td>
<td>Infarct; cortical necrosis, Papillary necrosis, Thrombosis of small vein, Hemosiderin deposition in tubules, Acute pyelonephritis (L) kidney</td>
<td>320 (R), 380 (L)</td>
</tr>
<tr>
<td>7</td>
<td>Basilar artery thrombosis</td>
<td>64</td>
<td>Cortical loss (2–3 mm thick), Vascular sclerosis, Interstitial fibrosis with tubular atrophy, Focal glomerulosclerosis</td>
<td>250 (R), 200 (L)</td>
</tr>
<tr>
<td>8</td>
<td>Superior sagittal sinus thrombosis</td>
<td>53</td>
<td>Cortical thinning, Increased interstitial tissue, Venous congestion, Hemosiderin deposition in tubules</td>
<td>280 (R), 260 (L)</td>
</tr>
<tr>
<td>11</td>
<td>HVT</td>
<td>25</td>
<td>Infarct, Papillary necrosis, Cortical thinning, Focal hyalinization, Atrophy of tubules, Thrombosis of small vein, Uric acid nephropathy</td>
<td>350 (R), 270 (L)</td>
</tr>
<tr>
<td>22</td>
<td>Intrarenal hydronephrosis</td>
<td></td>
<td>Capillary congestion, Tubular atrophy, Hemosiderin deposition in tubules, Infarct</td>
<td>210 (R), 210 (L)</td>
</tr>
<tr>
<td>13</td>
<td>HVT</td>
<td></td>
<td>Papillary necrosis, Cortical thinning</td>
<td>210 (R), 210 (L)</td>
</tr>
<tr>
<td>18†</td>
<td>Alive — age 35</td>
<td></td>
<td>Infarct, Papillary necrosis, Cortical thinning</td>
<td>Not weighed</td>
</tr>
</tbody>
</table>

*Average normal weight: 150 g.
†Left nephrectomy for ureteral infarct.
decreased tubular function and ureteral dilitation in her remaining kidney following left nephrectomy. Four patients (cases 2, 17, 18, and 22) had renograms consistent with cortical infarction; this finding correlated well with IVPs in these patients.

**Autopsy Findings (Table 2)**

Autopsies were performed in seven patients (cases 3, 4, 6, 7, 8, 11, and 13). Case 18 had a left nephrectomy after renal hemorrhage and infarction of the proximal one-third of the ureter.

**General**

Case 3 died of a subdural hematoma, case 8 of superior sagittal sinus and cortical vein thrombosis, and case 7 of basilar artery thrombosis. Hepatic venous thrombosis (HVT) was the cause of demise in three patients, (cases 6, 11, and 13), and an associated finding in two others, (cases 7 and 8). Case 4 died with both HVT and cryptococcal sepsis. Cases 11 and 13 also had thrombosis and obstruction of the inferior vena cava below the entrance of the hepatic vein. Pulmonary thrombi or emboli were documented in five cases (cases 4, 6, 8, 11, and 13). Diffuse submucosal hemorrhage of the gastrointestinal tract, ureter, and bladder were noted in five patients (cases 4, 6, 8, 11, and 13). A gastric ulcer was found in Case 6.

**Renal (Table 2).** All patients had moderate to heavy hemosiderin deposits in the proximal tubules. Kidney weights ranged from 150 to 300 g per kidney with an average weight of 258 g (compared to a normal average of 150 g). Four patients had renal infarcts (cases 4, 5, 11, and 18; See Fig. 2), three had cortical thinning (cases 7, 8, and 18) and three papillary necrosis (cases 3, 11, and 18). Additionally, 4 had marked hyalinization of the interstitium with scarring (cases 3, 4, 7, and 11) and two demonstrated vascular sclerosis (cases 3 and 7). An unusual finding was that case 11 had uric acid uropathy manifested by uric acid casts in the collecting tubules with generalized intrarenal hydronephrosis. Acute pyelonephritis was demonstrated in three cases (cases 3, 4, and 7).

**Adrenal.** Cases 3, 4, 7, 11, and 13 had atrophy of the adrenal cortex; and case 8 had lipid depletion. Case 4 also had had a blunted response to ACTH stimulation during life. Cases 7, 8, and 13 had never

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**Fig. 2.** A photomicrograph (H and E, 46 x magnification) of a biopsy from the edge of a renal cortical infarct obtained at the autopsy of case 4. Normal tissue is on the right. On the left there is interstitial scarring with preservation of some glomeruli.
been on adrenocorticosteroids. Whether the prolonged androgen (mainly fluoxymesterone) therapy, which most of these patients had, bore any relationship to adrenal atrophy remains unknown.

DISCUSSION

A generalized thrombotic tendency has been clearly recognized as a major complication and cause of death in PNH. Peytremann and her associates reviewed thrombosis in PNH and discussed etiologic factors, vascular distribution, and clinical manifestations, both obvious and subtle.4

Despite clinical, histologic, and biochemical evidence of diffuse venous thrombosis involving every organ of the body, very little has been written regarding renal complications of PNH patients. In our experience patients with PNH have had both acute and chronic renal insufficiency unattributable to other disease.

Acute reductions in renal function may occur during severe hemoglobinuric crisis. In case 2 this occurred during each of three crises as judged by decreased creatinine clearance and azotemia. The reduced function was remarkably short lived, and renal function returned to normal by 6–8 days after the termination of the crises. Hemoglobinuria was massive during these episodes, and in one instance, amounted to the excretion of 181 g of hemoglobin in 36 hr. Creatinine clearance fell to 33 ml/min and 70 ml/min during 2 of these crises. The patient's normal creatinine clearance in the intervening chronic, steady state was 120–130 ml/min.

It is tempting to speculate that this acute renal insufficiency was secondary to massive hemosiderin-deposition in the proximal tubules and renal cortex, particularly since acute hemoglobinuria crises undoubtedly increase the renal iron load. However, available evidence points toward a relatively slow turnover of renal iron. If the acute renal insufficiency seen in PNH is secondary to augmented hemosiderin deposits in the proximal tubules, then the duration should be much longer than 6–8 days such as noted in case 2. In our cases 4, 11, and 13, renal arteriograms performed during severe hemoglobinuric crisis failed to visualize the cortical arterioles, and a prolonged venous phase was noted. The nature of the small vessel insult is unknown but may represent venous thrombosis or, as suggested by Strübing, sludging of erythrocyte ghosts in the venous side of the capillary systems.9 Regardless of its etiology, the acute renal insufficiency associated with hemoglobinuric crisis in PNH appears to be short lived and may leave very little apparent residual functional damage.

There is also a chronic component to the renal insufficiency in PNH. In 12 of our 19 patients creatinine clearances were abnormal in the chronic, steady state. In three patients the creatinine clearances declined with time, indicating the progressive nature of this renal pathology. In a fourth patient the decline in creatinine clearance was abrupt following an episode of acute pyelonephritis with gram negative sepsis (case 5, discussed earlier).

Further evidence of early progressive renal disease is demonstrated by the development of abnormal Fishberg concentration tests in seven patients, 3-4 yr before the decline in creatinine clearance (Table 1). Case 15 had the remarkable finding of a creatinine clearance of 133 ml/min at the time that she was able to develop a maximum urine osmolality of only 480 milliosmols/liter after 24 hr of dehydration.

Whether this inability to produce a concentrated urine is secondary to early renal insufficiency produced by medullary microinfarction or secondary to the inability of hemosiderin-laden renal tubular epithelium to sustain a maximum osmotic gradient between the urine and plasma has not been established. The autopsy findings of infarction, papillary necrosis, and interstitial scarring indicate diffuse vascular damage occurring in the PNH kidney. Interestingly, PNH kidneys are markedly larger than normals. We presume this is due to venous congestion and sludging; similar findings have been reported in kidneys removed from sickle cell anemia patients because of hematuria.20 Were a PNH patient to progress to end stage renal disease before other causes of death supervened, we would expect the kidneys eventually to contract from scarring. It is likely that this microvascular insult affects the counter-current multiplier system and is responsible for the hyposthenuria in PNH, as interstitial microinfarction does in sickle cell anemia.21,22

Tubular function was studied by PSP excretion in 9 patients and 6 were found to be abnormal (Table 1). The excretion of PSP depends upon renal flow and intact tubular function. Unfortunately, in no patient was renal plasma flow measured. However, two patients (cases 3 and 7) had normal glomerular filtration rates (as measured by creatinine clearances) at the time they were first found to have abnormal PSP excretions. Thus the low PSP excretion probably reflects abnormal function of the proximal tubule. Riley et al. have reported proximal renal tubular acidosis in a patient with PNH, and pointed out that because urinary pH drops as systemic acidosis supervenes this condition may be overlooked. Indeed two of our patients (cases 3 and 5) had persistent metabolic acidosis with a normal urine pH and may have suffered from proximal renal tubular acidosis, as well
as having exhibited decreased PSP excretion. Whether abnormal tubular function is related to hemosiderin deposition in the proximal tubule or to ischemic change of microinfarction is unknown. In light of other evidence of diffuse microinfarction, we find the latter explanation attractive.

All patients with radiologic evidence of renal infarction also had low or falling creatinine clearances, presumptive evidence of a causal relationship. Further evidence that microscopic infarction plays a significant role in the chronic renal failure in PNH is demonstrated by the autopsy findings of renal infarcts, cortical thinning (felt to represent multiple small infarcts), papillary necrosis, and hyalinization of interstitial tissue with scarring.

REFERENCES

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DA Clark, SA Butler, V Braren, RC Hartmann and DE Jr Jenkins