Kidney International, Vol. 4 (1973), p. 390–400

Diagnostic procedures and long-term prognosis in bilateral renal cortical necrosis

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Diagnostic procedures and long-term prognosis in bilateral renal cortical necrosis. Thirty-eight patients with bilateral renal cortical necrosis (BRCN) were studied with special reference to etiology, diagnostic procedures and ultimate prognosis. BRCN was of obstetrical origin in 26 patients and more frequent during the third trimester of pregnancy (21%) than earlier (1.5%). Renal biopsy, renal arteriography and hemodynamic data were useful procedures in the early differentiation of total from patchy BRCN. In patients with patchy BRCN, the percentage of destroyed glomeruli on the kidney biopsy specimen was lower than in those with total BRCN, renal arteriography showed that the cortical nephrogram was present but non-homogeneous and mean renal blood flow (MRBF) (^{85}Kr method) fell within the range observed in patients with acute tubular nephropathy undergoing full recovery. In patients with total BRCN, cortical tissue was uniformly necrotic, the cortical nephrogram was completely absent, MRBF was always below 50 ml/100 g·min and a first component was never recognizable. Biological evidence of intravascular coagulation was inconstant. Intrarenal vascular thrombi were only found in the renal biopsy specimens of those patients with short survival. Partial recovery occurred in 16 patients and GFR increased over a one year period. Subsequent deterioration of renal function occurred in nine patients requiring chronic hemodialysis and/or renal transplantation.

Diagnostic et pronostic lointain des nécroses corticales bilatérales des reins. Trente-huit malades atteints de nécrose corticale bilatérale des reins (NCR) ont été spécialement étudiés du point de vue de l'étiologie, des méthodes de diagnostic et du pronostic lointain. La NCR a été d'origine obstétricale chez 26 malades et a été plus souvent observée pendant le troisième trimestre de la grossesse (21%) que plus précocement (1, 5%). La biopsie rénale, l'artériographie rénale et les données hémodynamiques ont été utiles pour distinguer les NCR totales et partielles. Chez les malades atteints de NCR partielle, la biopsie rénale a montré que le pourcentage de glomérules détruits était plus bas que dans les NCR totales, l'artériographie rénale a montré que la néphrographie corticale était présente mais non-homogène et le flux sanguin rénal moyen (FSRM) (méthode au ^{85}Kr) restait compris dans les limites observées chez les malades atteints de néphropathie tubulaire aiguë avec guérison complète. Chez les malades atteints de NCR totale, le tissu rénal cortical était uniformément nécrotique, la néphrographie corticale totalement absente, le FSRM était toujours inférieur à 50 ml/100 g·mn et aucun premier composant n'était individualisable. Les preuves biologiques d'une coagulation intravasculaire ont été inconstantes. Des thrombi vasculaires intrarénaux n'ont été rencontrés en biopsie que chez les malades ayant une courte survie. Une récupération partielle a été observée chez 16 malades et la FG a continué à s'élever au-delà de la première année. Une aggravation secondaire de la fonction rénale est survenue chez neuf malades, nécessitant des hémodialyses périodiques et/ou une transplantation rénale.

Received for publication July 10, 1973;
and in revised form August 31, 1973.

Bilateral renal cortical necrosis (BRCN) is a well known cause of irreversible renal damage in adults with acute renal failure [1]. Prolonged survival of patients with BRCN has been described in only 16 patients according to a recent review by Woods and Williams [1] and to our knowledge has been reported in only 16 additional patients [2–11]. Patchy BRCN was present in many of these cases. The exact frequency of patchy BRCN in partially recovering patients with acute renal failure is questionable, since BRCN is not always documented in such patients [12–14].

From 1953 to 1972 we observed 38 patients with BRCN, of whom 16 partially recovered, four patients subsequently died, five are now being treated by chronic hemodialysis and seven are alive without support of chronic hemodialysis. We attempted in this study to answer two main questions: 1) how can early diagnosis of BRCN be established in patients with acute renal failure?, and 2) can the course of BRCN be predicted during the anuric stage, i.e., can total cortical necrosis be differentiated from patchy cortical necrosis?

Methods

Thirty-eight patients with BRCN were admitted to the Necker Hospital between 1953 and 1972, among

approximately 2,000 patients with acute renal failure hospitalized during the same period. There were 31 female and seven male patients ranging in age from 14 to 66 years. The clinical features and clinical course of these patients are summarized in Table 1.

Diagnosis of BRCN was established in two patients by the presence of cortical calcifications on X-rays, 60 and 75 days after the acute onset. In all the remaining patients, the diagnosis was based on unquestionable evidence of cortical necrosis on autopsy material (16 patients) or renal biopsy specimens (20 patients). Renal biopsy specimens were obtained by a surgical procedure using a Ducrot-De Montera needle in the first 15 patients, and percutaneously using a Vim-Silverman needle in the last five patients. Renal tissue was fixed in Dubosq-Brazil solution and embedded in paraffin. Sections for light microscopy were stained with Masson's trichrome stain or hematoxylin and eosin. Immunofluorescent studies were performed in five biopsies. Pieces of renal tissue were frozen in isopentane cooled in liquid nitrogen and cut in a cryostat at 3 μ. Labeled goat antisera

Table 1. Clinical features and clinical course in 38 patients with BRCN

Patient	Age at onset	Sex	Etiology	Diagnostic procedures			Duration of oliguria *days*	Duration of survival without H or T *years*	Follow-up *years*	Final outcome
				Renal histology	Renal X-ray films[a]	Selective renal arteriography				
1	23	F	Postpartum	A	—		11[b]	—		D
2	32	M	Acute pancreatitis	A	—		18[b]	—		D
3	42	M	Sepsis	B/A	—		27[b]	—		D
4	25	F	Postpartum	A	—		4[b]	—		D
5	33	F	Postpartum	A	—		15[b]	—		D
6	22	F	Septic abortion	A	—		4[b]	—		D
7	59	M	Sepsis	A	—		9[b]	—		D
8	32	F	Septic abortion	A	—		6[b]	—		D
9	28	F	Postpartum	B	—		16	10	11	H, D
10	30	F	Toxic?	B	—		24	9	9	CC 23
11	33	F	Septic abortion	B	—		22	10	11.6	H,D
12	20	F	Transfusion incompatibility	A	—		7[b]	—		D
13	34	F	Postpartum	B	+		12	8	8	UC 41
14	37	F	Septic abortion	A	—		8[b]	—		D
15	31	F	Septic abortion	B/A	—		40[b]	—		D
16	35	F	Septic abortion	A	—		7[b]	—		D
17	14	M	Sepsis	A	—		5[b]	—		D
18	33	F	Postpartum	B	—		19	5	10	T, D
19	17	F	Postpartum	A	—		8[b]	—		D
20	34	F	Postpartum	A	—		17[b]	—		D
21	23	F	Postpartum	B/A	—		10[b]	—		D
22	33	F	Postpartum	B	—		26	4	4	CC 47
23	58	F	Sepsis		+		18	1	1	UC 10
24	19	F	Postpartum	A	—		20[b]	—		D
25	18	F	Postpartum	B	+		40	1.6	1.6	D
26	30	M	Mediastinal dysembryoma	A	—		20[b]	—		D
27	42	F	Septic abortion	A	—		23[b]	—		D
28	66	F	Cancer of the tongue + HUS	B/A	—		40[b]	—		D
29	36	F	Postpartum	B	—		—	4	4	CC 73
30	43	F	Toxic?	B	—		31	0.3	5	H
31	40	F	Postpartum	B	—		13	0.3	3	H
32	30	F	Postpartum	B	—	+	35	1.2	3	H
33	41	F	Septic abortion		+	+	60	1.7	3	H
34	20	M	Malignant hypertension + HUS	B/N[c]	—	+	540[b]	—	1.6	H, T, D
35	19	F	Mediastinal dysembryoma	B[c]	—		8[b]	—		D
36	22	F	Postpartum	B[c]	—	+	25	2	2	CC 58
37	29	F	Postpartum	B[c]	—	+	27	0.3	1.2	H
38	36	F	Postpartum	B[c]	—	+	23	1	1	CC 58

Abbreviations: F = female; M = male: HUS = hemolytic-uremic syndrome; A = autopsy; B = biopsy; N = nephrectomy; H = hemodialysis; T = transplantation; D = dead; CC = creatinine clearance, ml/min; UC = urea clearance, ml/min.

[a] Presence of calcifications on current X-ray films or nephrotomograms.

[b] Death during the oliguric period.

[c] Percutaneous needle biopsy.

to human IgA, IgM, IgG and β_1C globulins (Hyland Laboratories) and rabbit antiserum to fibrin (Hyland Laboratories) were used (Dr. J. Berger).

In 11 patients, coagulation data were obtained within the first five days according to previously reported techniques [15]. Blood samples were collected before dialysis and no patient was transfused with large amounts of stored blood, or received heparin or thrombolytic therapy. Normal values were as follows: thrombocytes, 150,000 to 300,000/mm^3 (range); fibrinogen, 0.20 to 0.40 g/100 ml; factor V, 80 to 120%.

In the last six patients surviving the acute renal insult, renal arteriography was performed using the Seldinger technique under fluoroscopic control. All patients were fasted and received 25 mg of promethazine hydrochloride and 25 mg of pethidine by intramuscular injection approximately 30 min before the study. Three to 8 ml of sodium and methylglucamine diatrizoate at 76 percent were injected for selective arteriography. Subsequent aortic injection of 30 to 50 ml of contrast medium was performed in four cases.

In five patients who underwent arteriography, the renal blood flow and its distribution was measured with the Krypton-85 method, as previously described [16]. Mean renal blood flow (MRBF) was calculated from the initial slope of the curve. The curves were analyzed graphically using the peeling method; the value obtained at 3 min was subtracted as an approximation of the two slowest components. Component I was considered as representative of cortical perfusion; the percentage of total flow in component I (% I) was calculated from the zero-time intercept of the first rapid slope. Normal values obtained in control subjects (potential kidney donors on normal sodium diet) were $396 \pm$ SEM 23 ml/100 g/min ($N=15$) for MRBF and $61 \pm$ SEM 3 ($N=15$) for component I.

Plasma renin activity (PRA) was assayed in two patients using the method of Boucher et al [17] and in two other patients by radioimmunoassay of angiotensin I according to a technique derived from Haber et al [18]. Normal values in peripheral blood of subjects on a normal sodium diet were 0 to 1.3 ng/ml/hr (bioassay, $N=21$) and 1.4 ± 0.5 ng/ml/hr (immunoassay, $N=8$). Renal venous blood samples were collected during selective catheterization of the renal vein, either before (three patients) or 30 min after angiography (one patient). Correct position of the catheter in the renal vein was checked by fluoroscopy. Renin secretion rate (RSR) was calculated from the renal veno-arterial difference of PRA and mean renal plasma flow derived from MRBF and hematocrit. RSR was expressed in units per min per gram of perfused renal tissue.

An attempt was made to differentiate, on the basis of clinical, biological and hemodynamic data, those patients with and those without BRCN. For this purpose, patients with BRCN were compared with patients recovering fully from acute tubular nephropathy studied during the past six years (1966 to 1972) at the Necker Hospital. Oliguria and anuria were defined as a urine output of less than 500 ml and 100 ml per day for more than three successive days, respectively. Surviving patients were followed by routine clinical and laboratory techniques. Serial urinalyses and serial determinations of blood urea nitrogen and serum creatinine were performed in all patients. Creatinine clearance was used as an index of glomerular filtration rate (GFR). The criteria for full clinical recovery were as follows: a urea clearance of more than 50 ml/min/1.73 m^2 and/or a creatinine clearance greater than 100 ml/min/1.73 m^2.

Results

Etiology. The most common source of acute renal failure secondary to BRCN was the obstetrical patient. BRCN followed postpartum accidents in 18 patients and septic abortion in eight patients. During the period from 1966 to 1972 (in which more detailed clinical information was available) 670 patients with acute renal failure were treated. Among 52 patients with postpartum renal failure, BRCN was diagnosed in 11 (21%), while among 136 patients with postabortum renal failure, BRCN was diagnosed in only two (1.5%).

A comparison of clinical data was made between 18 patients with postpartum BRCN and 20 fully recovered patients (i.e., without BRCN) with postpartum acute tubular nephropathy (Table 2). In both groups, renal failure could only be explained by factors presumably related to pregnancy, i.e., concealed placental or puerperal hemorrhage, placenta praevia, or amniotic embolism. Patients with nonspecific factors such as transfusion incompatibility or puerperal sepsis were excluded. In comparing the mean duration of oligoanuria, only BRCN with recovering diuresis was considered.

Results presented in Table 2 demonstrate that age, number of pregnancies and presence of initial shock, puerperal hemorrhage or abruptio placentae were not significantly different in patients with or without BRCN. However, certain distinctive clinical features were noted in patients with BRCN; *a*) acute renal failure occurred earlier in pregnancy than in patients without BRCN (average: 28.8 *vs.* 34.0 weeks; $P < 0.001$); *b*) toxemic symptoms including seizures were rarer ($P < 0{\cdot}01$); *c*) oliguria was present in 17 of 18

Table 2. Comparison of clinical data in patients with postpartum renal failure with or without BRCN

Clinical data		BRCN ($N=18$)	Acute tubular nephropathy with full recovery ($N=20$)
Age	mean ± SEM	27.8 ± 1.6	29.9 ± 1.3
Number of pregnancies	mean ± SEM	3.7 ± 0.7	3.6 ± 0.4
Weeks of pregnancy	mean ± SEM	28.8 ± 1.4	34.0 ± 0.5[a]
Toxemia	no. of cases	3	13[b]
Epileptic seizures	no. of cases	1	6
Initial shock	no. of cases	7	6
Puerperal hemorrhage	no. of cases	7	5
Concealed placental hemorrhage	no. of cases	8	6
Duration of oligoanuria (days)			
urine output < 200 ml/day	mean ± SEM	18.2 ± 2.7 ($N=11$)[c]	5.9 ± 1.6 ($N=7$)[d]
< 500 ml/day	mean ± SEM	25.5 ± 3.6 ($N=11$)[c]	8.9 ± 1.6 ($N=8$)[e]
No oliguria	no. of cases	1	12[f]

[a] t:3.78; $P<0.001$.
[b] X^2:7.20; $P<0.01$.
[c] only patients who recovered with diuresis have been considered.
[d] t:3.34; $P<0.01$.
[e] t:3.71; $P<0.01$.
[f] X^2:10.18; $P<0.001$.

patients with BRCN, but in only eight of 20 patients without BRCN ($P<0.001$). One patient with BRCN had no oliguria; *d*) the oliguric or anuric stage was significantly more prolonged in patients with BRCN ($P<0.01$).

Renal and extrarenal pathology. BRCN was assessed in 36 patients by histological examination performed between the 4th and 90th day (most within the first month) after onset of acute renal failure. Diagnosis of BRCN was only retained if characteristic renal changes were present [19]. Eight female patients with acute tubular nephropathy and incomplete recovery, but without clearcut histological evidence of BRCN, were consequently excluded from this series.

Fourteen renal biopsies contained sufficient cortical tissue to be representative, i.e., at least 15 glomeruli were present for evaluation. Careful analysis of these specimens indicated that renal tissue was not uniformly necrotic (Table 3). Non-necrotic areas were found in ten of 11 specimens including juxtamedullary tissue. Such areas were rarer in the superficial layer of the cortex (eight of 14 specimens). A diagnosis of patchy cortical necrosis was made on renal biopsy specimens more frequently in patients with than without prolonged survival ($P<0.05$). In addition, the percentage of destroyed glomeruli was significantly higher in patients without prolonged survival ($P<0.01$). A positive correlation was noted between the percentage of necrotic glomeruli and the duration of the oliguric stage ($r=0.53$; $P=0.05$). Arterial, arteriolar and glomerular fibrinoid thrombi were only found in four patients who survived less than 20 months without chronic hemodialysis (Table 3). No IgG, IgA, IgM, β_1C globulin or fibrin deposits were found with immunofluorescent staining in five patients.

Autopsy was performed in 20 patients who did not survive beyond the anuric stage. This group included four patients in whom BRCN had been previously diagnosed on a kidney biopsy specimen. Examination of the whole kidney showed that only ten patients had total BRCN, i.e., 90% or more of the cortex destroyed; this percentage ranged between 20 and 80% in the remaining ten patients. It is worth emphasizing that renal fibrinoid thrombi were found in each autopsied patient. In 13 patients widespread renal thrombi occluded more than 50% of the arteriolar or glomerular vessels. Four patients with partial BRCN were autopsied 4 to 30 days after renal biopsy was performed. Examination of the whole kidney confirmed the diagnosis of partial BRCN; however, whereas renal fibrinoid thrombi were only found in glomerular intracapillary lumens on biopsy specimens, they always extended into intrarenal arterioles and arteries at autopsy. Extrarenal necrosis was also present in 16 patients and mainly involved the adrenals (six patients), the spleen (five patients), the lungs (three patients), the pancreas (three patients), the uterus (three patients) and the digestive tract (two patients). Disseminated fibrin thrombi were found in only one patient autopsied six days after the onset of acute renal failure.

Table 3. Renal biopsy findings in 14 cases of BRCN with recovery of diuresis

Patient	Presence of non-necrotic areas		Destroyed glomeruli		Fibrinoid thrombi		
	Superficial cortex	Juxtamedullary region	No.	%	arterial	arteriolar	glomerular
			Patients with survival < 20 months[a]				
25	0	0	25/25	100	+	+	+
30	0	±	29/31	94	+	+	+
31	0	+	39/52	75	0	0	0
32	0	±	24/26	92	+	+	+
34[b]	+[c]		12/19	63	+	+	+
37[b]	0	±	16/18	89	0	0	0
avg	1/6	4/5		85 ± 7[d]	4/6	4/6	3/6
			Patients with survival > 20 months[a]				
9	0	+	11/15	73	0	0	0
10	+	+	5/30	16	0	0	0
11	+		2/20	10	0	0	0
13	+	+	9/27	33	0	0	0
18	+	+	11/22	50	0	0	0
22	+	+	6/26	23	0	0	0
29	+	+	16/40	40	0	0	0
36[b]	+		7/16	43	0	0	0
avg	7/8[e]	6/6		36 ± 8[f]	0/8	0/8	0/8

[a] without chronic hemodialysis.
[b] percutaneous needle biopsy. All other patients underwent open surgical biopsies.
[c] patient with BRCN + renal thrombotic microangiopathy.
[d] mean ± SEM.
[e] corrected X^2: 4.43; $P < 0.05$.
[f] $P < 0.01$ (Mann and Whitney test).

Coagulation studies. Coagulation data were significantly different in patients with BRCN than in those with nonobstetrical acute tubular nephropathy with full recovery (Table 4, group 1 *vs.* group 2). Mean fibrinogen levels differed significantly in patients with postpartum BRCN and in fully recovered patients with postpartum acute tubular nephropathy (group 3 *vs.* group 4), but thrombocyte counts and factor V levels were not statistically different. Fibrin degradation products in peripheral blood were found in three of six patients with BRCN, but also in six of nine patients without BRCN. Euglobulin lysis time was normal in ten patients.

Renal arteriograms. In four patients selective renal

Table 4. Coagulation data in patients with acute renal failure with or without BRCN

	N	Thrombocytes/mm³ × 10³	Fibrinogen *g/100 ml*	Factor V, %
1. Acute renal failure with BRCN	11	70.2 ± 13.2[a]	0.23 ± 0.04[a]	71 ± 10[a]
2. Acute tubular nephropathy with full recovery				
a. obstetrical	81	113.4 ± 10.2[b]	0.28 ± 0.01[b]	56 ± 04[b]
b. nonobstetrical	58	142.5 ± 10.1[c]	0.39 ± 0.02[c]	81 ± 03[d]
3. Postpartum renal failure with BRCN	9	76.4 ± 16.6	0.19 ± 0.05[c]	72 ± 11
4. Postpartum acute tubular nephropathy with full recovery	14	146.1 ± 37.5[e]	0.34 ± 0.05[f]	75 ± 10[e]

[a] mean ± SEM.
[b] NS: comparison with group 1 (Student's *t* test).
[c] $P < 0.02$: comparison with group 1 (Student's *t* test).
[d] $P < 0.05$: comparison with group 1 (Student's *t* test).
[e] NS: comparison with group 3 (Mann and Whitney test).
[f] $P < 0.05$: comparison with group 3 (Student's *t* test).

arteriography was performed within the first four weeks of the disease (patients 34, 36–38). Kidney size ranged from 11×5 cm to 14.5×6 cm and was not different on early films or tomograms in patients with total or patchy BRCN or in those with acute renal failure without BRCN. In all patients the interlobar arteries showed delayed filling with poor arborization. The filling of the capsular arteries was prominent. Circulation time was prolonged and contrast material remained in renal arteries later than in other abdominal branches.

In two patients the cortical nephrogram was completely absent (Fig. 1a). Definitive anuria was observed in patient 34, patient 37 recovered diuresis but chronic hemodialysis was required. In two other patients (36 and 38) the cortical nephrogram showed a mottled and nonhomogeneous appearance (Fig. 1b). Both patients partially recovered. A similar arteriographic pattern with prolonged circulation time and complete absence of the corticogram was observed in five patients who developed acute rejection with renal cortical necrosis within the first 24 hours after renal transplantation.

In two patients (32 and 33) selective renal angiography was performed 4 and 16 months after the onset of acute renal failure. Kidney size was markedly reduced and no cortical nephrogram was seen. Cortical calcifications were present in patient 33.

Hemodynamic measurements (Table 5). Hemodynamic data were obtained for four patients during the early oliguric phase of renal failure. In two patients (36 and 38) cortical necrosis was partial on renal histology and incomplete functional recovery occurred later. In both patients component I was recognized on the wash-out curves and MRBF exceeded 100 ml/100 g/min. In two other patients, renal biopsy specimen showed patchy BRCN with thrombotic microangiopathy (patient 34) or total BRCN (patient 37) and definitive hemodialysis was required. No first component was recognized on the wash-out curves and MRBF was below 50 ml/100 g/min. Similar results were obtained in a fifth patient with partial recovery who was studied 16 months after the onset of anuria and in whom chronic hemodialysis was required three months later (patient 32). Such data should be compared with results obtained for nine patients without BRCN during the oliguric phase of renal failure. In these nine patients (11 curves), MRBF ranged from 105 to 262 ml/100 g/min; no component I was recognized in four curves obtained from three patients.

PRA was normal or slightly elevated in peripheral or renal venous blood. RSR was calculated in four patients (six measurements), including two with hypertension (patients 32 and 34); RSR was positive in three cases and zero or negative in three other cases. Mean RSR (0.08 U/g/min) was lower than mean values obtained in eight fully recovered patients (nine measurements) with acute tubular nephropathy.

Immediate and long-term prognosis. Twenty-one patients died early as anuria persisted from four to forty days. Most of them (20 patients) were observed before 1968, i.e., before the systematic use of prophylactic hemodialysis. In one additional patient death occurred from septicemia four months after renal transplantation (patient 34). In the other cases death was precipitated by gastrointestinal hemorrhage (five patients), acute respiratory failure (four patients),

Table 5. Renal hemodynamics in five cases of BRCN

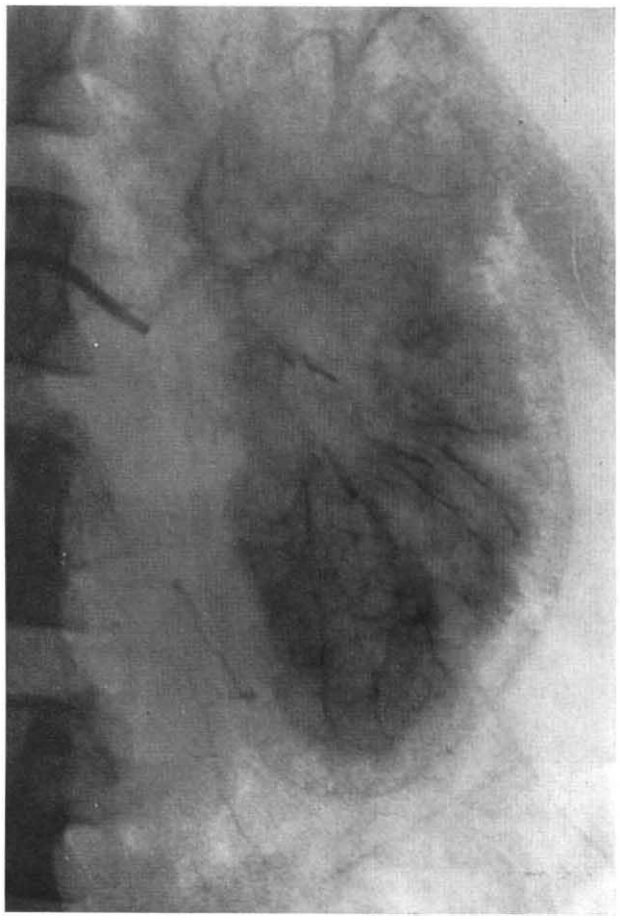
Patient	Time after onset of renal failure	MRBF *ml/100 g/min*	Component I, $\%Kr_1$	Plasma renin activity, *ng/ml/hr*			Renin secretion rate, *U/g/min*
				method	arterial blood	renal venous blood	
32	16 mo	15/30	0/0	BA	2.9	1.4/3.7	−0.2/0.2
34	30 days	42	0	BA	0.6	0.6/0.9	0/0.1
36	19 days	260/280[b]	40/46				
37	5 days	40	0	IA	2.0	3.4	0.4
38	8 days	106	15	IA	1.2	1.2	0
Acute tubular nephropathy without BRCN[a]		172±17[c] (N=11)	O(N=4) 15±3 (N=7)	IA	5.4±2.0 (N=10)	6.9±2.1 (N=12)	3.3±1.9 (N=9)

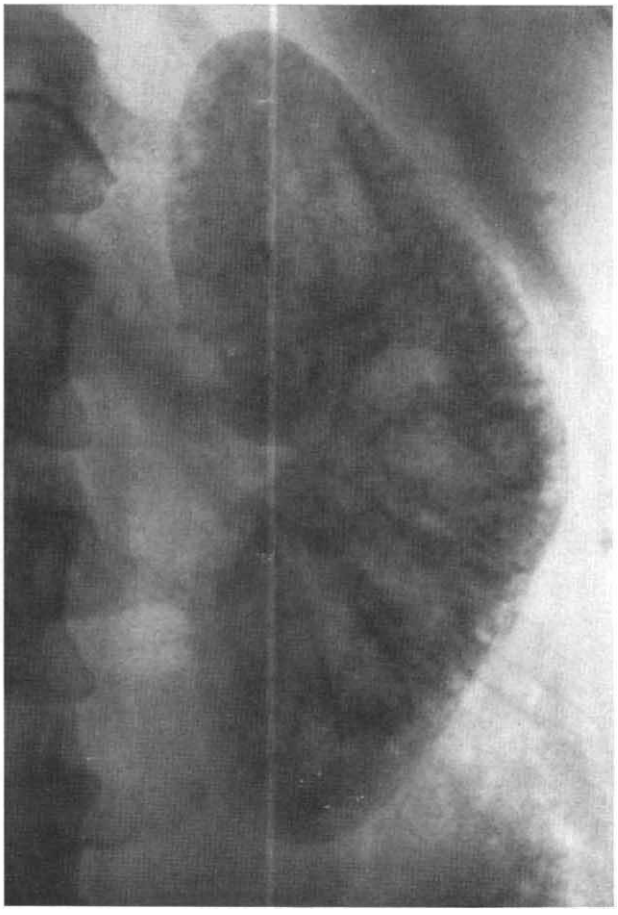
Abbreviations: MRBF = mean renal blood flow; BA = bioassay; IA = immunoassay.

[a] oliguric patients on low sodium diet.

[b] determination performed on both kidneys four days before onset of diuresis.

[c] mean ± SEM.





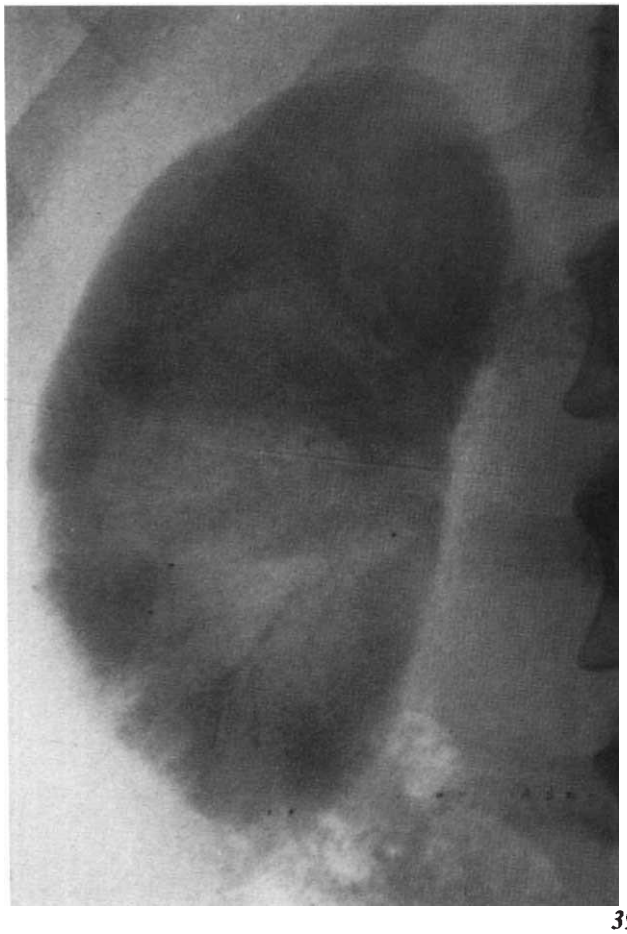


Fig. 1a. *Total BRCN (patient 37).* Selective left renal arteriography. Nephrographic phase (12th sec). Circulation time in interlobar arteries is markedly prolonged. Cortical nephrogram is absent. The outer edge of the cortex is poorly outlined and separated from the inner layer by a clear, nonvascularized area.

Fig. 1b. *Partial BRCN (patient 38).* Selective left renal arteriography. Nephrographic phase (12th sec). Cortical nephrogram is nonhomogeneous with alternation of clear, necrotic areas and dense striped vascularized regions. Appreciable zones of the inner cortex seem spared. (Note that the distance between vascularized inner cortex and the outer edge of the cortex appears shorter than in Fig. 1a.)

Fig. 1c. *Acute renal failure with full recovery.* Selective right renal arteriography. Nephrographic phase (12th sec). The kidney is enlarged, the cortical nephrogram is homogeneous and the outer edge of the cortex is well outlined.

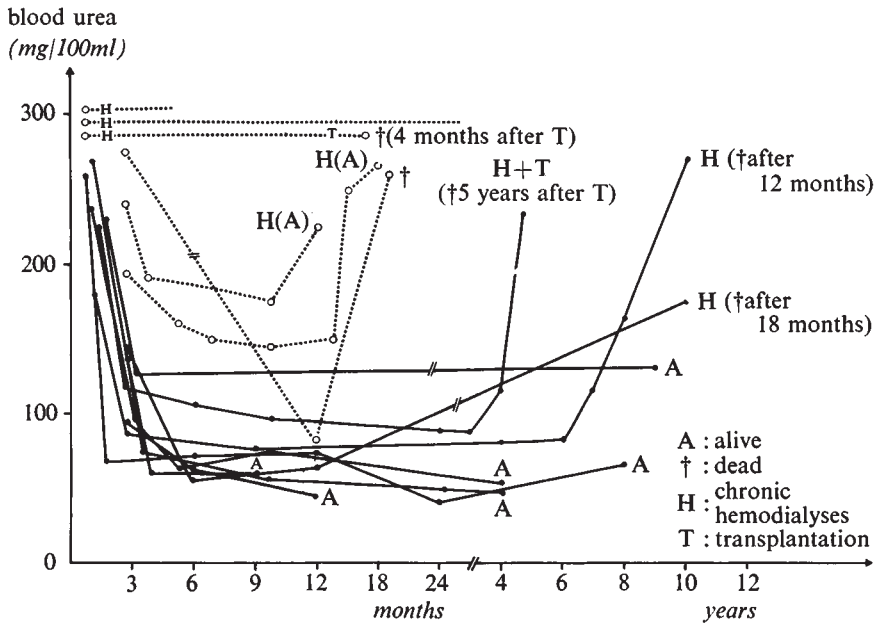


Fig. 2. *Long-term evolution of blood urea in 15 patients with BRCN.*

hyperkalemia (four patients), septicemia (two patients), pulmonary artery thrombosis (one patient), intracranial hemorrhage (one patient) or myocardial infarction (one patient).

In 15 patients the diuretic phase occurred after an anuric period lasting from 12 to 60 days. Two to 16 hemodialyses were required before diuresis occurred. In one patient anuria persisted and in another patient there was no oliguria. The subsequent course is known for 17 patients (Table 1 and Fig. 2). One patient died 18 months after BRCN before dialysis could be instituted. Chronic hemodialysis was required in four patients, within the first three months. In four other patients hemodialysis was reinstituted 1.2, 1.7 and 10 years (two patients) after BRCN. An additional patient received a renal homograft five years after BRCN. The seven remaining patients are still alive without the aid of hemodialysis. This group includes two patients surviving four years after BRCN and two patients surviving eight and nine years after BRCN.

A progressive decrease in kidney size was a common feature in all surviving patients and was roughly correlated with declining renal function. Renal calcifications were apparent in only four of 17 patients within the first six months after BRCN. Four patients developed moderate to severe hypertension with grade 2 or 3 (Keith-Wagener) funduscopic findings a few months before hemodialysis was again required. In these patients the appearance of hypertension may have been a contributing factor to the further decline of renal function. Hypertension was present in two other patients who survived with conservative management only for four and eight years, respectively, with a rather stable course (patients 13 and 29). Antihypertensive therapy was required in one of these patients. Malignant hypertension was present in another patient with definitive anuria (patient 34). There was an associated hemolytic-uremic syndrome and bilateral nephrectomy was necessary.

Sequential studies of creatinine clearance were performed in seven patients within the first year after BRCN (Fig. 3). A progressive increase in creatinine clearance occurred during the first year in six patients; in one patient, the creatinine clearance remained below 20 ml/min, declined further within the next several months and the patient was then treated with hemodialysis.

Two patients underwent renal transplantation. In neither was acute or hyperacute rejection observed.

Discussion

The present results indicate that BRCN occurs in approximately 2% of adult patients with acute renal failure. As previously stated [1, 20], the incidence of BRCN is highest in obstetrical patients, especially in late pregnancy. BRCN is no more frequent in postabortum renal failure (developing during the first quarter of pregnancy) than in acute renal failure of nonobstetrical etiology (1.5%). However, the incidence of BRCN in postpartum renal failure developing in late pregnancy was 21%. Moreover, if only those conditions specifically related to

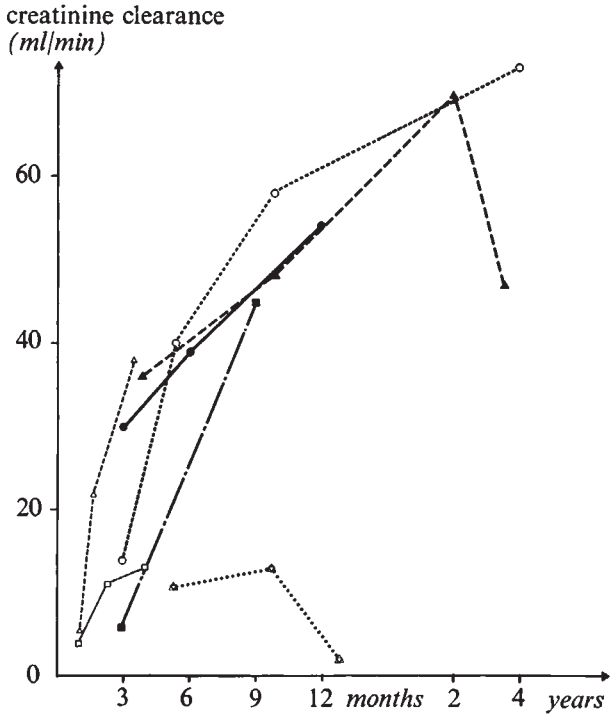


Fig. 3. *Sequential follow-up of creatinine clearance in seven patients with BRCN.*

pregnancy were considered, the incidence of BRCN would have increased up to 50% in our series. In patients with postpartum renal failure several clinical features may indicate the presence of BRCN. The frequency of BRCN is not related to age of patients or to parity, but to the number of weeks of gestation [1]. In our experience, its occurrence was much higher during the third quarter, before the 30th week of pregnancy. In addition, the risk of BRCN was high if anuria was prolonged over 15 days. Premature separation of the placenta was present in 45% of patients with postpartum BRCN but its incidence was not different from that observed in postpartum renal failure without BRCN (Table 2). At variance with previous findings [1], symptoms of toxemia or eclampsia were less frequently observed in the former than in the latter patients.

The histopathological results emphasize the extreme importance of the renal biopsy in establishing the diagnosis of BRCN. On the other hand, renal calcifications on X-ray appear too late to be useful for diagnosis and are not even found in all cases [3–5, 8, 21]. Renal cortical necrosis was recognized on biopsy specimens obtained within the first week of the disease and the extent of cortical necrosis could often be determined from renal biopsy. The percentage of necrotic glomeruli and the presence of spared superficial cortical areas correlated well with the degree of functional recovery. Non-necrotic areas were frequently found in the juxtamedullary cortex. The lack of involvement of this layer, which is well known to occur in BRCN [19], had no predictive value in our series, however.

Selective arteriography is the second most useful procedure in early recognition of BRCN as was shown previously in one patient by Deutsch et al [10] and confirmed in four patients in our series. Evidence of major cortical ischemia was apparent as early as the third day of anuria. In addition, partial BRCN was suspected in two patients in whom corticograms were nonhomogeneous and later confirmed by renal biopsy. Except in one patient with thrombotic microangiopathy without BRCN [22], such an arteriographic picture was quite different from that found in 15 patients with acute renal failure and full recovery [23] (Fig. 1c). In three of the latter patients, corticograms showed small nonvascularized areas on selective arteriography, but appeared homogeneous on aortography; renal vasoconstriction after selective injection may account for this discrepancy.

Renal hemodynamic measurements have shown that total renal blood flow is reduced to one third of normal values in patients with acute renal failure. In addition, ^{133}Xe washout curve analysis has documented preferential cortical ischemia in these same patients [24]. A MRBF of less than 50 ml/100 g/min was usually found in patients with total BRCN in the series of Hollenberg et al [24] as well as in ours. Preliminary results indicate that MRBF is not reduced to such a low level in acute tubular nephropathy without BRCN. In 11 cases studied in our department no patient had MRBF lower than 100 ml/100 g/min [23]. No detectable first component of the wash-out curves was found in patients with total BRCN, but such an absence has also been seen in patients with acute tubular nephropathy [23, 24]. Hemodynamic data could not differentiate between patients with partial BRCN and those with acute tubular nephropathy undergoing full recovery. RSR from the kidneys was very low even in two patients with hypertension. These results are in accordance with those of Shibagaki et al [25] who found a low renin content in two patients with renal cortical necrosis.

The high frequency of BRCN in obstetrical patients has usually been ascribed to coagulation disorders and/or to renal circulatory disturbances secondary to "obstetrical shock" [20]. Attention has been recently paid to coagulation abnormalities in pregnancy. In normal pregnant women, thrombocyte count, fibrinogen and factor VII, VIII, IX and X levels are increased and fibrinolytic activity is reduced [26–28], thus

facilitating the development of intravascular fibrin deposition. Intravascular coagulation may be triggered by the release of thromboplastic material from placental or amniotic origin [29]. Decreased plasminogen and high levels of fibrin degradation products in patients with premature separation of the placenta indicate secondary fibrinolysis [30]. Fibrin deposition in renal vessels and glomeruli may also be facilitated by the harmful effect of antifibrinolytic drugs such as epsilon aminocaprioic acid. This drug was administered in three of our patients. However, the pathogenetic role of coagulation disorders was not clearly demonstrated in our own observations and cases of BRCN with biological evidence of DIC are rare [6, 31]. It has also been stated that preeclampsia and toxemia represent a chronic state of intravascular coagulation [32]. In this regard, it should be noted that toxemia was rare in our patients with postpartum BRCN, suggesting that different mechanisms are involved in toxemia and BRCN.

It is worth emphasizing that fibrinoid thrombi were never seen on renal biopsy specimens in patients with partial BRCN and long survival, but were frequently found in patients with short survival. Moreover, in patients who died during the acute stage with extensive as well as with nonextensive BRCN, widespread renal thrombi were a common finding at postmortem examination. Extrarenal thrombi were also frequently encountered, though they were disseminated in only one case. The significance of renal microthromboses at autopsy is unclear. In patients with the hemolytic-uremic syndrome [33] and in pregnant patients dying from Gram negative sepsis with BRCN [18, 34] arteriolar and/or glomerular thrombi were considered as anatomical proof of intravascular coagulation. They have, however, been reported with some frequency in acute renal failure of obstetrical origin without BRCN [34] and even in nonobstetrical patients without evidence of intravascular coagulation, suggesting that in some cases they may be a preterminal event [35]. Whatever the pathogenetic significance of vascular thrombi, their presence particularly within the kidneys indicates a poor prognosis.

Renal biopsy, selective arteriograms and hemodynamic measurements are the most useful procedures in predicting further recovery, which can now be expected in all cases of partial BRCN. Reexamination of our autopsy material and long-term followup of surviving patients demonstrated that about 50% of patients with BRCN have sufficient kidney tissue spared to survive without chronic hemodialysis, provided compensatory hypertrophy of the remaining nephrons develops [4]. Our results indicate that GFR may increase over a one year period. In the case of Effersoe, Raaschou and Thomsen [36], renal function improved until the third year. Patients with partial BRCN usually recover appreciable renal function once the anuric phase has been overcome with the help of dialyses [1, 4, 7, 36]. In such patients, patchy BRCN may not be recognized if renal biopsy and/or renal arteriography are not performed. Therefore, the frequency of BRCN may have been underestimated in the past. Nevertheless, long-term follow-up demonstrated that subsequent deterioration of renal function occurred in more than half of our recovering patients requiring chronic hemodialysis and/or renal transplantation. It should be recalled that our two transplanted patients had no acute rejection. This observation was contrary to the findings of Gelfand and Friedman [37] who pointed out the high risk of acute rejection in patients with previous BRCN.

Acknowledgments

We are very much indebted to Prof. J. Hamburger for criticism of the manuscript. We thank Dr. P. Kamoun for angiotensin I radio-immunoassay data, Dr. F. Josso and Dr. C. Gazengel for coagulation data and D. Pasques, F. Vuille and C. Darras for technical assistance.

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