PART VII
NEPHROLOGY
Chairman: Dr C Mion
Clinicopathological Correlations in Acute Glomerulonephritis

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Fifty patients with acute endocapillary glomerulonephritis (GN) were hospitalised between 1958 and 1969 at the Necker Hospital. We attempted to predict the long-term prognosis of acute GN from early clinicopathological findings observed in these patients.

PATIENTS AND METHODS

Diagnosis of acute GN was based on the following criteria:

1 Clinical criteria
   (a) acute onset with proteinuria more than 2g/day and microscopic or macroscopic haematuria
   (b) transient rise in blood pressure with or without renal failure
   (c) appearance of oedema, acute circulatory failure, epileptic seizures or oliguria
   (d) no extrarenal or laboratory findings consistent with a systemic disease
   (e) no past history of renal disease, proteinuria or hypertension.

2 Pathological criteria
   (a) diffuse mainly mesangial endocapillary proliferation
   (b) with (35 cases) or without (15 cases) exudative changes (Hamburger et al, 1968)

All patients had a first renal biopsy within six months of clinical diagnosis. A second renal biopsy was performed in 6 patients at intervals from 3 to 30 months. The period of follow-up ranged from 2 to 16 years in 39 patients. The nephrotic syndrome was defined as proteinuria of more than 3g/day, total serum protein less than 6g/100ml and serum albumin less than 3g/100ml.

The criteria for clinical recovery were as follows:

(a) return of proteinuria to normal (less than 0.05g/day)
(b) disappearance of haematuria (less than 5,000 red blood cells per min)
(c) urea clearance more than 50ml/min/1.73m² and/or creatinine clearance more than 80ml/min/1.73m².

Renal biopsies have been examined by light and electronmicroscopy (22 cases) and after immunofluorescent staining (9 cases). The techniques used have been reported elsewhere (Garcia-Torres et al, 1973).

RESULTS

Clinical Features

The age of the patients ranged from 7 to 66 years. Twenty-five were children and 25 adults. There were 37 males and 13 females.

Initial clinical features are listed in Table I. The most frequently observed features were transient renal failure, oedema, hypertension and oliguria.

<table>
<thead>
<tr>
<th>Table I. Initial clinical features (50 cases)</th>
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<tbody>
<tr>
<td>percentage of cases</td>
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<tr>
<td>Proteinuria &gt; 2g/day</td>
</tr>
<tr>
<td>Haematuria &gt; 100,000/min</td>
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<tr>
<td>Renal failure (transient)</td>
</tr>
<tr>
<td>Oedema</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Oliguria</td>
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<tr>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Epileptic seizures</td>
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<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Preceding infection (8-21 days before acute onset)</td>
</tr>
<tr>
<td>ASO titre (Todd Units) &gt; 400</td>
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<tr>
<td>Progressive elevation of the ASO titre</td>
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</table>

The nephrotic syndrome was mild and inconstant. An infectious episode often preceded the onset of renal symptoms by one to three weeks. ASO titre was inconstantly elevated and a progressive elevation of the ASO titre was noted in only twenty instances.

One patient died four months after onset from infectious complications related to immunosuppressive therapy, and 10 patients were lost to follow-up during the first year. The long-term prognosis was evaluated in the 39 remaining patients. Clinical remission occurred within the first twelve months in 28 patients, during the second year in 2 patients and during the fourth year in 3 other patients. Six patients with exudative GN did not recover,
with proteinuria or microscopic haematuria or both persisting for 31 to 123 months. Only one of these patients had renal insufficiency with a creatinine clearance of 58ml/min/1.73m² after 31 months.

In patients with exudative GN, clinical remission occurred in 23 of 30 patients (77%). Recovery was obtained earlier in children than in adults with mean values of 8.8 months and 15.3 months respectively, and the percentage of recovering patients was higher in children (95%) than in adults (70%). All patients with non-exudative GN recovered fully after 2 to 21 months.

The prognostic value of the initial clinical features was evaluated in patients with exudative GN. The incidence of nephrotic syndrome was significantly higher in patients who did not recover (71% against 17%, p < 0.05). Prolonged renal failure of more than 2 months and anuria were also more frequent, but the observed difference was not statistically significant.

Pathological Features

A) Patients with exudative GN. In 35 patients, renal specimens examined by light microscopy showed (a) diffuse endocapillary proliferation, moderate in 12 cases, pronounced in 18 cases and severe in 5 cases; (b) polymorphonuclear leukocytes within capillary lumens; (c) eosinophilic deposits on the outer side of the basement membrane or humps. These humps had a lumpy appearance in 27 patients (typical humps) and were voluminous and contiguous in 8 patients (atypical humps). Focal epithelial crescents were present in 15 patients involving less than 40% of glomeruli. In 3 other patients, crescents were diffuse, involving more than 70% of glomeruli. The glomerular basement membrane was usually of normal thickness with silver stain. Thirteen patients had focal lesions of the capillary walls which appeared irregular and sometimes double-layered, although such an appearance was never as diffuse as in membranoproliferative GN. Thin section examination revealed that apparent thickening of the capillary walls was due to mesangial interposition between the lamina densa and the endothelium.

Immunofluorescent studies showed beta-1C and IgG globulin deposits within the humps in 5 cases and only beta-1C deposits in 2 cases.

The prognostic value of the initial pathological picture was analysed two years after onset (Table II). Pronounced or severe mesangial proliferation and atypical humps were more frequent in non-recovering patients. Diffuse epithelial crescents always indicated a poor prognosis and were observed in 3 patients who did not recover after 31, 46 and 123 months. However, the incidence of clinical remissions was not significantly different in patients with or without capillary wall lesions or focal crescents, and remission was not significantly delayed by the presence of focal crescents (an average of 14.9 against 12.1 months, p > 0.1).
Table II. The prognostic value of the initial histological picture in exudative GN. Situation two years after onset (29 cases)

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>% of histological lesions</th>
<th>Patients recovering (n=20)</th>
<th>Patients who did not recover (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocapillary proliferation +</td>
<td></td>
<td>60</td>
<td>11*</td>
</tr>
<tr>
<td>Endocapillary proliferation ++ or +++</td>
<td></td>
<td>40</td>
<td>89*</td>
</tr>
<tr>
<td>Typical Humps</td>
<td></td>
<td>100</td>
<td>44**</td>
</tr>
<tr>
<td>Atypical Humps</td>
<td></td>
<td>0</td>
<td>56**</td>
</tr>
<tr>
<td>Capillary wall lesions</td>
<td></td>
<td>15</td>
<td>44+</td>
</tr>
<tr>
<td>Focal Crescents</td>
<td></td>
<td>40</td>
<td>66+</td>
</tr>
<tr>
<td>Diffuse Crescents</td>
<td></td>
<td>0</td>
<td>100</td>
</tr>
</tbody>
</table>

+NS   *p < 0.05  **p < 0.01

B) Patients with non-exudative GN. Fifteen patients had diffuse endocapillary proliferation without humps or capillary wall lesions. Mild focal crescents were seen in only 3 instances. Immunofluorescence of glomeruli showed IgG, IgM and beta-1C globulin deposits in one patient and no glomerular deposits in another patient.

Serial Renal Biopsies

Six patients had a second renal biopsy. In one patient, the first biopsy on the twenty-first day showed severe mesangial proliferation, atypical humps, focal crescents and capillary wall lesions. Three months later, renal failure persisted and a new biopsy showed widespread glomerular sclerosis. Another patient had a second biopsy at 27 months because of moderate renal failure. Of 13 glomeruli, 9 were sclerosed and 4 had mild mesangial hypertrophy. In four other patients who were biopsied one to twenty months after clinical recovery mild isolated mesangial hypertrophy was observed.

DISCUSSION

Several factors should be considered in assessing long-term prognosis in patients with acute GN: (a) the precise histological appearance is of importance, since the prognosis of acute GN with diffuse endocapillary proliferation, often following streptococcal infection, is more favourable than that of diffuse extracapillary proliferation with crescents as in the rapidly progressive GN which infrequently follows streptococcal infection; (b) follow-up should be prolonged since clinical recovery both in children and in adults may occur more than two years after the onset of the disease (Earle & Jennings, 1959;

In patients with exudative GN, the initial clinical features and renal pathology may be useful in predicting further prognosis. The nephrotic syndrome, anuria and prolonged renal failure were more frequently observed in patients who did not recover. All patients who fully recovered had typical humps. Mild mesangial proliferation and typical humps, without crescents or capillary wall lesions, are fair indicators of prompt recovery. Atypical humps were only encountered in non-recovering patients studied two years after onset; three of them however recovered after the third year. If severe mesangial proliferation, focal crescents with or without capillary wall lesions are present, the prognosis should be guarded. However, rapid recovery occurred in 50% of our patients with these lesions.

Isolated endocapillary proliferation, non-exudative GN, is frequently encountered in incompletely resolved acute GN (Kushner et al, 1961; Jennings & Earle, 1961; Heptinstall, 1966; Lewy et al, 1971). Full recovery is to be expected.

ACKNOWLEDGMENTS

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REFERENCES


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OPEN DISCUSSION

K LANGE (New York): What makes you select 2g of proteinuria as being a positive indication of the presence of glomerulonephritis? We have seen numerous cases where proteinuria was certainly below 2g/day but with active glomerulonephritis based on immunologic, histologic and electronmicroscopic evidence.

Secondly, did you do any serum complement determinations, and what was their relation to the clinical course of the cases? And thirdly approximately 20% of the cases became chronic, which is much more than generally is assumed. I feel, that if you had done more follow-up biopsies after five and ten years, especially with immunohistology, you would have found probably a still higher percentage. Your data confirm again my impression that the acute glomerulonephritis is not such a harmless disease as we are very frequently made to believe.

Finally, why do you think that the immune deposits that you have on your biopsies are humps? Do you have any positive evidence that these are the same structures as humps, and not immune deposits within the basement membrane or within the capillary. When you do biopsies a little bit later on you can very often see with good staining and good antisera that the entire wall of the capillary is immunologically active and that you have subendothelial and subepithelial deposits.

KLEINKNECHT: First we did not choose 2g proteinuria as an arbitrary limit for definition. We observed that in all patients at some time during the course of the disease, proteinuria was always above 2g/day. For the second question, I did not mention serum complement levels, because serum complement has only been determined since 1969 in our unit, and the study was stopped in 1970. We have not enough serial measurements to correlate with the clinical and histological picture. We now have many more patients to follow up and I think that we will answer this question next year.

Third, we had serial biopsies in eight instances. I had no time to develop this point, but serial renal biopsies showed that in patients who did not recover clinically, there was only mild mesangial proliferation or mesangial hypertrophy with some glomerulosclerosis.

LANGE: What do you consider full recovery clinically and how do you determine it?

KLEINKNECHT: The features of clinical recovery were proteinuria less than 0.05g/day, disappearance of microscopic haematuria, and creatinine clearance above 80ml/min/1.73m².
H-C BURCK (Tübingen): I have one rather provocative question. I would like to know whether it is justified to introduce another classification: exudative-non-exudative glomerulonephritis after Habib and Bohle have already suggested a classification based on more than 2,000 biopsies? Do you have any real indication that your classification of exudative glomerulonephritis offers us something more?

The second question is, Drs Bohle and Habib both found a lot of cases where they had initial improvement in the clinical state as you have shown, but on second biopsy the morphology showed definite signs of progressive disease. Did you find cases with these discrepancies?

KLEINKNECHT: To your first question, we found that clinical criteria may not correspond to the morphological findings. With the same clinical picture, we observed 15 patients who had a variety of morphological features: for example, in 15 patients with rapidly progressive glomerulonephritis we found epithelial, or endothelial and epithelial proliferation without humps in 5 cases, diffuse membrano-proliferative glomerulonephritis in 4, IgG and IgA in 3, minimal changes with focal glomerulosclerosis in 2 and deposit disease in one, and the clinical outcome was entirely different in these patients. Two were lost to follow-up, 3 died, and among the 10 remaining patients only one had clinical remission and this was a case of diffuse membrane proliferative glomerulonephritis followed for fourteen years. All the other patients had proteinuria or haematuria; in only one instance was there renal insufficiency.

For your second question, we did not observe, on repeated serial biopsies, that there was any argument for progressive disease in patients who had clinical criteria of acute glomerulonephritis, or if you prefer, glomerulonephritis of acute clinical onset.

BURCK: I think remissions can only be judged if we have a second and third biopsy to see the histological follow-up. I do not think it is good to base the judgment of remission only on clinical data.

KLEINKNECHT: May I add one comment about that? I think that acute glomerulonephritis is a pure clinical entity, but that various pathological pictures may underlie this entity.