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Diffuse Mesangial Cell Proliferation in Focal Sclerosing Glomerulonephritis*

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Summary. Morphometrical and clinical investigations were performed in 34 patients with the so-called hypercellular form of focal glomerulosclerosis (FGS), i.e., a form showing clear diffuse mesangial hypercellularity beside focal sclerosis with the light microscope. This form was compared with focal glomerulosclerosis without remarkable mesangial hypercellularity, with mild mesangioproliferative glomerulonephritis (gn), as well as with normal kidneys.

The results were as follows:

1. Morphometrically both the increase in relative mesangial volume as well as in mesangial cell count is statistically significant in the hypercellular form compared with the nonhypercellular form and with controls. Comparison with mild mesangioproliferative gn shows no difference.

2. Even the so-called nonhypercellular form contains more mesangial matrix and mesangial cells than the controls.

3. The frequency of the hypercellular form is higher in males and in older patients.

4. All of our patients with hypercellular FGS had at the time of biopsy manifested nephrotic syndrome. The frequency of additional clinical symptoms (hematuria, hypertension, renal insufficiency) corresponds with the nonhypercellular form, but is different in mild mesangioproliferative gn.

5. Therapeutic response and prognosis is worse in the hypercellular form.

The hypercellular form of FGS has to be separated from the nonhypercellular form as a defined entity.

Key words: Focal glomerulosclerosis — Focal sclerosing glomerulonephritis — Mesangial cell proliferation — Nephrotic syndrome.

Focal sclerosing glomerulonephritis, called focal glomerulosclerosis (FGS), has been given increased attention in recent years. Some authors consider it a distinct entity [1, 7, 15, 17], others as a special form of focal nephritis [19], and some even stress the relationship to minimal change lesions with nephrotic syndrome (n.s.) and MPI nephritis with n.s. respectively [2, 4].

The first opinion is understandable, considering that in FGS most of the glomerula appear unchanged under the light microscope. Only with the use of exact morphometric methods [2, 23] or electron microscopy [3, 20, 21] can it be proved that the so-called focal sclerosing gn is a diffuse disease of all glomerula with special focal changes in some glomerula, generally beginning with those in juxtamedullary position.

As reported by Habib [9] and Hyman [14], we have in recent years repeatedly observed cases of FGS with variable histologic findings of focal and segmental glomerular lesions, but a mild proliferation of mesangial cells in all

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glomerula. This gave rise to the question whether and how such a focal sclerosing gn with remarkable diffuse mesangial hypercellularity—the so-called hypercellular form—differs from the nonhypercellular FGS. In the latter, the minimal mesangial cell proliferation can be detected only by morphometric methods [2, 23]; with the light microscope the glomerula seem to be normal.

To solve this problem, we compared cases of FGS with light microscopically visible mesangial hypercellularity to nonhypercellular forms, further to mild mesangioproliferative gn without focal sclerosis, as well as to normal kidneys (Fig. 1).

In each different group morphometric measurements were performed on non focal sclerotic glomerula of 15 patients using the method of Hara (3–5 μm thick paraffin sections, PAS stain [12]). We analyzed the relative mesangial volume [R.M.V. (%)] and the mesangial cell count [M.C.C. (per 1,000 μm^2 glomerular area)]. The 15 cases to be measured of group B were taken from the collected material of Bohle et al. [2[. In all patients of all groups—except the controls—we evaluated the distribution of sex and age and the clinical parameters: nephrotic syndrome, hematuria, hypertension, renal insufficiency, and response to therapy.

Needle biopsies or wedge excisions in the following groups were examined:

Table 1

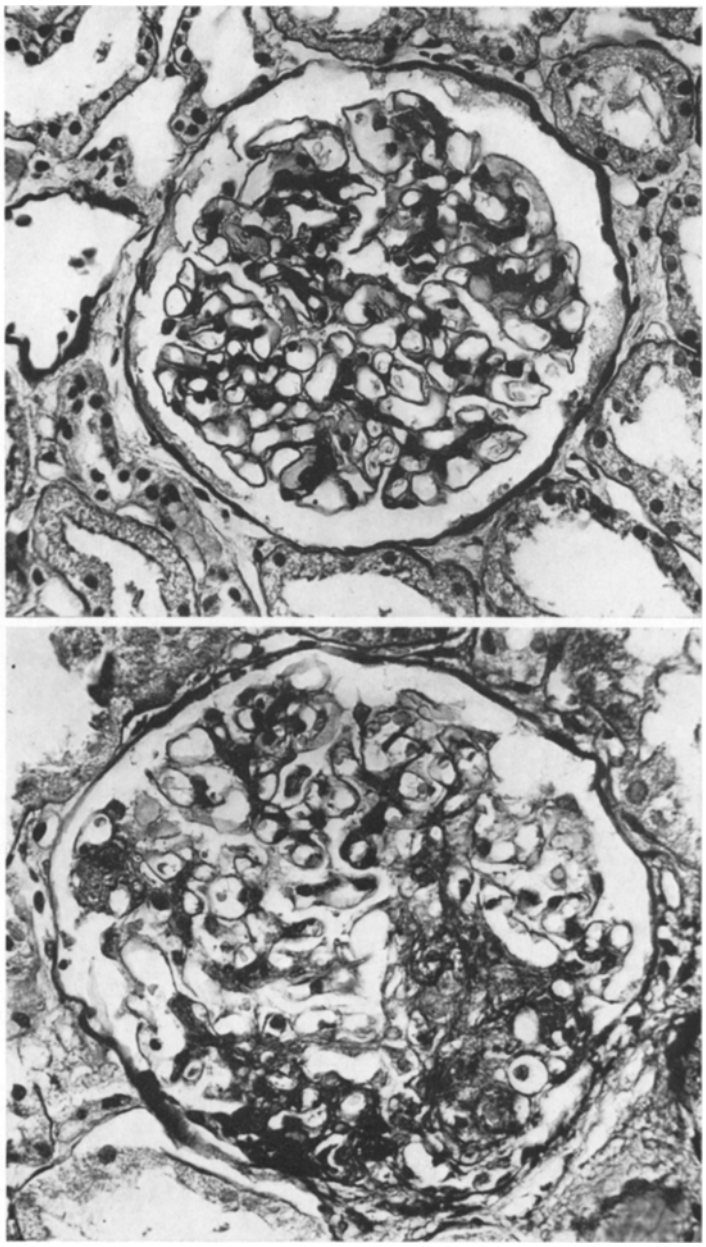
		n	♂ : ♀
A	Normals	20	1 : 1
B	MPI + focal sclerosis = FGS nonhypercellular	100	1.2 : 1
C	FGS hypercellular	34	1.8 : 1
D	Mild mesangioproliferative gn	40	3 : 1

Results

Morphometrical methods show in the hypercellular form of FGS a statistically highly significant increase of the relative mesangial volume, compared with the nonhypercellular form and the controls (Fig. 2). Comparison with the mild mesangioproliferative gn (group D) shows no difference. On the other hand, we are also able to ensure a significant mesangial increase in nonhypercellular FGS as compared with the controls. With respect to the mesangial cell count (Fig. 2) the findings are similar. Significant statistical differences are found in hypercellular form. The mean value in group B is higher than in group A, even if significance here is not ensured.

In the sex distribution of the patients the hypercellular form is more frequent in males (Table 1). Both forms of FGS are rare within the first decade of life. The highest incidence of the nonhypercellular form is seen between the ages of 11 and 20 whereas the hypercellular FGS shows peaks between 40 and 60 and after 70 years (Fig. 3).

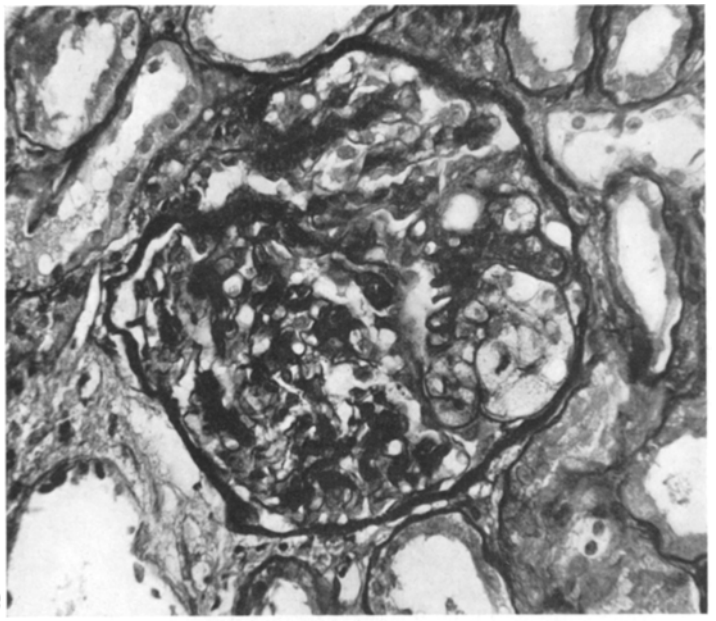
Considering the clinical symptoms (Fig. 4), both forms of FGS are remarkably similar but differ in most parameters from mesangioproliferative gn. It must be



1A

1B

Fig. 1 (A) Normal kidney (7310154). (B) Nonhypercellular FGS (706415) with slight focal increase of mesangial matrix, focal adhesions, and fatty degeneration of endothelial cells. (C) Hypercellular FGS (73111402) with mesangial hypercellularity and focal fatty degeneration of endothelial cells. (D) Mild mesangioproliferative gn (741070). All glomerula PAS stain, × 360



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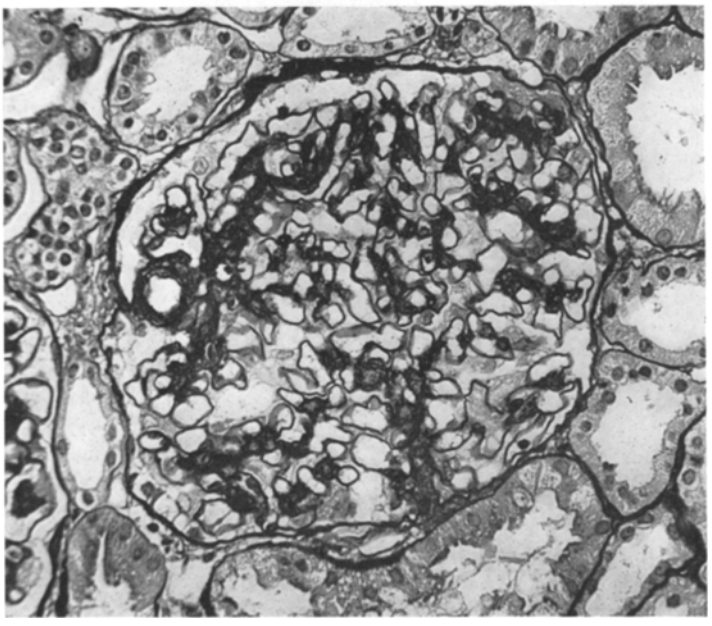

1D

stressed here that without exception, all patients with the hypercellular form had a nephrotic syndrome at the time of biopsy. The following table (Table 2) shows the therapeutic response and the prognosis of both forms of FGS.

It is evident that the hypercellular form has the worse therapeutic results and especially steroids seem ineffective in hypercellular FGS.

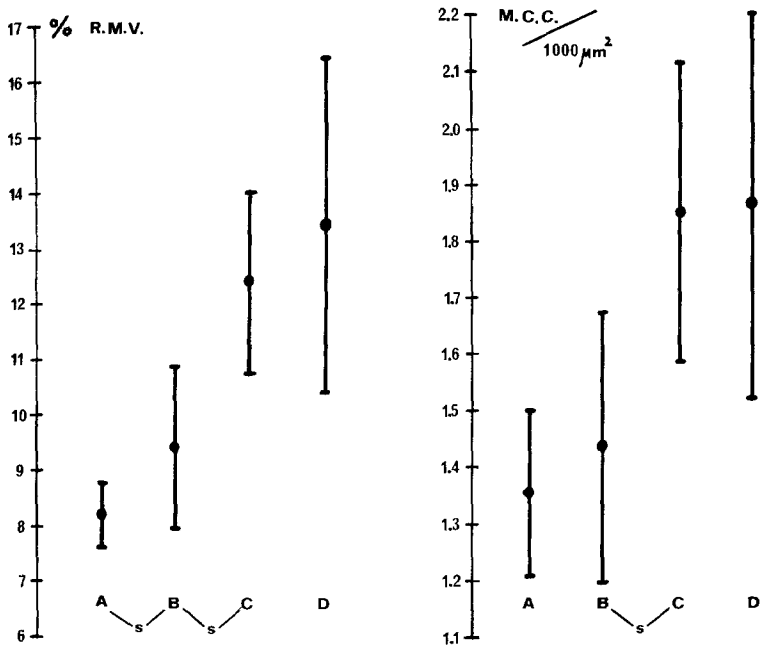

Fig. 2. Results of morphometry in the groups A to D. *R.M.V.* Relative mesangial volume. *M.C.C.* Mesangial cell count (per 1,000 µm² glomerular area). *s* Significance ($P \leq 0.05$) in Student-test

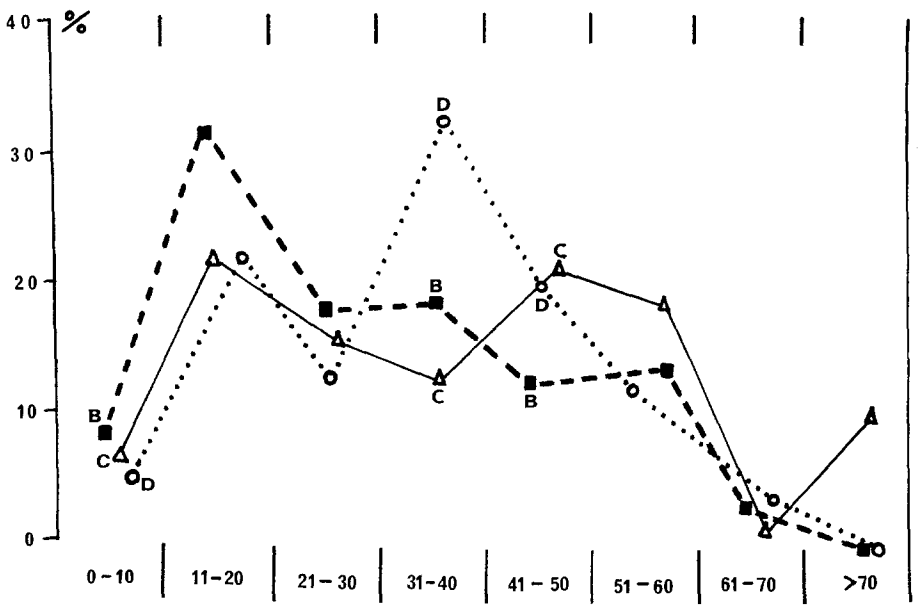

Fig. 3. Age distribution in the groups B, C, and D (percentage of patients)

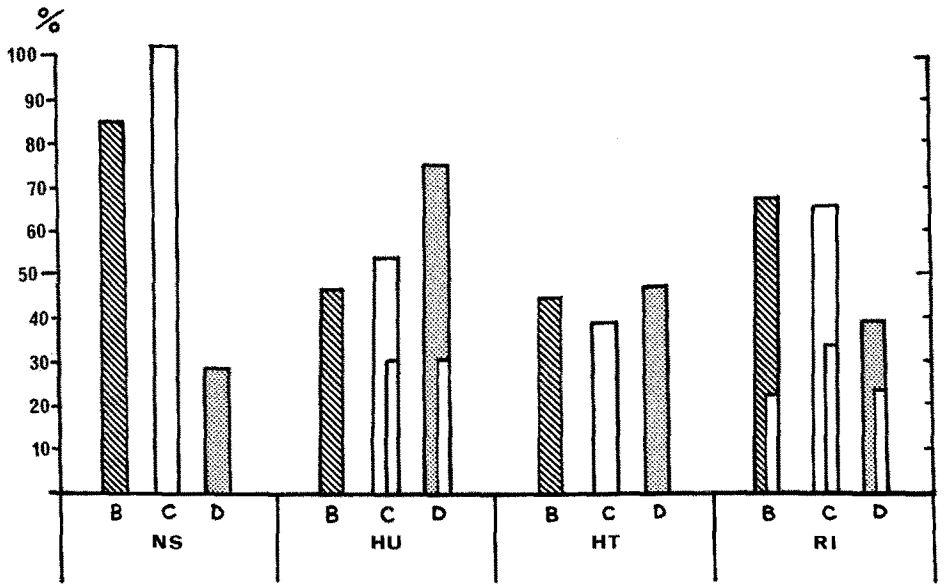

Fig. 4. Frequency of clinical symptoms at the time of biopsy in the groups B, C, and D. *NS* nephrotic syndrome. *HU* microhematuria (small columns: macrohematuria). *HT* hypertension (b.p. syst. $\geqq 160$ mmHg, diast. $\geqq 95$ mmHg). *RI* renal insufficiency (crea $>$ 2 mg% (small columns: severe: crea >4 mg%)

Table 2

Results	Nonhypercellular form $n=77=100\%$			Hypercellular form $n=30=100\%$		
	Therapy			Therapy		
	Steroids and/or Immuno-suppr.	Other drugs or no therapy	Sum	Steroids and/or Immuno-suppr.	Other drugs or no therapy	Sum
Improved	31%	17%	48%	13%	20%	33%
Unchanged	14%	15%	29%	33%	13%	46%
Deteriorated	14%	8%	22%	20%	0%	20%

Discussion

Morphometrically the hypercellular form of FGS shows highly significant differences in relative mesangial volume and mesangial cell count, compared with the nonhypercellular form and the controls. Moreover, the hypercellular FGS and mild mesangioproliferative gn cannot be differentiated by morphometric methods.

Our impression of mesangial cell increase of hypercellular FGS in the light microscope can be ensured by exact morphometric measurements.

On the other hand, even the nonhypercellular FGS shows an increase of mesangial volume and an higher cell count, compared with the controls, although the differences are not so striking as in counts done on more difficult semithin sections [23]. This emphasizes the relationship of these FGS forms to MPI nephritis with nephrotic syndrome [2, 3, 4]. In the latter, a minimal proliferation of mesangial cells can also be proved morphometrically [23].

We observe more males than females in hypercellular FGS (1.8:1), a remarkable difference to nonhypercellular form which shows a nearly balanced ratio (1.2:1). Most of the published literatures confirm the latter [5, 9, 17, 24]. Whether the observed sex distribution correlates to the general observation, that the worse clinical course of many glomerular diseases occurs mostly in males, cannot be rejected if we consider our clinical observations (Table 2). On the other hand, many authors report exclusively about children so that a direct comparison with our data—our patients being mostly adults—is difficult.

The majority of our patients with the hypercellular form of FGS are mainly of older age groups. This can hardly be based on the spontaneous appearance of focal sclerosis in the process of aging; because, genuine focal glomerular sclerosis is found predominantly in juxtamedullar glomerula, focal sclerosis based on age alterations is found to be subcortical. Further, both are different in morphologic findings [8, 10].

The clinical symptoms of hypercellular and nonhypercellular FGS are very similar. There are also analogies to MPI nephritis with nephrotic syndrome [2, 4]. Compared, on the other hand, to mild mesangioproliferative gn the differences are obvious, except for the parameter hypertension. Without exception all patients in the group of hypercellular FGS showed at the time of biopsy manifested nephrotic syndrome (n.s.) compared with 85% n.s. in nonhypercellular FGS and 95% n.s. in MPI nephritis with n.s. [2]. This fact suggests that in focal sclerosis mesangial cell proliferation is regularly accompanied by a considerable alteration of the glomerular basement membrane.

It is generally accepted, tha the appearance of focal sclerotic lesions in minimal change nephritis (= MPI nephritis) with n.s. worsens the prognosis [5, 6, 9, 13, 14, 16, 18, 24]. As can be seen from our table the percentage of improved cases in both FGS forms is far below the value of 73% healing or improvement observed in steroid-treated MPI nephritis with n.s. (2).

In the comparison of both forms of FGS, it seems obvious that hypercellularity causes additional worsening of therapeutic response, when superimposed on focal glomerulosclerosis.

Considering all the subjective and objective data, as well as the relative small amount of hypercellular forms investigated, it can be stressed that FGS with hypercellularity is less favorable. A comparative follow-up study of 5 of our patients confirmed this conclusion.

As a result of our investigation, a hypercellular form of FGS can be separated as a defined entity from a nonhypercellular form. Both forms probably represent variants in the family of MPI nephritis with n.s. [2, 3, 4, 16, 32]. The hypercellular form is a disease of older age groups and of males and has less therapeutic response with worse prognosis.

Despite intensive investigation and experiments [6, 8, 20] the etiology of this family of diseases remains unknown. Some authors report serial biopsies whereby in single cases, focal sclerosis seemed to be superimposed on preexisting cell proliferation [10, 14, 18]. In our opinion these cases probably belonged to the hypercellular form of FGS, sclerotic glomerula not being discovered at the first biopsy.

It must be made clear in further investigations, whether there are any etiologic, pathogenetic, or temporal connections between the appearance of focal sclerotic lesions and mesangial cell proliferation. Further it remains unknown which factors determine the morphologic and clinical findings as well as the course of illness.

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