Clinical Studies on Primary Glomerular Disease

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The purpose of this study can be divided into two main categories: I) recent study of the mechanism of development of primary glomerular disease and II) recent problems in the treatment of advanced glomerular disease.

1. The morbid types and development of primary glomerular disease

Classification of primary glomerular disease has been studied by many investigators and has been the subject of much debate, but the author thinks the following classification is most appropriate clinicopathologically.

1. Proliferative glomerulonephritis (acute or chronic)
2. IgA nephropathy
3. Membranoproliferative glomerulonephritis
4. Membranous nephropathy
5. Lipoid nephrosis (minimal change group of nephrotic syndrome)
6. Focal glomerulosclerosis
7. Focal glomerulonephritis

The above-mentioned diseases that we could clarify in this study are discussed pathologically and immunologically in terms of the development pattern: the complement system, a new field, is also touched on.

(a) IgA nephropathy and proliferative glomerulonephritis

IgA nephropathy has traditionally been included in the category of proliferative glomerulonephritis. Berger suggested IgA nephropathy as a new disease, attracting world attention.1) That is, the following features were cited as differing from those of proliferative glomerulonephritis:

(1) By the fluorescent antibody technique, IgA is stained in the mesangium and other immunoglobulins (Igs) are stained more faintly than IgA;
(2) Proliferative glomerular changes hardly occur in IgA nephropathy; and
(3) Clinically, there are few progressive factors, except for hematuria, showing mild nephritis. However, the author considers that it is necessary in attempting to ascertain the pathogenesis in IgA alone to observe patients in whom other Igs are not stained at all. Changes in the clinical course and prognosis when IgA nephropathy is strictly defined were observed. The following results were obtained: (1) IgA nephropathy has various morphological stages according to the degree of proliferation; (2) From the clinical features, the high incidence of hematuria is in accordance with the report of Berge, but the clinical features occasionally show nephrotic syndrome; (3) The disease progressively develops to renal failure in 10 to 15 years, and some patients die of uremia.

(b) Focal glomerulosclerosis and lipid nephrosis

It is not necessarily easy to differentiate focal glomerulosclerosis from lipid nephrosis from the standpoint of the technique of renal biopsy. In other words, when a puncture needle is placed just on the site of focal glomerulosclerosis in renal biopsy, the kidney can be ascertained definitely to have focal glomerulosclerosis. However, after that, it becomes difficult to make a differential diagnosis of focal glomerulosclerosis from lipid nephrosis when normal tissues are biopsied. In such a case, there is no other way than to note the clinical features alone. The common clinical features of focal glomerulosclerosis, such as

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hematuria (appearing occasionally), hypertension, steroid-resistant nephrotic syndrome, etc., are helpful for the differential diagnosis.

The possible pathogeneses can be cited for focal glomerulosclerosis. First, a glomerular capillary is occluded for some reason (e.g., hypercoagulability at local sites in the glomeruli) during the course of lipoid nephrosis; Second, thrombi occur in the capillary due to the increase in coagulation fibrinolytic activity at local sites in the glomeruli. The second pathogenesis is based on the concept that this disease is quite different from lipoid nephrosis. In many cases of focal nephrosclerosis, thrombi have been demonstrated in a part of the glomerular capillaries.

(c) Membranoproliferative glomerulonephritis

It is known that this disease has two morphological types: one in which the basement membrane of the glomeruli is thickened irregularly accompanied by mesangial interposition and the other in which the basement membrane is thickened accompanied by dense deposits. Both types are accompanied by proliferation of mesangial cells. Many cases of membranoproliferative nephritis having such narrowing of the capillary lumina show hematuria and nephrotic syndrome, and the renal function decreases progressively. Steroids are ineffective for the disease; that is, according to the follow-up of the prognosis by the author, about 25% died 10 years after onset.

This disease exists mostly as an independent condition. However, from the fact that it is also observed as a complication in patients with partial lipodystrophy, a congenital disease, at a high incidence, it is considered to be related to a congenital abnormality.

In this disease, low complement titer is observed, the same as in acute glomerulonephritis, and C3NeF, an antibody specific to C3bBb, is demonstrated in some cases.

(2) Changes in the complement system in primary glomerular disease

In general, detailed analysis of the complement system has very recently been started. The way in which the complement system changes in renal disease is very interesting.

(a) Glomerular diseases showing a low complement titer in serum

Acute proliferative glomerulonephritis in the early stage, membranoproliferative glomerulonephritis, lupus nephritis, etc., are cited as nephritis with decreased CH50. These diseases have their own characteristics when the complement titer is low. That is, low complement titer is observed transiently in acute proliferative glomerulonephritis only at the onset. In this case, the low complement takes an alternative pathway, in which the complement components of more than C3 decrease. In membranoproliferative glomerulonephritis, the complement is generally low although it varies greatly. The low complement takes an alternative or classical pathway, or both.

In lupus nephritis, the complement is continuously low unless the symptoms are otherwise improved. The low complement almost always takes a classical pathway in which the complement components of more than Clq decrease.

In the morbid types other than these above-mentioned three types, there are very few cases showing low complement titer. Instead, most show normal or high complement titer.

(b) Deposition of complements in the glomeruli

In these diseases in which such characteristic serum complement activity is shown, except for IgA nephropathy, deposition of complements in the glomeruli is observed in the same way as in changes in the serum complement activity.

In the case of acute proliferative glomerulonephritis, the early components such as C1, C4, etc. are faintly stained and components of more than C3 are the ones that are stained (Fig. 1).

In types I and II of membranoproliferative glomerulonephritis, classical and alternative pathways occur, respectively.

Each complement component in the serum is within the normal range in IgA nephropathy, but each complement component deposited in the glomeruli takes an alternative pathway in which the complement components of more than C3 accumulate. The reason for the difference in the pathway among the complement components only in IgA nephropathy remains
unknown (Fig. 2).

(c) Various factors that influence the metabolism of C3

C3 in the living body is activated by two pathways, that is a classical pathway and an alternative pathway. The activation of C3 through the classical pathway is controlled by C1INH, C4bp, I, etc., while that through the alternative pathway is controlled by H (β1H) and I. Thus, the complement system mainly consisting of C3 is controlled by these factors and is involved in the mechanism of protection of the living body. The activity of H, I, etc., definitely changes when renal diseases occur. In order to substantiate this view, the activity was determined according to renal disease.

When H (β1H) in serum was determined at the onset of each glomerular disease, the value was high in lipoid nephrosis and IgA nephropathy, but there was no significant difference in the value between normal healthy persons and patients, except for the two diseases. However, the value of H (β1H) determined in the patients with low complements showing CH50 of less than 25 and C3 of less than 40 was significantly lower than that determined in those with normal complements. This shows that the activity of complement is increased and the complement titer is still low, even though the control by H and I is added to suppress the increase. On the other hand, from the standpoint of H and I, the H value seemed to be decreased by the consumption of H.

(d) The relationship between C3NeF and membrandoproliferative glomerulonephritis

In some cases of membranoproliferative glomerulonephritis, the complement titer continues to be extremely low. The low complement titer is believed to be due to C3NeF in most cases. The author studied the characteristics of C3NeF in blood.

C3NeF is a kind of IgG and an autoantibody to C3bBb. C3NeF, which is resistant to heat, is converted into CcbBb-C3NeF and is retained in the living body without being further dissolved. C3bBb is stabilized in the presence of C3NeF. It is not influenced by intrinsic factors or controlling factors, such as H, I, etc. Powerful C3 convertase (C3bBb) is continuously present in the living body, and C3 continues to be low for the purpose of activating C3 in the serum.

(e) Factors that influence other complement systems

In addition to C3NeF, several kinds of substances influencing the activation of complement have recently been found. C42NeF, which was discovered in acute proliferative glomerulonephritis, chronic proliferative glomerulonephritis and SCL, can be cited as one of them. There are other factors including the one relating to an alternative pathway, which was discovered in the early stage of acute proliferative glomerulonephritis by Fujita of our department and the one that was discovered in membranoproliferative glomerulonephritis by Ohi, also of our department. The latter is composed of the combined substance of IgG and complement, and its size in the serum is 18–19S. In the serum, it does not stabilize C3bBb.

The other factor that was discovered by Seki of our department activates the alternative pathway in membranoproliferative glomerulonephritis in a manner similar to C3NeF. However, it is nonresistant to heat, unlike C3NeF.

II. New treatments of primary glomerular disease

(1) Plasma exchange

Plasma exchange has been applied to the treatment of glomerulonephritis. The purpose of such treatment is to remove physiological noxious substances, such as antigen antibody bound substance. This treatment is used for the rapidly advancing type of nephritis and lupus nephritis in the active stage in which immune complex (I.C.) is observed in the blood. We have experienced several patients whose erythrocyte sedimentation and blood viscosity were improved by this treatment and whose renal function and clinical symptoms were also dramatically improved. However, it seems that I.C. is not always improved by a Clq binding assay in proportion to the change in clinical symptoms. Therefore, care should be taken in the analysis of data obtained by Clq binding assay.

(2) Blood purification

Since various methods of treatment of renal failure have been developed in the past few
years, we have recently begun to use the term “blood purification” instead of “dialysis.”

3) CAPD\textsuperscript{10-14}

CAPD is a method in which dialysis is performed continuously. An indwelling catheter is inserted into the peritoneum and the dialysis fluid is continuously injected into a plastic bag outside the body.

By means of such peritoneal dialysis, CAPD is able to exhibit an excellent effect in removing substances with middle-sized molecules, such as guanidino compounds.

The largest number of dropouts from CAPD are due to peritonitis. There are also some dropouts due to occlusion of the catheter or complications of myocardial infarction. Some cases of renal failure associated with diabetic nephropathy drop out from CAPD due to lactic acidosis. In the near future, CAPD is expected to be more widely applied clinically based on studies of the composition of the dialysis fluid.

III. Conclusion

Primary glomerular disease has been discussed above from the clinical standpoint. Probably due to the experience of our many predecessors, the mortality of renal disease is decreasing markedly according to recent death statistics by the Ministry of Health and Welfare for fiscal 1981. Despite the fact that the morbidity has not changed, the mortality has been decreasing markedly. This trend is due to the development of modern nephrology. In particular, countermeasures for renal failure have been rapidly developing, resulting in the marked decrease in mortality. It is also hoped that the therapeutic effect will be improved in this field.

REFERENCES


