原 著

小児腎疾患におけるフィブリノゲン, 第 VIII 因子,
第 XIII 因子上辻 秀和* 谷 一正* 谷口 明*
安井 資司* 岩垣 克己* 福井 弘*Fibrinogen, factor VIII and factor XIII levels in children
with various renal diseasesHidekazu KAMITSUJI*, Kazumasa TANI*, Akira TANIGUCHI*,
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Key words : fibrinogen, factor VIII, factor XIII, renal
disease, intraglomerular coagulation

要 約

小児急性糸球体腎炎 (AGN), ネフローゼ症候群 (NS), および紫斑病性腎炎 (PN) の腎糸球体光顕像とフィブリノゲン (Fg), 第 VIII, XIII 因子の血中濃度 および 糸球体内沈着度について比較検討した。

AGN 急性期の光顕像が Diffuse mesangial proliferation を呈する患児の糸球体毛細管壁には Fg, 第 VIII 因子関連抗原 (VIII R : AG), 第 XIII 因子 Subunit A (XIII-A), Subunit S (XIII-S) の軽度の沈着が見られ, また同時期の血中 Fg 量は軽度高値を, 一方第 XIII 因子は逆に低下する傾向にあった。これに対し遷延期や恢復期の患児の糸球体内には VIII R : AG, XIII-A の沈着はなく, また, 血中 Fg, 第 XIII 因子は正常域にあった。

NS 増悪期の血中 Fg, 第 VIII, XIII 因子

は高値を, 寛解期では正常域に復していた。Minimal change を呈する患児の糸球体内には各凝固因子の沈着はなかったのに対し, Mesangial proliferation や Focal sclerosing を呈する患児では, Fg の沈着が強く, また VIII R : AG, XIII-A, XIII-S の軽度の沈着が認められた。

PN 急性期の血中 Fg, 第 VIII 因子活性 (VIII : C), VIII R : AG は高値にあった。また光顕像で半月体形成を伴う患児では, 発症後の時期には関係なく, 血中 XIII 因子の低下がみられた。PN 患児の大部分の糸球体内には, Fg, VIII R : AG, XIII-A, XIII-S の沈着がみられまた強い Fg の沈着が特徴的であった。Fg の沈着は, 半月体内にも観察されたのに対し, VIII R : AG, XIII-A, XIII-S は半月体内には存在せず, 管腔内にみられた。

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Summary

Fibrinogen (Fg), factor VIII and factor XIII levels in the plasma were found to correlate closely with the results of renal biopsy in 29 children with renal disease, including 9 cases of acute glomerulonephritis (AGN), 9 of nephrotic syndrome (NS) and 11 of purpura nephritis (PN). At the acute phase of AGN, mild deposition of Fg, factor VIII related antigen (VIII R : AG), factor XIII subunit A (XIII-A) and factor XIII subunit S (XIII-S) were limited to the glomerular capillaries together with a slightly increased Fg level and a low factor XIII in the plasma. In recovery or persistent cases, these values showed normal levels, and no deposition of VIII R : AG and XIII-A was detected.

In NS, the Fg, factor VIII and factor XIII levels were elevated in the relapse phase, but these changes were reversed in patients with remission. Minimal changes were not associated with detection of these coagulant factors within the glomeruli. On the other hand, intense deposition of Fg with mild VIII R : AG, XIII-A and XIII-S was detected in cases with mesangial proliferation or focal sclerosing lesions.

High levels of Fg, factor VIII procoagulant activity (VIII : C) and VIII R : AG were found in the acute phase of PN, and cases with crescent formation revealed an increased level of Fg accompanied with a decrease in factor XIII. In PN, intraglomerular deposition of Fg, VIII R : AG, XIII-A and XIII-S were almost present, and a tendency to form intense or dense Fg deposits was characteristic of this disease. Deposition of Fg was observed in the crescents, but VIII R : AG, XIII-A and XIII-S deposits were not present in such lesion.

Introduction

Intrarenal coagulation appears to occur in a wide variety of glomerular diseases as a primary or secondary event. In some renal diseases, there is evidence that intraglomerular fibrin deposition may be a significant factor in the clinical progress and pathological changes. In an attempt to elucidate the role of intraglomerular coagulation, we have studied children with various renal diseases by measuring on a serial basis plasma Fg, factor VIII and factor XIII levels, and these information thus obtained were correlated with the glomerular pathological changes such as deposition of these coagulant factors in the glomeruli.

Material and method

The present study involved a total of 29 children including 9 with AGN, 9 with NS and 11 with PN on whom a renal biopsy was performed between January, 1977 and February, 1979.

Light microscopic examinations of the renal biopsy material were made with

Fig. 1 Changes in plasma fibrinogen, factor VIII and factor XIII levels in the time course of 9 children with acute glomerulonephritis.

× Diffuse mesangial proliferation
 ● Moderate mesangial proliferation
 ○ Mild mesangial proliferation

Fig. 2 Intraglomerular deposition of fibrinogen, factor VIII related antigen, factor XIII subunit A or subunit S in the time course of 9 children with acute glomerulonephritis.

× Diffuse mesangial proliferation
 ● moderate mesangial proliferation
 ○ Mild mesangial proliferation

H-E and P.A.S. stains. Depositions of intraglomerular Fg, VIII R : AG, XIII-A or XIII-S was detected by a direct immunofluorescence microscopic method employing fluorescence labeled human Fg, VIII R : AG, XIII-A or XIII-S rabbit antiserum, respectively. The plasma Fg level was measured by T-G meter, VIII : C by the one stage method of Hardisty¹⁾, VIII R : AG, XIII-A and XIII-S, by the Laurell method²⁾, and factor XIII activity by the M.C.A. method³⁾.

Result

Acute glomerulonephritis: At the acute phase of AGN, the renal morphological findings revealed diffuse mesangial proliferation, but in recovery or persistent cases, these findings were of mild to moderate mesangial proliferation.

In the time course of AGN, the Fg level was slightly increased in a few cases during the 1st week, and normal values were found at to 3 to 4 weeks later. The VIII : C and VIII R : AG levels fell within the normal range. On the other hand, the factor XIII activity, XIII-A and XIII-S showed a low level in a few cases in the acute phase, but in recovery or persistent cases, these values

were in the normal range (Fig. 1).

At the acute phase of AGN, similar evidence of mild Fg deposition within the glomerular capillary walls accompanied by deposition of VIII R : AG, XIII-A and XIII-S was obtained. However in recovery or persistent cases, deposition of VIII R : AG and XIII-A was not observed (Fig. 2).

Fig. 3 gives the relation between plasma level and degree of intraglomerular deposition of Fg, VIII R :

Fig. 3 Relation between plasma level and degree of intraglomerular deposition of fibrinogen, factor VIII related antigen, factor XIII subunit A or subunit S in 9 children with acute glomerulonephritis.

- × Diffuse mesangial proliferation
- Moderate mesangial proliferation
- Mild mesangial proliferation

Fig. 4 Changes in plasma fibrinogen, factor VIII and factor XIII levels in the time course of 9 children with nephrotic syndrome.

- Minimal changes
- Mesangial proliferation
- × Focal sclerosing changes

Fig. 5 Intraglomerular deposition of fibrinogen, factor VIII related antigen, factor XIII subunit A or subunit S in the time course of 9 children with nephrotic syndrome.

- Minimal changes
- Mesangial proliferation
- × Focal sclerosing changes

AG, XIII-A and XIII-S. The degree of intraglomerular deposition of Fg or VIII R : AG shows a positive correlation with the respective plasma levels, but a negative correlation has for XIII-A.

Nephrotic syndrome : Minimal changes or mesangial proliferation were seen through every stage, but focal sclerosing changes were seen in cases of frequent relapse during the later stages.

In the relapse phase of NS, the levels of Fg, factor

Fig. 6 Relation between plasma level and degree of intraglomerular deposition of fibrinogen, factor VIII related antigen, factor XIII subunit A or subunit S in 9 children with nephrotic syndrome.
○ Minimal changes
● Mesangial proliferation
× Focal sclerosing changes

Fig. 7 Change in plasma fibrinogen, factor VIII and factor XIII levels in the time course of 11 children with purpura nephritis.
○ Mesangial proliferation without crescents
● Mesangial proliferation with crescents

Fig. 8 Intraglomerular deposition of fibrinogen, factor VIII related antigen, factor XIII subunit A or subunit S in the time course of 11 children with purpura nephritis.
○ Mesangial proliferation without crescents
● Mesangial proliferation with crescents

VIII and factor XIII were elevated, but on remission, there was a gradual return to normal levels (**Fig. 4**).

In cases with minimal changes, deposition of Fg was not prominent. However, intense Fg deposition and mild deposition of VIII R : AG, XIII-A and XIII-S were observed in cases with mesangial proliferation or focal sclerosing lesions (**Fig. 5**).

As regards Fg and VIII R : AG, there was no obvious correlation between plasma level and degree of deposition whereas a negative correlation obtained for XIII-A or XIII-S (**Fig. 6**).

Purpura nephritis: In cases with mesangial proliferation without crescents, there was no evidence of reduced renal function, and only mild abnormal urinalysis was detectable in the time course of PN. On the other hand, the cases with mesangial proliferation with crescents were characterized by massive proteinuria, hematuria and variable edema, and in the majority of cases, these features persisted.

High levels of Fg, VIII : C and VIII R : AG were observed in the acute phase, and an increased level of Fg was noted in cases with mesangial proliferation with crescents. Such cases were frequently accompanied with decreased level of factor XIII (**Fig. 7**).

The degree of glomerular deposition of Fg, VIII R : AG, XIII-A or XIII-S proved to be more intense in this type of nephritis than in other types of nephropathy. Deposition of Fg was seen in the glomerular capillaries or crescents, whereas deposition of VIII R : AG, XIII-A and XIII-S were limited to the glomerular capillaries only (**Fig. 8**).

In cases showing dense deposition of Fg and VIII R : AG in the glomeruli, increased levels of Fg and VIII R : AG were found. On the other hand, low levels of XIII-A and XIII-S were seen in most cases showing XIII-A and XIII-S depositions in the glomeruli (**Fig. 9**).

Fig. 9 Relation between plasma level and degree of intraglomerular deposition of fibrinogen, factor VIII related antigen, factor XIII subunit A or subunit S in 11 children with purpura nephritis.
○ Mesangial proliferation without crescents
● Mesangial proliferation with crescents

Discussion

In glomerulonephritis, the endothelium of the glomeruli is damaged by deposition of complement leading to an inflammatory reaction. This reaction is followed by intraglomerular coagulation, resulting in fibrin deposition in the glomeruli^{4~7)}.

At the acute phase of AGN, evidence of mild fibrin deposition along the glomerular capillaries accompanied by deposition of VIII R : AG, XIII-A and XIII-S was obtained, whereas deposition of VIII R : AG and XIII-A were not found in recovery or persistent cases. These results for AGN suggest that intraglomerular coagulation may develop at the acute phase as a result of some other pathological process, and that it may be a single or short lived phenomenon. VIII R : AG deposition at an early stage may be due to injury of the vascular endothelium, or to the enhanced synthesis in the endothelial cell^{8~11)}.

As shown above, discrepancy was observed between XIII-A and XIII-S regarding their glomerular deposition in persistent or recovery cases. A consistent interpretation of these conflicting results may be that while XIII-A is identical with factor XIII, XIII-S is a carrier protein of this factor, XIII-A therefore interferes with intrarenal fibrin formation, resulting in the disappearance of antigenicity in persistent or recovery cases, while XIII-S remains unaffected by this reaction and persists in the glomeruli. The plasma Fg level was slightly increased at the acute phase and showed a positive correlation with the degree of Fg deposition in the glomeruli. In contrast, a low level of factor XIII was found in a few cases at the acute phase. A negative correlation existed between the plasma XIII-A level and the degree of its glomerular deposition. The underlying mechanism of this is unknown, although it is considered that it may be due to a low production of factor XIII in the liver.

In NS, plasma hypercoagulability existed at the relapse phase. Kendall¹²⁾ and Thompson¹³⁾ reported high levels of Fg and factor VIII in NS. We¹⁴⁾ have also shown that fibrinolytic activities are depressed in NS. This may further enhance the tendency towards thrombosis. In the cases with minimal changes, Fg deposition was not prominent, and intraglomerular deposition of VIII R : AG, XIII-A and XIII-S were not found. The above increases may be attributable to enhanced hepatic synthesis in response to heavy proteinuria.

Intense deposition of Fg and mild deposition of VIII R : AG, XIII-A and XIII-S were observed in the cases with steroid resistant or frequent relapses, which were characterized by mesangial proliferation or focal sclerosing lesions on light microscopic study. In these patients, repeated stimuli for fibrin formation may have caused intrarenal coagulation frequently, together with enhanced synthesis in the liver.

PN was almost always accompanied by the intraglomerular deposition of Fg,

VIII R : AG, XIII-A and XIII-S, and tendency to form intense or dense Fg deposits was characteristic of this disease. Urizar and Herdman¹⁵⁾ found "fibrin" in the absence of immunoglobulins in early cases of Schönlein-Henoch disease which revealed no or only minimal signs of renal disease, and no significant glomerular abnormalities on light microscopy. These findings suggest that alteration of the coagulation system may be of pathogenetic importance in this disease, which may reflect a hastened coagulation in the glomeruli following glomerular vasculitis. Glomerular crescents, however, were intensely stained by anti-Fg but not by anti-VIII R : AG, XIII-A and XIII-S. The absence of VIII R : AG, XIII-A or XIII-S deposition in the crescents suggests that a different process, not closely related to coagulation, may be involved, and that passage of plasma-derived fibrin or Fg across the capillary wall occurring in a variety of basement membranes may lead to crescent formation¹⁶⁾.

At the acute phase of PN, high levels of Fg, VIII : C and VIII R : AG were found, and cases with mesangial proliferation with crescents showed an increased level of Fg accompanied by a decrease of factor XIII during the time course of this disease. Factor VIII increases may reflect vessel damage at the acute phase since factor VIII protein is synthesized in the endothelial cell of the normal vessel intima.

The finding of a decreased factor XIII in cases with crescent formation suggests its degradation by proteolytic enzymes during the inflammatory process¹⁷⁾, or its utilization in glomerular coagulation. Further, the persistence of a low level of factor XIII in the plasma may lead to damage in the glomeruli.

In some cases, the changes in plasma fibrinogen, factor VIII, factor XIII and factor XIII levels were different from the above-mentioned results. It is therefore suggested that the behavior of clotting factors in peripheral blood may not always reflect local coagulation in glomeruli following an immunological process in glomerulonephritis.

The main points of this paper were presented at the 4th International Society of Hematology (Seoul, Korea. June, 28, 1979).

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