Prediction of Membranoproliferative Glomerulonephritis in Nephrotic Children from Clinicolaboratory Data

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Summary: Prediction of the histology of MPGN was performed without doing a renal biopsy by a univariate and multivariate analysis of three histological groups in nephrotic children: membranoproliferative glomerulonephritis (MPGN, N=13), proliferative glomerulonephritis (PGN, N=11) and minimal change nephrotic syndrome (MCNS, N=10). If the Ŷ value of the following equation exceeded 0.41, the probability of MPGN was very high with a misdiscrimination rate of 4.8%. A Ŷ value less than 0.41 eliminated the possibility of MPGN.

Ŷ = 0.1738X17 − 0.0119X19 − 0.1808X23 + 0.4606X27 − 0.0743X32 + 0.2740X35 + 0.4591

(X17=serum Ca, mg/dl; X19=serum C3, mg/dl; X23=serum total protein, g/dl; X27=serum beta globulin, g/dl; X32=hematuria by paper test, 0=negative, 1=+, 2=++, 3=++; X35=presence of urinary granular cast, 0=None, 1=present)

Key words: membranoproliferative glomerulonephritis — proliferative glomerulonephritis — minimal change nephrotic syndrome — nephrotic children — clinicolaboratory data — multivariate analysis

Introduction

Membranoproliferative glomerulonephritis (MPGN) cannot be effectively treated with steroids. Massive steroid therapy as in minimal change nephrotic children, tended to induce rapid deterioration of renal function and/or cause severe side effects, such as hypertension (White et al. 1966). These difficulties necessitated predicting the histology of MPGN without doing renal biopsy, before the initiation of steroid therapy. The International Study of Kidney Disease in Children (ISKDC) reported an equation with such objectives (ISKDC 1978), however, it was not valid for Japanese nephrotic children for the following reasons: Possibly different clinicolaboratory data; different measuring method for serum C3; no availability of Addis count. Therefore, we compared the clinical and laboratory data from three histological groups based on renal biopsy findings and formed an equation to predict the presence of MPGN with 6 variables.

Patients and Methods

Thirty-four nephrotic children diagnosed by the criteria in the ISKDC (Barnett, 1978) were divided into three histological groups based on the renal biopsy: 13 MPGN, 10 MCNS and 11 PGN. There were 18 males and 16 females between 3 and 15 years of age. Univariate analysis (t-test) was used to determine the characteristic features of each group. Initialy 35 clinical and laboratory items were compared. This was reduced to 13 after the repeated univariate analysis.
Then, multivariate analysis was applied to the 13 items. Finally, 6 items were confirmed as the essential variables and an equation to predict MPGN was developed by the method of least squares. Serum complement C3 was measured by M-Partigen (Hoechst) and was expressed as mg/dl of $\beta_1$ C. Paper sticks by Ames Company were used for the detection of urinary occult blood. The number of granular casts and red cells in the urinary sediment were counted in a high power field (ca. 400×). The sediments were obtained by centrifugation (1,500 rpm; 5 min.) of 10 ml of urine.

**Results**

The following 35 items of clinical and laborotory data obtained during the diagnosis were selected for comparison in the three histological groups by univariate analysis (t-test): (1) The age at the time of the diagnosis; (2) sex; (3) presence of edema; (4) systolic blood pressure; (5) diastolic blood pressure; (6) BUN; (7) serum creatinine; (8) Ht; (9) Hb; (10) RBC; (11) WBC; (12) ESR; (13) serum cholesterol; (14) Na; (15) K; (16) Cl; (17) Ca; (18) P; (19) serum C3; (20) IgG; (21) IgA; (22) IgM; (23) serum total protein; protein fraction: (24) albumin, (25) $\alpha_1$ globulin, (26) $\alpha_2$ globulin, (27) $\beta$ globulin, (28) $\gamma$ globulin; (29) proteinuria, g/day; (30) occult blood in urine; (31) urinary protein; (32) urinary protein concentration measured by sulfosalicylic acid method; (33) microscopic hematuria; (34) granular cast in urine and (35) macroscopic hematuria. Thirteen items for differentiating between histopathologic categories by t-test were selected as variables for the multivariate analysis (Table 1). The equation for the estimation of $\hat{Y}$ value was determined by the method of least squares. The variables

**TABLE 1**

*Comparison of 13 items in the three histological groups p values by univariate analysis (t-test)*

<table>
<thead>
<tr>
<th>Items</th>
<th>MPGN vs MCNS</th>
<th>MPGN vs PGN</th>
<th>MCNS vs PGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>0.0062***</td>
<td>0.2410</td>
<td>0.0002***</td>
</tr>
<tr>
<td>Edema</td>
<td>0.0000***</td>
<td>0.3271</td>
<td>0.0002***</td>
</tr>
<tr>
<td>BUN</td>
<td>0.6323</td>
<td>0.0223*</td>
<td>0.0201*</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.0043**</td>
<td>0.6687</td>
<td>0.0017**</td>
</tr>
<tr>
<td>ESR (mm/hour)</td>
<td>0.0000***</td>
<td>0.7796</td>
<td>0.0000***</td>
</tr>
<tr>
<td>Serum Na</td>
<td>0.0020**</td>
<td>0.4110</td>
<td>0.0013**</td>
</tr>
<tr>
<td>Serum Ca</td>
<td>0.0151*</td>
<td>0.1254</td>
<td>0.0062**</td>
</tr>
<tr>
<td>Serum C3</td>
<td>0.0000***</td>
<td>0.0001***</td>
<td>0.0698</td>
</tr>
<tr>
<td>Serum total protein</td>
<td>0.0016**</td>
<td>0.0890</td>
<td>0.0000***</td>
</tr>
<tr>
<td>Serum $\beta$ globulin</td>
<td>0.9704</td>
<td>0.0074**</td>
<td>0.0236*</td>
</tr>
<tr>
<td>Proteinuria (Sulfo.)</td>
<td>0.0333*</td>
<td>0.6690</td>
<td>0.0072**</td>
</tr>
<tr>
<td>Positive hematuria (Paper test)</td>
<td>0.0001***</td>
<td>0.0001***</td>
<td>0.0000***</td>
</tr>
<tr>
<td>Urinary granular casts</td>
<td>0.0001***</td>
<td>0.1157</td>
<td>0.0308*</td>
</tr>
</tbody>
</table>

Abbreviations (MPGN: membranoproliferative glomerulonephritis; PGN: proliferative glomerulonephritis; MCNS: minimal change nephrotic syndrome; Sulfo.: sulfosalicylic acid method.)
PREDICTION OF MPGN IN NEPHROTIC CHILDREN

TABLE 2

An equation for predicting membranoproliferative glomerulonephritis (MPGN)

\[ \hat{Y} = 0.1738X_{17} - 0.0119X_{19} - 0.1808X_{23} + 0.4606X_{27} - 0.0743X_{32} + 0.2740X_{35} + 0.4591 \]

where:
- \( X_{17} \) = serum Ca, mg/dl;
- \( X_{19} \) = serum C3, mg/dl;
- \( X_{23} \) = serum total protein, g/dl;
- \( X_{27} \) = serum \( \beta \) globulin, g/dl;
- \( X_{32} \) = hematuria by paper test, 0 = negative, 1 = +, 2 = ++, 3 = +++;
- \( X_{35} \) = presence of urinary granular cast, 0 = none, 1 = present.

Fig. 1. Distribution of \( \hat{Y} \) values in the patients with minimal change nephrotic syndrome (MCNS) / proliferative glomerulonephritis (PGN) and with membranoproliferative glomerulonephritis (MPGN).

were selected by the method of gradual reduction repeatedly. Finally, the following 6 variables remained as the essential components in the equation (Table 2): (1) The levels of serum Ca, (2) serum C3, (3) serum total protein, (4) serum \( \beta \) globulin, (5) positive hematuria by paper test and (6) the presence of urinary granular casts. The multiple correlation coefficient \( (R_0) \), contributing rate and F value of the equation were 0.8655, 0.749 and 13.434, respectively. These values indicate a high reliability of the equation. All the patients with a \( \hat{Y} \) value of more than 0.41 belonged to MPGN, except one patient who had a histology of MCNS. The probability of misdiscrimination was 4.8 % because one of 21 patients predicted as MPGN showed a different histology (MCNS) (Fig. 1). The mean \( \hat{Y} \) values of the MCNS/PGN group were significantly different from the MPGN group. (Mean ± SE: 0.096 ± 0.05 vs 0.845 ± 0.054, p<0.0001***).

Discussion

The equation yielded could predict MPGN with a misdiscrimination rate of 4.8 % which was lower than that in the equation proposed by ISKDC (ISKDC 1978). The probability of predicting MPGN as MCNS or PGN was zero, which was the same as in the equation in ISKDC. Therefore, the discrimination between MPGN and other groups was very sharp using the equation yielded (Fig. 1).

The variables for the equation for Japanese nephrotic children were different from those in ISKDC. In ISKDC, the variables were (1) serum C3, (2) edema, (3) serum creatinine, (4) albumin and (5) hematuria. The variables for Japanese nephrotic children were (1) serum C3, (2) serum total protein, (3) serum \( \beta \) globulin, (4) serum Ca, (5) hematuria and (6) urinary granular casts. In our series all patients, except one MPGN, had normal serum creatinine levels. It should be emphasized that MPGN children in our series were detected at an early stage due to a school urinalysis or routine health checks.

Serum calcium correlated well with the total serum protein concentration (Table 3), and did not correlate with creatinine clearance, BUN and serum phosphate levels in our series. Low total serum protein and low serum Ca levels contributed to the discrimination of MCNS from MPGN and PGN. In this equation, a significantly low level of serum C3 could discriminate MPGN from other groups and significantly increased serum \( \beta \) globulin could differentiate PGN...
from MPGN or MCNS. A significantly increased serum β globulin in PGN was difficult to explain. Positive hematuria and the presence of urinary granular casts had the same incidence in the MPGN and PGN groups. This could discriminate these two groups from MCNS. The equation invariably predicted MPGN and discriminated between MCNS and PGN. The application of the equation in nephrotic children is recommended before starting steroid therapy to avoid the unfavorable side effects of massive steroid therapy. The equation could also be used as an indicator for renal biopsy.

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References