Serum Immunoglobulin E Can Predict Minimal Change Disease Before Renal Biopsy

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Abstract: *Objectives:* Minimal change disease (MCD) is a major cause of nephrotic syndrome in both children and adults. The diagnosis of MCD in adults relies on findings of renal biopsy. Complications, although rare, may occur. This invasive procedure is also a suffering experience for some patients. Although Shu et al described the increase of serum immunoglobulin E (IgE) level in patients with MCD, whether IgE could be a predicting factor of MCD has not been determined. *Methods:* The sample was composed of 76 nonlupus patients with nephrotic range (≧3.5 g/d/1.73 m^2) proteinuria and normal creatinine level who received renal biopsy since January 2006 to December 2007. Twenty-four demographic, clinical, and laboratory variables as predictors of MCD, including IgG, IgA, IgM, and IgE, were retrospectively gathered by chart review 1 day before renal biopsy. *Results:* The overall prevalence of MCD in this group (nonlupus and normal creatinine level) was 27.6% (21 of 76). The independent Student t test identified that 3 of 24 variables is statistically significant ($P < 0.05$). Serum IgE was found to have a good discriminative power (area under the receiver operating characteristic curve 0.868 ± 0.053; $P < 0.001$) according to the area under the receiver operating characteristic curve. *Conclusions:* Serum IgE exhibited high discriminative power in predicting MCD. Serum IgE is a straightforward and easily applied evaluative tool with good predictive abilities.

Key Indexing Terms: Minimal change disease; Immunoglobulin E; renal biopsy; Nephrotic syndrome. **[Am J Med Sci 2009;338(4):264–267.]**

Minimal change disease (MCD) is a major cause of nephrotic syndrome in both children and adults. The disorder currently seems to underlie 10% to 15% of all cases of adult nephrotic syndrome.[1] In children, a presumptive diagnosis of MCD is normally based on clinical findings at presentation. However, adults with MCD present with clinical features that are also consistent with other glomerular diseases and do not necessarily respond to a short course of glucocorticoids. Therefore, the diagnosis of MCD in adults relies on findings on renal biopsy. Complications, although rare, may occur and are mostly related to bleeding.[2] This invasive procedure is also a suffering experience for some patients before and after it. The increase of serum immunoglobulin E (IgE) level in patients with MCD (median, 630 IU/mL) was observed and reported in 1988 and may serve as a prognostic indicator in terms of steroid responsiveness in MCD.[3] However, whether IgE could be a predicting factor of MCD has not been investigated. Therefore, this retrospective study attempts to identify whether any predictor could be used for MCD prediction before renal biopsy, including IgE.

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METHODS

Patient Information and Data Collection

The local institutional review board approved this study and waived the requirement for informed consent. This data collection by chart review was undertaken in a 100-bed specialized nephrology ward at a 2000-bed University Hospital in Taiwan, between January 2006 and December 2007. In total, 76 patients with nephrotic range (≧3.5 g/d/1.73 m^2) proteinuria who received renal biopsy were enrolled. Exclusion criteria were as follows: proteinuria not achieved nephrotic range, patients with systemic lupus erythematosus, positive antinuclear antibody, and abnormal creatinine (creatinine >1.4 mg/dL).

The following data were retrospectively gathered by chart review: demographic variables 1 day before renal biopsy, comorbidity, indication for renal biopsy, and histopathology report.

Definitions

MCD was diagnosed based on normal appearing glomeruli by light microscopy, and the absence of complement or immunoglobulin deposits by immunofluorescence microscopy.[4] All specimens were reviewed by expert pathologists. Microscopic hematuria was defined as >20 red blood cells in high-power field microscopy in centrifuged urine.

Laboratory Methods

To measure total serum immunoglobulin level, electrochemiluminescent immunoassay (Roche Diagnostics, Indianapolis, IN) with high analytical sensitivity up to 0.08 IU/mL was used. To measure proteinuria, colorimetric methods (Beckman Coulter, Fullerton, CA) with analytical sensitivity up to 20 mg/dL were used.

Statistical Analysis

Continuous variables were summarized by mean and standard deviation unless otherwise stated. The primary analysis compared patients with MCD with non-MCD patients. All variables were tested for normal distribution by performing the Kolmogorov-Smirnov test. The Student t test was used to compare the means of continuous variables and normal distributed data; otherwise, the Mann-Whitney U test was used. Categorical data were tested using the χ^2 test.

Calibration was assessed with the Hosmer-Lemeshow goodness-of-fit test (C statistic), which was performed to compare the numbers of observed and predicted MCD cases. Discrimination was explored with the area under a receiver operating characteristic curve (AUROC). The two resulting AUROC curves were compared using a nonparametric approach.[5] AUROC analysis was also performed to calculate the cutoff values, sensitivity, specificity, overall correctness, and positive/negative predictive values. Finally, cutoff points were calculated from the best Youden index (sensitivity + specificity − 1).[6]

TABLE 1. Patient demographic data and clinical characteristics

	MCD (n = 21)	Non-MCD (n = 55)	*P*
Age (yrs)	35 ± 4	45 ± 2	0.015
Sex (M/F)	13/8	25/30	NS
Comorbidity			
Hypertension (yes/no)	3/18	11/44	NS
Cardiac event history (yes/no)	0/21	1/54	NS
DM (yes/no)	0/21	2/53	NS
Liver cirrhosis (yes/no)	0/21	1/54	NS
HBs Ag (yes/no)	3/18	7/48	NS
HCV Ab (yes/no)	2/19	1/54	NS
BUN (mg/dL)	20.5 ± 3	16 ± 1	NS
Creatinine (mg/dL)	0.93 ± 0.1	0.93 ± 0	NS
AST (U/L)	26 ± 4	25 ± 2	NS
ALT (U/L)	21 ± 2	21 ± 3	NS
Alk-P (U/L)	54 ± 3	59 ± 7	NS
Total bilirubin (mg/dL)	0.4 ± 0.1	0.4 ± 0	NS
Na (mEq/L)	136 ± 2	137 ± 3	NS
K (mEq/L)	3.8 ± 0.1	4.0 ± 0.1	NS
Creatinine clearance (mL/min)	101 ± 10	90 ± 6	NS
Urinary protein loss (g/d)	10.8 ± 2.0	5.9 ± 0.6	0.032
C3 (mg/dL)	130.3 ± 8.8	115.0 ± 4.0	NS
C4 (mg/dL)	32.6 ± 3.1	25.7 ± 1.8	NS
IgG (mg/dL)	650.5 ± 106.5	707.5 ± 47.7	NS
IgA (mg/dL)	306.3 ± 33.8	264.2 ± 21.4	NS
IgM (mg/dL)	209.4 ± 32.6	154.6 ± 19.2	NS
IgE (IU/mL)	1196.8 ± 378.4	202.5 ± 53.9	0.024

MCD indicates minimal change disease; DM, diabetes mellitus; HBs Ag, hepatitis B virus surface antigen; HCV Ab, hepatitis C virus antibody; BUN, blood urea nitrogen; AST, aspartate aminotransaminase; ALT, alanine aminotransaminase; Alk-P, alkaline phosphatase; C3, complement component 3; C4, complement component 4; IgG, IgA, IgM, IgE, immunoglobulin G, immunoglobulin A, immunoglobulin M, immunoglobulin E; NS, not significant.

TABLE 2. Indications for renal biopsy and histological results of renal biopsy

	Number	Percentage
Indications		
Proteinuria	46	60.5
Proteinuria + hematuria(m)[a]	30	39.4
All	76	100
Results		
MCD	21	27.6
Focal segmental glomerulosclerosis	1	1.3
Membranous glomerulonephritis	27	35.5
IgA nephropathy	15	19.7
IgM nephropathy	1	1.3
Membranous proliferative glomerulonephritis	1	1.3
Mesangial proliferative glomerulonephritis	3	3.9
Diffuse proliferative glomerulonephritis	2	2.6
Amyloidosis	2	2.6
Glomerulosclerosis	3	3.9
All	76	100
The prevalence of MCD (n = 21) in patients with different indications		
Proteinuria with MCD	18	85.7
Proteinuria + hematuria(m) with MCD	3	14.2
All	21	100

[a] Microscopic hematuria definition in Chang-Gung memorial hospital: >20 red blood cell in high-power field.

MCD indicates minimal change disease; Hematuria(m), microscopic hematuria.

RESULTS

Subject Characteristics

Between January 2006 and December 2007, 76 non-lupus patients with nephrotic range proteinuria and normal creatinine level were enrolled. Their mean age was 43 years (median age, 41 years); 38 patients were men (50%) and the other 38 patients were women (50%). The overall MCD prevalence for the entire group was 27.6% (21 of 76). Table 1 shows patient demographic data and clinical characteristics of patients with/without MCD. Table 2 shows the indications for renal biopsy and the histopathology report of these patients. Most patients with MCD presented proteinuria only and 14.2% (3 of 21) patients presented both proteinuria and microscopic hematuria.

Predictors for Minimal Change Disease

The independent Student *t* test identified 3 of 24 variables as being statistically significant ($P < 0.05$) for MCD. These variables were younger age, larger amount of 24 hours urine protein loss (g/d), and elevated serum IgE level (Table 1).

Table 3 shows the goodness-of-fit as measured using Hosmer-Lemeshow χ^2 statistic of predicted MCD, the predictive accuracy of the age, amount of daily urine protein loss, and serum immunoglobulin levels (IgG, IgA, IgM, and IgE). Table 3 also lists the discrimination by age, amount of daily urine protein loss, and serum immunoglobulin levels (IgG, IgA, IgM, and IgE). Computation for the AUROC reveals that the serum IgE had significantly better discriminatory power ($P < 0.05$) than age and amount of daily urine protein loss.

Indices for Predicting Minimal Change Disease Before Renal Biopsy

The sensitivity, specificity, overall correctness of prediction, and positive and negative predictive values were computed to obtain the predictive values of selected cutoff points for predicting hospital mortality. Table 4 presents these data calculated by the cutoff point providing the best Youden index. The serum IgE level had the best Youden index and the largest overall correctness of prediction.

Figure 1 illustrates the relationship between serum IgE and MCD, revealing a correlation. The prevalence of MCD was 0 in patients with serum IgE level lower than 71 IU/mL, the value of the cutoff point provided by the Youden index. But 13 of 29 patients with IgE levels between 90 and 1100 did not have MCD.