

Prognostic Value of Renal Pathological Findings in Children With Atypical Hemolytic Uremic Syndrome

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Introduction. Atypical hemolytic uremic syndrome (HUS) is accompanied by a poor prognosis and high mortality rate. We investigated the predictive value of severity of renal involvement, as evaluated by pathologic examination, for long-term outcome of atypical HUS.

Materials and Methods. Kidney biopsies of 29 children diagnosed with atypical HUS between 1992 and 2005 were reviewed. The severity of glomerular, vascular (arteriolar and arterial), interstitial, and tubular involvement were determined. Scores of renal involvement were determined by re-evaluating kidney specimens. The outcome measures were death, chronic kidney disease (CKD), hypertension, and proteinuria.

Results. After a mean of 3.7 years of follow-up, 24.1% of the patients had normal kidney function and blood pressure, 24.1% showed proteinuria, and 41.4% had CKD, and 10.3% had unknown prognosis. Overall, 24.1% of the patients died due to emergent hypertension with or without CKD. The existence of arteriolar and arterial thrombosis attributed to severe CKD (risk ratio, 3.67; 95% confidence interval, 1.63 to 8.2). Presence of thrombosis in the vessels, and thickening of the arterial medial and intimal layers had brought about a significantly higher mortality rate. Chronic kidney disease was more frequent in the children with vascular scores higher than 0.14 and a final score of more than 0.2.

Conclusions. The severity of renal pathological involvement, especially the degree of vascular damage, is a good predictor of long-term outcome of patient with atypical HUS.

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INTRODUCTION

Hemolytic uremic syndrome (HUS) is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and kidney failure. Atypical HUS, traditionally named “diarrhea negative,” is due to nonenteric bacterial infections, viruses, drugs, malignancy, pregnancy, malignant hypertension, vasculitis, and systemic diseases, which can also be familial and may follow a relapsing or progressive course.¹⁻⁴ Atypical HUS has a poor prognosis; 50% to 70% of the cases reach to

chronic kidney damage following several episodes of relapses in the course of the disease or may lead to hypertension or proteinuria in long-term.^{5,6} The early stages of HUS are characterized by diffused mesangio proliferative glomerular damage, and the later stages, by focal segmental glomerulosclerosis with hyalinosis.⁷

Clinically, the presence of persistent oliguria or anuria, central nervous system involvement, severe initial presentation, and the need for dialysis are indicative of poor prognosis.^{6,8,9} The presence of

global sclerosis and cortical necrosis in pathology can be a sign of developing into chronic kidney disease (CKD).^{7,10,11} Few studies have been done about the relation between pathological findings and long-term outcomes of atypical HUS. This study is aimed to answer whether the severity of renal pathological involvement has a prognostic value among patients with atypical HUS.

MATERIALS AND METHODS

In a historical cohort study, we reviewed the files of 102 patients with a diagnosis of HUS in Ali-Asghar Children Hospital, admitted between 1992 and 2005. The inclusion criteria were a diagnosis of microangiopathic hemolytic anemia with fragmented erythrocytes, thrombocytopenia (platelet count, $< 140 \times 10^9/L$), kidney failure (azotemia) in the absence of diarrhea within 7 days of the onset of HUS, and negative stool, blood, and urine culture for microorganisms, along with either the presence of low serum complement levels, death or HUS in siblings of a consanguineous couple, or relapse in the index case. The exclusion criteria were drug-induced HUS and thrombotic microangiopathy secondary to vacuities, *Shigella* or Shiga toxin-induced HUS, and pneumococcal infection. Twenty-nine children were included (6 with low serum complement, 2 with low factor H level with normal serum complement, and the 5 with ADAMTS13 deficiency, and 17 with recurrent HUS), all of whom had undergone kidney biopsies.

Kidney specimens were reviewed by a pathologist who was not aware of the course of the disease, and they were then scored according to the severity of involvement at the glomerular level (zero to 24), vascular level including arteriolar (zero to 18) and arterial (zero to 12), interstitial level (zero to 9), tubular level (zero to 9), and medullary level (zero to 6). The final score was estimated by summing up the scores of all the items. The renal slides were reviewed for changes in glomeruli (sclerosis, narrowing of capillary lumens, mesangial fibrillary changes, thickening of capillary walls, thrombosis, congestion, segmental solidification, and crescent formation), arteries (medial thickening, intimal thickening, thrombosis, necrosis, intimal lipid, and reduplication of internal elastic membrane), arterioles (thrombosis, necrosis, hyperplastic thickening, and luminal narrowing), interstitium (fibrosis and acute or chronic inflammatory

cells infiltration), medullary vessels (congestion and leukocyte accumulation in vasa recta), and tubules (necrosis, casts, or atrophy).¹²⁻¹⁴ Each item was scored from zero to 3 based on the severity of involvement and total final renal score was calculated from zero to 78. Then, the total and individual scores were presented as the percentage of involvement.

Follow-up records were completed by sending an invitation letter or making a phone call, as some of the patients who lived in remote cities would be regularly visited by local physicians. All survived children were asked to return to the hospital to have their blood pressure measured and to undertake laboratory studies including blood test, urinalysis, and 24-hour urine collection for measuring serum creatinine and urine protein, creatinine and volume. Glomerular filtration rate (GFR) was calculated as follows:

$$\text{GFR (mL/min/1.73 m}^2\text{)} = (\text{urine creatinine} \times \text{urine volume}) / \text{plasma creatinine}$$

The final outcome was defined as death or CKD stage 3 or higher (glomerular filtration rate less than 59 mL/min/1.73 m² lasting more than 3 months) with or without hypertension, proteinuria, or hematuria. A blood pressure higher than 95 percentile for age and height was defined as hypertension. The detection of more than 500 mg protein in a 24-hour aliquot was defined as moderate-to-severe proteinuria, and the hematuria was the presence of more than 10 erythrocytes per high-power field in 3 fresh urine samples.

The SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA) was used for statistical analyses. Using 2 × 2 tables, risk ratios (RRs) and 95% confidence interval (CI) were calculated. The receiver operating characteristic curve area was used to determine the correlation between long-term outcome and renal pathology score and the validity of it. *P* values less than .05 were considered significant.

RESULTS

A total of 29 children (8 girls and 21 boys) were included. The parents of 10 children (34.5%) were consanguine. The history of death of a sibling was reported in 5 cases (17.2%). Nineteen children (65.5%) had hypertension at the time of admission. Three patients had a history of exchange transfusion during neonatal periods secondary

to severe hyperbilirubinemia. Kidney biopsy had been performed at least 2 weeks after presentation; however, some of the children had been followed up since infancy as idiopathic thrombocytopenic purpura in other centers.

Two patients had received plasmapheresis, 13 had received fresh frozen plasma, and 11 had received fresh frozen plasma with intravenous immunoglobulin. The remaining children underwent dialysis. Antihypertensives, including loop diuretics, were administered to 22 children during the course of therapy. All of the patients were under regular follow-up, but those who lived in remote cities were visited by local pediatricians who reported laboratory tests results and clinical conditions of the patients by phone to our department.

The last follow-up visits were conducted an average of 3.7 years after disease onset (range, 0.03 to 12.5 years). Seven patients (24.1%), who were on hemodialysis or continuous ambulatory peritoneal dialysis, died of malignant hypertension, pulmonary edema, and congestive heart failure. One of the 3 deaths occurred in the first 3 months of diagnosis. All deaths occurred in those who received fresh frozen plasma. Twenty-two children (75.9%) were still alive, 3 of whom returned to their hometowns. Those who were hypertensive at the time of admission developed CKD on follow-up (RR, 3.7; 95% CI, 1.6 to 8.7; $P < .001$). Mortality did not correlate with gender ($P = .60$), hypertension ($P = .09$), administration of fresh frozen plasma ($P = .70$), or administration of antihypertensives ($P = .51$).

In all, 7 patients (24.1%) had normal kidney function and blood pressure, 18 (62.1%) had proteinuria (3 with hypertension and 3 with isolated proteinuria), 1 (3.4%) had persistent hematuria, and 12 (41.4%) suffered from CKD concomitant with hypertension and proteinuria. The most glomerular involvements were reduction in the capillary lumen, thickening of the capillary wall, mesangial cell proliferation, and fibrillary changes (Figure 1). All the abovementioned findings were according to glomerular thrombosis microangiopathy. Regarding arteriolar lesions, reduction in the diameter of arteriolar lumen and hyperplastic thickening of arteriolar wall were the most common findings, whereas arterial lesion manifested mostly by intimal and medial thickening

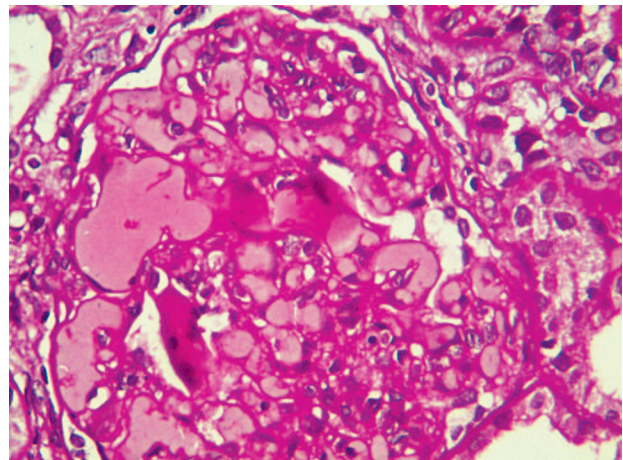


Figure 1. Chronic kidney disease in a child with atypical hemolytic uremic syndrome. Some glomerular capillary lumens contain fibrin thrombi, a few are closed as a result of thickening of capillary walls, and some are ectatic because of mesangiolysis (periodic acid shift, $\times 400$).

(Figure 2). The patients with arteriolar lesion were 3.67 more likely to develop chronic CKD (95% CI, 1.63 to 8.2; $P = .003$). Table 1 illustrates the mean pathological scores among HUS patients with different outcomes. Those who did not survive had significantly higher final pathological scores. This observation was true for the cases with CKD, too.

Pathological scores were expressed as the percentage and receiver operating characteristic curve area was used to evaluate its validity for prediction of CKD (Table 2 and Figure 3). Vascular score and final score had significant correlations with CKD. The patients with vascular lesion scores higher than 0.14 were at a higher risk of developing CKD (RR, 2.82; 95% CI, 1.11 to 7.16;

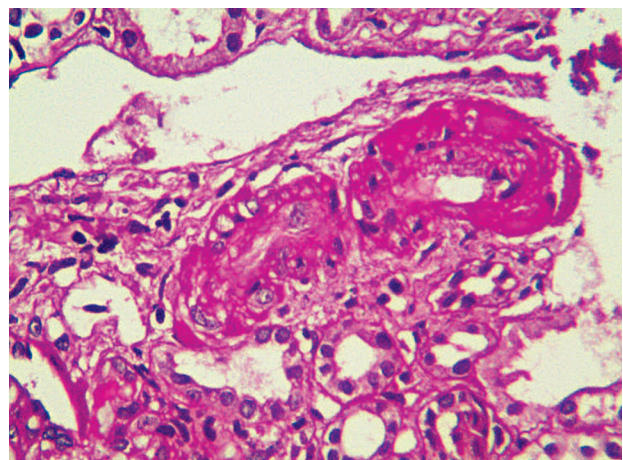


Figure 2. Arteriolar fibrinoid necrosis in a patient with atypical hemolytic uremic syndrome (periodic acid shift, $\times 400$).

Table 1. Severity of Renal Involvement by Final Outcome in Children With Atypical Hemolytic Uremic Syndrome*

Pathology	Kidney Disease (n = 12)		Hypertension (n = 16)		Proteinuria (n = 18)		Hematuria (n = 13)		Death (n = 7)	
	Score	P	Score	P	Score	P	Score	P	Score	P
Glomerular	12.33 ± 3.31	.11	12.18 ± 3.52	.16	11.36 ± 3.36	.73	11.38 ± 3.20	.91	12.70 ± 3.49	.17
Arteriolar	5.33 ± 2.70	.003	4.56 ± 2.80	.005	3.68 ± 3.00	.69	4.46 ± 3.23	.10	6.00 ± 3.26	.004
Arterial	4.50 ± 4.00	.04	4.00 ± 3.74	.01	2.78 ± 3.00	.70	4.30 ± 4.00	.04	5.70 ± 4.68	.08
Interstitial	1.75 ± 1.40	.98	1.80 ± 1.50	.99	2.05 ± 1.58	.20	1.76 ± 1.48	.44	2.40 ± 1.27	.16
Medullary vessels	1.25 ± 1.00	.63	1.25 ± 1.12	.40	1.10 ± 1.14	.99	1.30 ± 0.85	.01	1.70 ± 1.38	.21
Tubular	2.66 ± 1.15	.46	2.60 ± 1.14	.54	2.60 ± 1.16	.46	2.46 ± 1.12	.73	3.28 ± 0.75	.02
Final	29.33 ± 9.00	.005	27.56 ± 9.45	.01	24.63 ± 8.50	.65	25.90 ± 9.78	.28	34.57 ± 7.41	< .001

*P values are related to comparisons of the mean score of that group with the mean score of the remaining patients.

Table 2. Validity of Renal Pathology Scoring System in Predicting Chronic Kidney Disease in Patients With Atypical Hemolytic Uremic Syndrome*

Score Cutoffs	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC	P
Final > 0.20	84.2 (60.4 to 96.4)	71.4 (29.3 to 95.5)	63	89	0.85	.007
Vascular > 0.14	84.2 (60.4 to 96.4)	85.7 (42.2 to 97.6)	67	94	0.83	.009
Arteriolar > 0.17	68.4 (43.5 to 87.3)	85.7 (42.2 to 97.6)	50	93	0.80	.02
Arterial > 0.06	73.7 (48.8 to 90.8)	71.4 (29.3 to 95.5)	50	88	0.79	.02
Glomerular > 0.33	57.9 (33.5 to 79.7)	85.7 (42.2 to 97.6)	43	92	0.80	.02
Interstitial > 0.05	52.6 (28.9 to 75.5)	85.7 (42.2 to 97.6)	40	91	0.67	.18
Tubular > 0.33	57.9 (33.5 to 79.7)	57.1 (18.8 to 89.6)	33	77	0.62	.33

*Values in parentheses are 95% confidence intervals. PPV indicates positive predictive value; NPV, negative predictive value; and AUC, area under the curve.

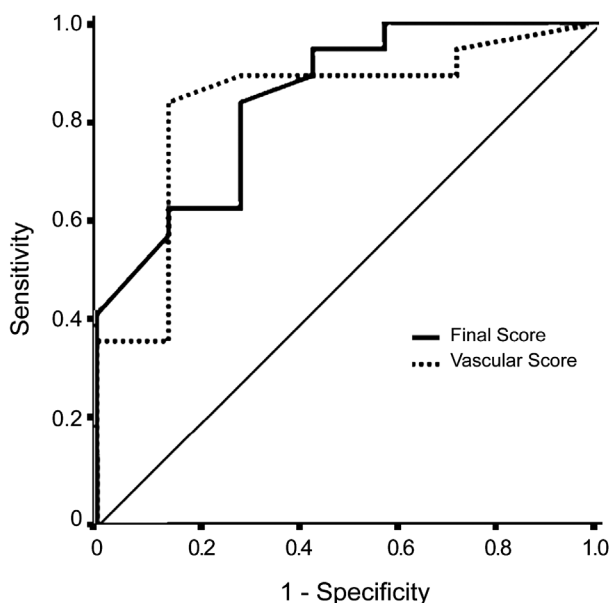


Figure 3. Receiver operating characteristic curve for renal pathology scoring as a predictor of developing chronic kidney disease.

$P = .001$); however, the RR reduced for developing persistent hypertension (RR, 0.15; 95% CI, 0.04 to 0.56; $P = .001$). When the final score was higher than 0.2, the RR was 0.45 (95% CI, 0.28 to 0.71;

$P = .02$) for the need for dialysis, 2.55 (95% CI, 0.8 to 8.0; $P = .01$) for developing CKD, and 0.68 (95% CI, 0.5 to 0.9; $P = .11$) for mortality.

DISCUSSION

Young age, Shiga-toxin-induced HUS, leukocytosis, and involvement of extrarenal organs have been suggested as the prognostic factors of outcomes in children with HUS.^{8-10,15} There are a few studies about the relation between renal pathological findings and long-term prognosis in these patients (Table 3). Habib and colleagues classified HUS renal pathology to glomerular, arteriolar, and cortical necrosis and showed that arteriolar involvement was predominantly seen in diarrhea-negative HUS.¹⁶ This pathology was more associated with the occurrence of severe hypertension, CKD, and worse prognosis.¹⁶ When autopsy was performed in the acute phase of the typical HUS, arterial or glomerular thrombosis were rather involved.¹⁷ On the other hand, those with glomerular sclerosis developed renal insufficiency or proteinuria.^{11,12}

According to the time of performing kidney biopsy, atypical HUS has been divided into early glomerular thrombotic microangiopathy, in which

kidney biopsy is performed in less than 2 months of initial presentation, and late ischemic thrombotic microangiopathy.^{5,11} The latter pathologic feature is associated with a significant percentage of the patients developing CKD or dying.^{5,11,18} In contrast, we observed that patients with atypical HUS had similar scores of glomerular and the arteriolar involvement that were 0.33 ± 0.11 versus 0.29 ± 0.23 , respectively.

Despite hemodialysis or peritoneal dialysis, 24% of our patients died due to a sudden increase in blood pressure, consequent heart failure, and pulmonary edema. This finding suggests the importance of tight control of blood pressure in this group. The etiology of hypertension in acute phase of HUS is not clear, but it has no correlation with urinary kallikrein excretion or plasma renin activity.^{19,20} Urinary endothelin excretion is high in hypertensive patients. Thus, increased endothelin production from renal endothelial cells may have a significant role in producing high blood pressure.²¹

None of the available studies have focused on the correlation between the severity of kidney involvement and prediction of long-term renal outcome. It is not possible to determine the etiology of atypical HUS based on pathological findings, yet. However, for the first time, we tried to predict the prognosis of HUS by using the score of the severity of renal involvement in biopsies. The present study indicated that the probability of kidney disease among the patients with a vascular score of more than 0.14 was 5 times as high as those with a lower score, although the confidence interval was wide due to the small number of specimens. Considering the score before simplification, the probability of development into severe CKD was 3.5 times higher in the presence of arteriolar and arterial thrombosis. Also, the presence of thrombosis and the thickening of media and intima layers of arterial vessels were associated with higher mortality rates. All the patients who died had hypertension and some degrees of kidney failure.

Many of the patients in our cohort had been diagnosed with or were under observation for anemia or idiopathic thrombocytopenia for a couple of years before the diagnosis of HUS made.^{22,23} Since the onset of atypical HUS was not quite clear, we used the severity of renal involvement rather than the time of performing biopsy in order to predict the prognosis. Nevertheless, a prospective study

with a larger number of patients is needed to identify the real value of each pathological index and their correlation with the outcome.

CONCLUSIONS

The severity of renal pathological involvement, especially the degree of vascular damage measured by using the scoring system, has a good prognostic value for the long-term outcome of patients with atypical HUS

CONFLICT OF INTEREST

None declared.

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