Renal Pathology and Long-term Outcome in Childhood SLE†

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Abstract

Renal histology is increasingly used as a guide for therapy and prognosis in SLE but data in children are few and/or short-term. We assessed renal histological features in 19 children with SLE to determine whether these features are useful in predicting long-term outcome. Mean age at biopsy was 10±1.7 years old, male to female ratio was 1:2.8. Fourteen patients (73%) had diffuse proliferative lupus nephritis. Renal histology was evaluated using an activity index (AI) and chronicity index (CI). Clinical assessment of renal function at biopsy and outcome were graded according to urinalysis and serum creatinine. Renal function at biopsy correlated well with AI ($p<0.001$) but not CI. At short-term follow-up (30 months), 3 patients had died from sepsis and another 2 reached end-stage renal disease. CI predicted poor clinical outcome, i.e. death or renal failure ($p<0.005$) but AI did not. At long-term follow-up (mean 92.1±26.8 months) only one more patient reached end-stage renal disease. In others renal function assessment showed improvement or were stable. Neither CI nor AI correlated with clinical outcome.

We conclude that although AI correlates well with renal function at biopsy and CI with short-term prognosis, neither can predict long-term outcome. Treatment may have altered the natural course of disease in these patients.

Renal biopsy has been widely used to assess the severity of lupus nephritis. However, controversy continues regarding the prognostic capability of the present WHO classification system[1-3]. Recently, activity and chronicity indices[4] were constructed and found to have prognostic value for identifying patients at risk of progressive renal failure[4-6].

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We assessed 2 renal histological features in 19 children with systemic lupus erythematosus (SLE) to determine whether these features are useful in predicting long-term outcome.

PATIENTS AND METHOD

All patients satisfied the criteria of the American Rheumatism Association for SLE[7] and had an adequate renal biopsy (more than 30 glomeruli). The renal biopsy specimens were studied by light, immunofluorescence, and electron microscopy. Renal tissue was examined by 2 independent and clinically-blind pathologists and reported as the sum of scores for individual active lesions; activity index (AI) and chronic, irreversible lesions; chronicity index (CI)[4]. Each feature was graded 0 to 3^+ (0 = absent, $1^+ < 25\%$, $2^+ = 25\text{-}75\%$, $3^+ > 75\%$) There was rarely a difference of greater than 1^+ for any feature among the observers. WHO classification was also determined[8]. Renal function of the patients was determined, according to urinalysis and serum creatinine, as described by Calermajer DS et al[9]. Grade 1 = normal renal function tests, normal or up to trace proteinuria; Grade 2 = 1^+ to 2^+ urine protein, hematuria, and a normal serum creatinine level; Grade 3 = 3^+ to 4^+ urine protein but not in the nephrotic range, and a normal serum creatinine; Grade 4 = severe, nephrotic range proteinuria (> 50 mg/kg/day) and/or abnormal serum creatinine (> 1.2 mg/dl) and/or BP of greater than 140/90 mmHg (> 95th percentile for age); Grade 5 = death from end-stage renal failure or dialysis/transplantation. Renal function grading (1 to 5) was recorded at the time of biopsy, 30 months after biopsy, and at last follow-up. Medication included oral prednisolone (2 mg/kg/d initially) with oral azathioprine (2-3 mg/kg/d) or intravenous pulse cyclophosphamide (0.5-1 g/M^2/dose monthly for 6 months then quarterly for another 2 years). Patients who died and/or reached end-stage renal disease were defined as having poor outcome.

Statistical analysis was correlation coefficient, Wilcoxon Rank Sum W Test and Receiver operating curve (ROC); $p < 0.05$ was considered significant.

RESULTS (Table 1)

From 1983 to 1988, 27 children with SLE were admitted to Siriraj Hospital. Renal biopsy was performed in 19, the other 8 patients had contraindications such as single kidney or bleeding tendency. Mean age at diagnosis was 10 ± 1.7 years old, male to female ratio was 1:2.8. Extra renal manifestations included arthritis (42%), CNS disturbances (26%), skin manifestations (53%), pleuritis and pericarditis (21%), autoimmune hemolytic anemia (32%).

Renal manifestations included edema (63%), nephrotic range proteinuria (37%), hypertension (BP > 95th percentile for age) (37%), acute renal failure (acute onset of renal function deterioration with serum creatinine > 2 mg/dl) (10%), abnormal serum creatinine (> 1.2 mg/dl) (32%). Renal pathology (WHO classifications) was diffuse proliferative glomerulonephritis in 73 per cent of patients. Renal function at biopsy correlated well with AI ($p < 0.001$) but not CI. At short-term follow-up (30 months), 3 patients had died from sepsis and another 2 had reached end-stage renal disease.

Table 1. Some demographic data results of the study.

mean age ± SD (yr)	10 ± 1.7		
male/female	1 : 2.8		
renal pathology			
- WHO class IV (%)	73		
- AI (mean ± SD)	6.42 ± 4.38 (range 1 - 15)		
- CI (mean ± SD)	2.32 ± 2.33 (range 0 - 8)		
Clinical renal function	at biopsy (n=19)	30 months (n = 16)[a]	long-term follow-up (n = 12)[b]
- grade III	15.7%	6.2%	16.7%
- grade IV	21.0%	6.2%	8.3%
- grade V	5.3%	12.5%	8.3%

note [a] : 3 patients died, 2 reached end-stage renal disease (excluding patients who were lost to follow-up)
[b] : 3 patients were lost to follow-up, 1 reached end-stage renal disease (excluding patients who were lost to follow-up)

Table 2. Statistical data of the study.

At biopsy	Correlation Coefficient
reanl function grading and AI	0.7318 (one - tailed $p < 0.001$)
renal function grading and CI	-0.0215 (NS)
At short-term follow-up	Mann-Whitney U-Wilcoxon Rank Sum W test (2 - tailed p)
Clinical outcome and AI	0.2212 (NS)
Clinical outcome and CI	0.0032
At longterm follow-up	
Clinical outcome and AI	0.5622 (NS)
Clinical outcome and CI	0.0934 (NS)

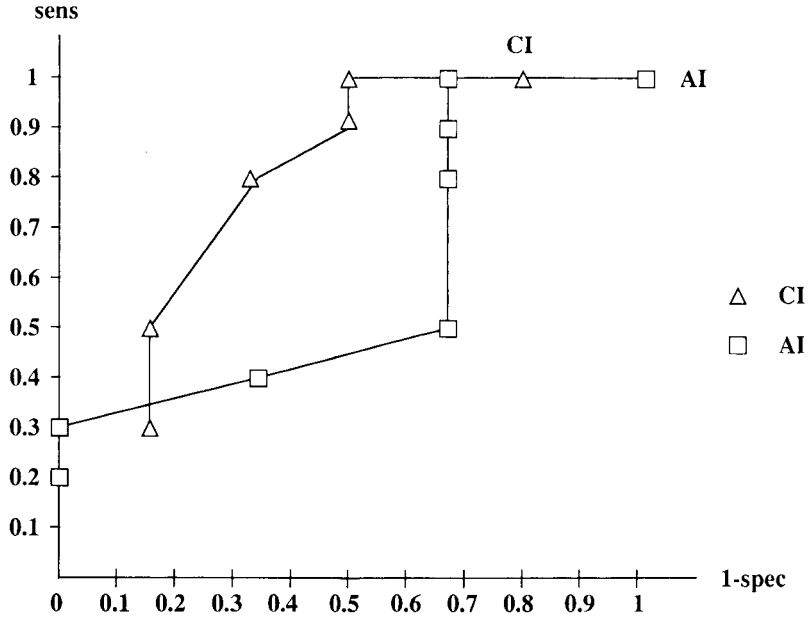

Fig. 1. Receiver operating curve showing AI and CI as indicators of longterm poor outcome.

CI predicted "poor" outcome ($p<0.005$) but AI did not. (Table 2) All the patients who died and/or had reached end-stage renal failure were in WHO class IV and most of them (80%) did so within 12 months after biopsy.

All patients received oral prednosolone (2 mg/kg/d initially) and most of them also received oral azathioprine according to the severety of the disease.

Four patients received at least 15 doses of pulse cyclophosphamide (0.5-1 g/M^2/dose), none of them had "poor" clinical outcome. At long-term follow-up (mean 92.1 ± 26.8 months) only one more patient (WHO IV) reached end-stage renal failure 64 months after biopsy. Neither CI nor AI correlated with the long-term clinical outcome (Table 2), although according to the ROC; CI ≥ 2 predicted poor outcome with the least false positive and false negative results. (Fig. 1) Moreover, AI may not be a reliable indicator of longterm poor outcome because of the "S shaped" ROC.

DISCUSSION

Although new drugs and treatment regimens have been introduced, the mortality rate in children with SLE is still high. Lehman TJA's

study in 23 SLE children less than 10 years old revealed a 26 per cent death rate due to sepsis (16%) and renal failure (10%), another 16 per cent of the patients required chronic dialysis[10]. In another study of 71 cases aged less than 18 years, 14 per cent died of active lupus and 22 per cent had chronic renal failure[11]. Recently in Thailand, Shayakul C in his study of 569 cases (mean age 28±10 yr, range 12 to 69 yr), the death rate was 15.6 per cent; mostly due to infection and 5 per cent reached end-stage renal disease[12]. These figures are comparable with this study in which 15.8 per cent died from sepsis and another 15.8 per cent reached end-stage renal disease.

As newer treatment modalities become available for patients with severe lupus nephritis, it becomes more important to identify patients at risk of poor outcome. Austin III HA studied 102 patients (adult and children) with SLE (mean follow-up period of 61 months) reported that those aged less than 23 years, CI, and treatment with prednisolone alone correlated with poor outcome[4]. Rush PJ studied 20 children with diffuse proliferative lupus nephritis (mean follow-up 48 months) and reported that CI predicted outcome but AI did not[6]. McCurdy's study in 71 children found that both the active lesions of fibrinoid necrosis, synechiae, tubular casts and vasculitic lesions and the chronic lesion of glomerular sclerosis correlated with progression to renal failure[11]. Our study also found that CI correlated with short term prognosis (30 months after biopsy) but neither CI nor AI predicted longterm outcome. Treatment may have altered the natural course in some of these patients, resulting in a better longterm outcome. Several studies have provided supportive evidence that intermittent pulse cyclophosphamide has a favorable therapeutic index in treatment of lupus nephritis[13,14].

The "S-shaped" result of the ROC in AI may have 2 explanations. Firstly, our group of patients is small and therefore may not distribute well. Secondly, the "poor-outcome" group may consist of more than one category of patients since the causes of death may vary and it is sometimes difficult to differentiate death from sepsis and active SLE.

We conclude that although AI correlates well with renal function at biopsy and CI with short-term prognosis, neither can predict long-term outcome. Treatment may have altered the natural course of disease in these patients.

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พยาธิสภาพที่ไตกับการพยากรณ์โรคในระยะยาวในผู้ป่วยเด็กโรค เอส แอล อี

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แพทย์มักใช้พยาธิสภาพที่ไตช่วยตัดสินใจในการรักษาและบอกถึงพยากรณ์โรคในผู้ป่วย เอส แอล อี แต่ข้อมูลในผู้ป่วยเด็กยังมีอยู่น้อย และ/หรือติดตามการดำเนินโรคเพียงระยะสั้น ผู้ทำการศึกษาจึงได้ศึกษาพยาธิสภาพที่ไตในผู้ป่วยเด็กโรค เอส แอล อี 19 ราย ว่าสามารถบ่งบอกถึงการพยากรณ์โรคระยะยาวได้หรือไม่ ผู้ป่วยมีอายุเฉลี่ยเมื่อทำการตรวจชิ้นเนื้อไต 10±1.7 ปี อัตราส่วนชายต่อหญิง = 1:2.8 พบว่า 14 ราย (ร้อยละ 73) มีพยาธิสภาพที่ไตเป็นแบบ difffuse proliferative glomerulonephritis (WHO IV) ประเมินพยาธิสภาพที่ไตโดยอาศัย activity index (AI) และ chronicity index (CI) และประเมินการทำงานของไตทางคลินิก โดยอาศัยค่าซีรั่มครีอะตินิน และการตรวจปัสสาวะ (urinalysis) พบว่าการทำงานของไตเมื่อตรวจชิ้นเนื้อไตมีความสัมพันธ์กับ AI ($p < 0.001$) แต่ไม่มีความสัมพันธ์กับ CI เมื่อติดตามผู้ป่วยไปนานเฉลี่ย 30 เดือน พบว่ามีผู้ป่วยเสียชีวิตจากภาวะติดเชื้อรุนแรงในกระแสโลหิต 3 ราย และ 2 รายมีไตวายเรื้อรังระยะสุดท้าย CI สามารถบอกถึงพยากรณ์โรคระยะสั้นที่ไม่ดี ($p < 0.005$) แต่ AI ไม่มีความสัมพันธ์กับการพยากรณ์โรคระยะสั้น เมื่อติดตามผู้ป่วยไปเป็นระยะเวลานาน (เฉลี่ย 92.1±26.8 เดือน) พบมีผู้ป่วยอีกเพียง 1 รายที่มีไตวายระยะสุดท้าย ส่วนผู้ป่วยรายอื่นๆ มีการทำงานของไตคงที่หรือดีขึ้น และพบว่าทั้ง CI และ AI ไม่มีความสัมพันธ์กับการพยากรณ์โรคระยะยาว

ผู้ทำการวิจัยสรุปว่า AI จะมีความสัมพันธ์กับการทำงานของไตเมื่อทำการตัดชิ้นเนื้อไต และ CI มีความสัมพันธ์กับการพยากรณ์โรคระยะสั้น แต่ทั้ง AI และ CI ไม่สามารถบอกถึงการพยากรณ์โรคระยะยาวในผู้ป่วย เชื่อว่า เนื่องจากผลของการรักษาได้เปลี่ยนแปลงการพยากรณ์โรคระยะยาวไป

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