Clinical Outcome of Children with Henoch-Schönlein Purpura Nephritis

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Objective: Evaluate the outcomes of pediatric patients with Henoch-Schönlein purpura nephritis and find the parameters correlated with outcomes of treatment.

Material and Method: Review of medical records was performed in twenty patients diagnosed with Henoch-Schönlein purpura nephritis. Demographic data, clinical parameters and records of treatment at diagnosis and the last visit were collected and analyzed.

Results: Median age at diagnosis was 8-year-old and median follow-up time was 39 months. All patients had urine protein to creatinine ratio (UPCR) of more than 1.0 g/g while ten patients had hypoalbuminemia. Renal pathology results were class I, II, and III in 2, 14, and 4 patients respectively. Prednisolone was prescribed in all patients and cyclophosphamide was given in 13 patients. All patients had first resolution of proteinuria at median time of six months (range 2-47 months). At the last visit, 13 patients (65%) had remission of proteinuria (remission group), while seven patients (35%) became proteinuric relapse (relapse group) with UPCR > 0.2 g/g. Interestingly, the remission group had median time to first resolution of proteinuria shorter than the relapse group (6 months and 19 months, p < 0.001). Moreover, estimated glomerular filtration rate at diagnosis correlated negatively with UPCR at the last visit (r = -0.773, p = 0.001).

Conclusion: Pediatric patients with Henoch-Schönlein purpura nephritis who presented with heavy proteinuria had favorable outcome after treatment. The patients who had early resolution of proteinuria remained in remission more than those who had late resolution.

Keywords: Henoch-Schönlein purpura, Outcome, Nephritis, Renal, Pediatric patients

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Henoch-Schönlein purpura (HSP) is a childhood vasculitis, characterized by inflammation of small vessel. Clinical presentations are palpable cutaneous purpura, arthritis, gastrointestinal involvement such as bleeding or abdominal pain and nephritis(1). Almost 40 to 50% of the patients develop Henoch-Schönlein purpura nephritis (HSPN) within 1 to 6 months(2,3). Recent data showed that galactose-deficient IgA1 is likely to have a role in the formation of nephritogenic immune complexes(2). Various medications were reported to manage these patients including corticosteroïd, cyclophosphamide, cyclosporine, azathioprine, and mizoribine. However, prednisolone is still the most common drug used to treat these patients despite the lack of evidence that steroid alone has any benefit(4,5). In Thailand, approximately 39-46% of children with HSP develop nephritis(3,5). Some of the patients have heavy proteinuria defined as urine protein to creatinine ratio > 1 g/g(6). In Department of Pediatrics, Ramathibodi Hospital, the authors selected cyclophosphamide in addition to prednisolone for treatment in children with HSPN because they are widely available in Thailand and these drugs are in the national essential medicine list. Thus, the present study aimed to evaluate the outcomes of patients with HSPN who presented with heavy proteinuria and to find the parameters correlated with outcomes of treatment.

Material and Method

The present study was approved by the ethic committee on human research at Faculty of Medicine.
Ramathibodi Hospital (ID 01-53-34). Review of medical records was performed in children who have been diagnosed with Henoch-Schönlein purpura according to the diagnostic criteria of the American College of Rheumatology 1990(7) at Pediatric Department, Ramathibodi Hospital between 1998 and 2010. The patients with urine protein to creatinine ratio (UPCR) of more than 1.0 g/g were identified and underwent renal biopsies. The renal biopsies were examined and reviewed by experienced renal histopathologists. Histological findings were classified according to the ISKDC classification. The authors collected demographic data, clinical parameters, and records of treatment with prednisolone and immunosuppressive drugs including oral or intravenous cyclophosphamide. Prednisolone and enalapril dosages were also adjusted according to the degree of proteinuria during follow-up visit and then tapered off if the proteinuria became absent. Time to first resolution of proteinuria is a period of time from diagnosis to the first visit with absence of proteinuria (UPCR < 0.2 g/g).

Results

Demographic data

Twenty patients (8 male and 12 female) were included in the present study. Median age at diagnosis was 8-year-old (range 5-13 years). Clinical parameters of the patients at diagnosis and the last visit are presented in Table 1. Renal biopsies were performed at median time of 1 month (0.5-8 months) after the onset of disease. The renal pathology results were class I, II, and III in 2, 14, and 4 patients respectively. Four patients had 7, 10, 10, and 16% of glomerular crescents. Three patients had segmental sclerosis of 5%, 11%, and 33% and one out of these three patients had 5% global sclerosis.

Treatment

All patients were treated with prednisolone 2 mg/kg/day and then tapered off according to degree of proteinuria during follow-up visit. Median time of prednisolone treatment was eight months (range 3-39 months). Twelve patients also received oral cyclophosphamide 2 mg/kg/day (maximum 100 mg/day) for three months while one patient also received monthly intravenous cyclophosphamide for six cycles (average dosage was 0.5 mg/kg/day). Fifteen patients received enalapril and subsequently stopped taking in eight patients. Median dosage of enalapril was 0.15 mg/kg/day.

Follow-up data

Median follow-up time was 39 months. All patients had first resolution of proteinuria at median time of 6 months (range 2 to 47 months). Thereafter, thirteen patients still had no proteinuria until the last visit (remission group) while seven patients became proteinuric relapse (relapse group) without hematuria. Clinical parameters of the relapse group and remission

Table 1. Clinical parameters of 20 patients at diagnosis and the last visit

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Diagnosis median (range)</th>
<th>Last visit median (range)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td>mmHg</td>
<td>120 (100 -140)</td>
<td>110 (84-130)</td>
<td>0.008</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>mmHg</td>
<td>75 (58-90)</td>
<td>58 (52-80)</td>
<td>0.001</td>
</tr>
<tr>
<td>UPCR</td>
<td>g/g</td>
<td>4.9 (1.1-13.5)</td>
<td>0.17 (0.1-1.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/L</td>
<td>27 (12-47)</td>
<td>39 (36-52)</td>
<td>0.002</td>
</tr>
<tr>
<td>Serum Cr</td>
<td>mg/dL</td>
<td>0.5 (0.4-1.2)</td>
<td>0.60 (0.4-0.8)</td>
<td>0.200</td>
</tr>
<tr>
<td>eGFR</td>
<td>ml/min/1.73m²</td>
<td>132 (56-177)</td>
<td>148 (111-210)</td>
<td>0.210</td>
</tr>
</tbody>
</table>

* p-value: Wilcoxon-signed ranked test
BP = blood pressure; UPCR = urine protein to creatinine ratio; Cr = creatinine; eGFR = estimated glomerular filtration rate
group are presented in Table 2. Kaplan-Meier plot of time to achieve first resolution of proteinuria of both groups is presented in Fig. 1. Correlation between parameters at diagnosis and the last visit was analyzed. Interestingly, estimated glomerular filtration rate at diagnosis correlated negatively with UPCR at the last visit ($r = -0.773$, $p = 0.001$).

### Discussion
There is no consensus guideline on the management of patients with HSPN who present with heavy proteinuria or nephritic syndrome. Corticosteroid therapy and immunosuppressive drugs including cyclophosphamide, azathioprine, mizoribine, and cyclosporine were prescribed in these patients$^{4,8-11}$. In Department of Pediatrics, Ramathibodi Hospital, the authors usually treat with prednisolone and/or

### Table 2. Clinical parameters and treatment of patients in relapse and remission group

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Relapse group (n = 7) median (range)</th>
<th>Remission group (n = 13) median (range)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At the diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td>9 (6-13)</td>
<td>8 (5-13)</td>
<td>0.231</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>mmHg</td>
<td>116 (100-140)</td>
<td>120 (116-126)</td>
<td>0.213</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>mmHg</td>
<td>70 (60-90)</td>
<td>75 (58-84)</td>
<td>0.632</td>
</tr>
<tr>
<td>UPCR</td>
<td>g/g</td>
<td>6 (1.1-7.3)</td>
<td>4.6 (1.3-13.5)</td>
<td>0.556</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/L</td>
<td>30 (24-37)</td>
<td>26 (12-47)</td>
<td>0.390</td>
</tr>
<tr>
<td>Serum Cr</td>
<td>mg/dL</td>
<td>0.60 (0.5-1.2)</td>
<td>0.5 (0.4-0.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>eGFR</td>
<td>ml/min/1.73m²</td>
<td>127 (56-148)</td>
<td>143 (94-177)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Treatment and clinical course</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of prednisolone</td>
<td>months</td>
<td>22 (7-39)</td>
<td>7 (3-13)</td>
<td>0.003</td>
</tr>
<tr>
<td>Treatment with CY</td>
<td>(%)</td>
<td>7/0 (100%)</td>
<td>6/7 (46%)</td>
<td>0.044**</td>
</tr>
<tr>
<td>Treatment with enalapril</td>
<td>(%)</td>
<td>7/0 (100%)</td>
<td>8/5 (61%)</td>
<td>0.11**</td>
</tr>
<tr>
<td>Time to first resolution of proteinuria</td>
<td>months</td>
<td>19 (9-47)</td>
<td>6 (2-12)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>At the last visit</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>mmHg</td>
<td>119 (106-130)</td>
<td>97 (84-114)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>mmHg</td>
<td>59 (54-80)</td>
<td>57 (52-60)</td>
<td>0.22</td>
</tr>
<tr>
<td>UPCR</td>
<td>g/g</td>
<td>0.46 (0.2-1.7)</td>
<td>0.1 (0.1-0.19)</td>
<td>0.001</td>
</tr>
<tr>
<td>Albumin</td>
<td>g/L</td>
<td>39 (36-45)</td>
<td>38 (37-52)</td>
<td>0.63</td>
</tr>
<tr>
<td>Serum Cr</td>
<td>mg/dL</td>
<td>0.60 (0.4-0.7)</td>
<td>0.6 (0.4-0.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>eGFR</td>
<td>ml/min/1.73m²</td>
<td>144 (115-210)</td>
<td>149 (111-204)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

* p-value: Mann-Whitney U test
** p-value: Fisher exact test
BP = blood pressure; UPCR = urine protein to creatinine ratio; Cr = creatinine; eGFR = estimated glomerular filtration rate; CY = cyclophosphamide
immunosuppressive drugs. Although the result of renal biopsy in the present study showed less than 25% of crescents in all patients but all of them had UPCR of more than 1.0 g/g and half of the patients had hypoalbuminemia (serum albumin < 25 g/L) which should be treated with immunosuppressive drugs.

After median follow-up time of 39 months, overall renal outcomes of the patients were favorable. Serum creatinine had a trend of increase along with their growth but eGFR did not change. Fortunately, at the last visit, there was no patient with eGFR less than 100 ml/min/1.73 m² but seven patients (35%) still had proteinuria without hematuria. Therefore, percentage of patients with remission in the present study was 65% comparing with 37%, 46%, 77%, and up to 79% in the study of Shennoy, Xia, Mir, and Park, respectively(9,10,12,13). Although most of the renal histopathologic results of patients in those studies were class II and III, high variation in the outcomes was observed. Among these reports, Park et al showed very good outcome after treatment with first course cyclosporine A in 23 of 29 patients after median follow-up time of 3.7 years. A recent study of Fujinaga et al(9) also reported 23 pediatric patients with HSPN who had UPCR more than 1.0 g/g, showed that 15 patients (65%) were still in remission after median follow-up time of 6 years while 8 patients experienced relapses of the disease. They concluded that HSPN is not uniphasic disease that require long-term follow-up even though the patients did not have nephritic syndrome at the onset.

Seven patients in the present study who had relapse were treated by re-induction of prednisolone for three to six months and increase the dosage of enalapril. Thereafter, reduction of UPCR was shown for three to six months and increase the dosage of enalapril. Thereafter, reduction of UPCR was shown for three to six months and increase the dosage of enalapril. The remission group might not be in true remission because follow-up renal biopsy did not show correlation with the outcome but eGFR at diagnosis showed negative correlation with UPCR at the last visit (r = -0.773, p = 0.001). This finding reflected that the lower the eGFR was at diagnosis, the higher the UPCR was at the last visit.

The authors recommend that pediatric patients with HSPN should be followed by a pediatric nephrologist until adulthood because some patients might experience relapse after remission. Biopsy should be performed in every case of HSPN who had UPCR > 1.0 g/g or renal impairment or severe nephritis. Prednisolone and anti-proteinuric drug (angiotensin converting enzyme inhibitor) should be introduced to the regimen while co-administration with cyclophosphamide or other immunosuppressive drugs are controversial.

The present study could not demonstrate any patients who progressed to CKD stage 5 with this short period of follow-up time. The remission group might not be in true remission because follow-up renal biopsy was not performed. A study that has larger and longer follow-up time is needed to predict the renal outcome of these patients.

**Conclusion**

At 3-year follow-up, patients with HSPN presented with heavy proteinuria had favorable outcome after treatment. The patients who had early resolution of proteinuria remained in remission more than those who had late resolution.
Acknowledgement
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Potential conflicts of interest
None.

References
การศึกษาผลลัพธ์ทางคลินิกของผู้ป่วยเด็กโรค Henoch Schönlein purpura ที่มีการอักเสบของไต

ช่วยข้อ ใจรัมหาย, กรานุษ, คุณราช, พิทักษ์, เทศ, ณัฐนันธ์, วิวัฒ, ประภพ

วัตถุประสงค์: เพื่อศึกษาผลลัพธ์ทางคลินิกของผู้ป่วยเด็กโรค Henoch Schönlein purpura ที่มีการอักเสบของไต และทางจิต
ที่มีผลต่อผลการรักษาของผู้ป่วย

วัสดุและวิธีการ: เก็บข้อมูลย้อนหลังผู้ป่วยโดยการสอบสวนประวัติของผู้ป่วยจำนวน 20 ราย ที่ได้รับการวินิจฉัยว่าเป็น Henoch Schönlein purpura ที่มีการอักเสบของไต โดยรวบรวมข้อมูลการรักษาและผลการตรวจ

ผลการศึกษา: ค่ามัธยฐานของอายุผู้ป่วยที่ได้รับการวินิจฉัยเท่ากับ 8 ปี และค่ามัธยฐานของระยะเวลาการติดตามวันเท่ากับ 39 เดือน ผู้ป่วยทุกรายมีค่าโปรตีนที่ปัสสาวะเทียบกับคริแอทินน์ในปัสสาวะมากกว่า 1 กรัม/กรัม และการเปรียบเทียบของผู้ป่วยที่เติบโตเนื้อเป็นเด็ก ผลการตรวจพบว่าเป็นระดับหนึ่ง 2 ราย ระดับสอง 14 ราย และระดับสาม 4 ราย ผู้ป่วยทุกรายได้รับการรักษาด้วยยาเพรดนิโซโลน และ 13 ราย ได้รับยาไซโคฟิสฟาไมด์ร่วมด้วย ผู้ป่วยทุกรายมีการลดลงของโปรตีนในปัสสาวะจนเป็นปกติใน Idealkubler และการตรวจพบว่า มีผู้ป่วยโรคอัตราวัน 13 ราย (ร้อยละ 65) คือมีเปรียบเทียบกับในกลุ่มปกติ แต่มีผู้ป่วยโรคอัตราวัน 7 ราย (ร้อยละ 35) คือคงมีเปรียบเทียบกับในกลุ่มปกติ (โปรตีนในปัสสาวะเทียบกับคริแอทินน์ในปัสสาวะมากกว่า 0.2 กรัม/กรัม) ผู้ป่วยกลุ่มที่โรคสงบมีการลดลงของ

ผลการตรวจพบว่าผู้ป่วยในกลุ่มปกติมีการเปลี่ยนแปลงทางสถิติที่มีความสำคัญทางสถิติ (6 เดือน และ 19 เดือน, p < 0.001)

สรุป: ผู้ป่วยเด็กโรค Henoch Schönlein purpura ที่มีการอักเสบของไตมีผลลัพธ์ที่ดีเมื่อการรักษา ผู้ป่วยกลุ่มที่มีการลดลง
ของโปรตีนในปัสสาวะจนเป็นปกติเร็วกว่าจะมีการลดลงของโรคมากกว่ากลุ่มที่มีการลดลงของโปรตีนในปัสสาวะจนอยู่ในเกณฑ์

ปัจจัยเร่งเพิ่ม