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 corticosteroid, 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[1,4]. 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.

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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). Outcome of patients including blood pressure (BP), serum albumin, serum creatinine, estimated glomerular filtration rate (eGFR), and UPCR at the last visit were also collected and analyzed. At the last visit, the relapse group was defined as a group of patients who had relapse of proteinuria (UPCR ≥ 0.2 g/g) after the first resolution of proteinuria while the remission group was defined as a group of patients who had no proteinuria (UPCR < 0.2 g/g) until the last visit.

Statistical analysis was performed by institutional licensed SPSS version 17.0. The clinical parameters were expressed as median and range. Comparison was performed by Wilcoxon-signed ranked test to evaluate parameter at diagnosis and the last visit. P-value of less than 0.05 is considered as statistical significance.

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

Parameters	Units	Diagnosis median (range)	Last visit median (range)	p-value*
Systolic BP	mmHg	120 (100 -140)	110 (84-130)	0.008
Diastolic BP	mmHg	75 (58-90)	58 (52-80)	0.001
UPCR	g/g	4.9 (1.1-13.5)	0.17 (0.1-1.7)	0.001
Albumin	g/L	27 (12-47)	39 (36-52)	0.002
Serum Cr	mg/dL	0.5 (0.4-1.2)	0.60 (0.4-0.8)	0.200
eGFR	ml/min/1.73m^2	132 (56-177)	148 (111- 210)	0.210

* 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).

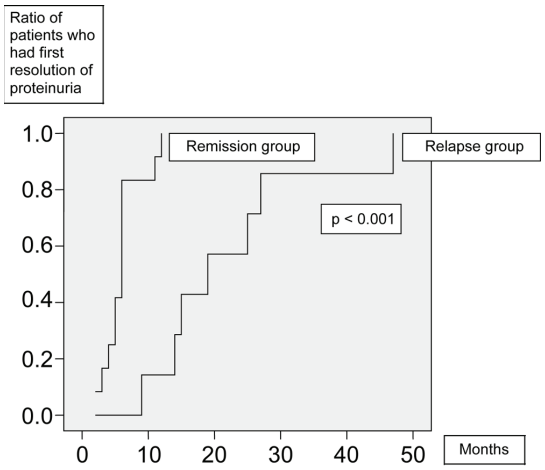

Fig. 1 Kaplan-Meier plot of time to achieve first resolution of proteinuria of both groups

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

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

* 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 m^2 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[6] 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 in all patients although some degrees of proteinuria were still detected at the last visit (median UPCR = 0.46 g/g). Comparing between groups of patients who still had proteinuria at the last visit (relapse group) and who did not (remission group), the relapse group had slightly higher serum creatinine at diagnosis than the remission group had, but eGFR, UPCR, serum albumin levels between both groups were not statistically different. Two of seven patients in the relapse group had poor renal histopathologic result at diagnosis. One patient had 5% segmental sclerosis, 5% global sclerosis and 16% crescent while the other patient had 33% segmental sclerosis. Interestingly, time to first resolution of proteinuria in the remission group was significantly shorter than in the relapse group ($p < 0.001$). This finding was concordant with the study of Park et al that reported excellent renal outcome in their patients with time to resolution of proteinuria less than 3 months[9]. On the other hand, Wakiki et al reported almost 50% of the patients who have nephrotic state lasting more than 3 months progressed to end state renal disease after median follow-up of 6 years[14]. However, decrease of proteinuria might be contributed by the effect of enalapril but the authors cannot define how much the effect is. At the last visit, the relapse group had not only greater proteinuria but also higher in systolic blood pressure than the relapse-free group had. These two parameters are well-recognized factors that determine the renal outcome in any glomerular diseases.

Previous studies found the parameters that correlated with the renal outcome in pediatric patients with HSPN included severity of clinical presentation, initial finding on renal biopsy, nephrotic stage lasting for more than 3 months and mean proteinuria during follow-up[14-16]. In the present study, severity on 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.

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Potential conflicts of interest

None.

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การศึกษาผลลัพธ์ทางคลินิกของผู้ป่วยเด็กโรค Henoch Schönlein purpura ที่มีการอักเสบของไต

ขวัญชัย ไพโรจน์สกุล, กาญจนา ตั้งนรารัชชกิจ, พนัส เฉลิมแสนยากร, วิวัฒน์ ตปนียโอฬาร

วัตถุประสงค์: เพื่อศึกษาผลลัพธ์ทางคลินิกของผู้ป่วยเด็กโรค Henoch Schönlein purpura ที่มีการอักเสบของไต และหาปัจจัยที่มีผลต่อผลการรักษาของผู้ป่วย

วัสดุและวิธีการ: เก็บข้อมูลย้อนหลังผู้ป่วยโดยการทบทวนเวชระเบียนของผู้ป่วยจำนวน 20 ราย ที่ได้รับการวินิจฉัยว่าเป็น Henoch Schönlein purpura ที่มีการอักเสบของไต โดยรวบรวมข้อมูลการรักษาและนำมาวิเคราะห์

ผลการศึกษา: ค่ามัธยฐานของอายุผู้ป่วยที่ได้รับการวินิจฉัยเท่ากับ 8 ปีและค่ามัธยฐานของระยะเวลาการติดตามรักษาเท่ากับ 39 เดือน ผู้ป่วยทุกรายมีค่าโปรตีนในปัสสาวะเทียบกับคริแอทินินในปัสสาวะมากกว่า 1 กรัม/กรัม และครึ่งหนึ่งของผู้ป่วยมีค่าแอลบูมินในเลือดต่ำ ผลการตรวจชิ้นเนื้อไตพบว่าเป็นระดับหนึ่ง 2 ราย ระดับสอง 14 ราย และระดับสาม 4 ราย ผู้ป่วยทุกรายได้รับการรักษาด้วยยาเพรดนิโซโลน และ 13 ราย ได้รับยาไซโคลฟอสฟาไมด์ร่วมด้วย ผู้ป่วยทุกรายมีการลดลงของโปรตีนในปัสสาวะจนเป็นปกติครั้งแรกที่ค่ามัธยฐานของเวลา 8 เดือนหลังการวินิจฉัย ณ การติดตามการรักษาครั้งสุดท้ายพบว่า มีผู้ป่วยโรคสงบ 13 ราย (ร้อยละ 65) คือมีโปรตีนในปัสสาวะอยู่ในเกณฑ์ปกติ แต่มีผู้ป่วยโรคกำเริบ 7 ราย (ร้อยละ 35) คือยังคงมีโปรตีนในปัสสาวะมากกว่าปกติ (โปรตีนในปัสสาวะเทียบกับคริแอทินินในปัสสาวะมากกว่า 0.2 กรัม/กรัม) ผู้ป่วยกลุ่มที่โรคสงบมีการลดลงของโปรตีนในปัสสาวะจนอยู่ในเกณฑ์ปกติครั้งแรกเร็วกว่ากลุ่มโรคกำเริบอย่างมีนัยสำคัญทางสถิติ (6 เดือน และ 19 เดือน, $p < 0.001$) นอกจากนั้นค่าอัตราการกรองของไตเมื่อแรกวินิจฉัยสัมพันธ์เชิงลบกับค่าโปรตีนในปัสสาวะเทียบกับคริแอทินินในปัสสาวะที่การรักษาครั้งสุดท้ายอย่างมีนัยสำคัญทางสถิติ ($r = -0.773$, $p = 0.001$)

สรุป: ผู้ป่วยเด็กโรค Henoch Schönlein purpura ที่มีการอักเสบของไตมีผลลัพธ์ที่ดีหลังการรักษา ผู้ป่วยกลุ่มที่มีการลดลงของโปรตีนในปัสสาวะจนเป็นปกติครั้งแรกเร็วจะมีการสงบของโรคมากกว่ากลุ่มที่มีการลดลงของโปรตีนในปัสสาวะจนอยู่ในเกณฑ์ปกติครั้งแรกช้า