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Treatment of Severe Henoch-Schoenlein Purpura Nephritis in Children

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= Abstract =

The overall prognosis of Henoch-Schoenlein purpura (HSP) is favorable, but severe nephritis has a high risk of progression to end stage renal failure. Recent studies emphasize the importance of early treatment in children with severe HSP nephritis, but the treatment of severe HSP nephritis still remains controversial due to the rarity of randomized controlled studies in this field. Nevertheless, several intensive therapies, such as intravenous high-dose methylprednisolone pulse, immunosuppressive/cytotoxic drugs, fibrinolytic therapy, anticoagulants, antiplatelet agent and plasma exchange, have been used in children with severe HSP nephritis. In this review, we focus on the treatment of severe HSP nephritis in children. **(J Korean Soc Pediatr Nephrol 2010;14:10-21)**

Key Words : Henoch-Schoenlein purpura, Severe Henoch-Schoenlein purpura nephritis, Intensive therapy, Children

Introduction

Henoch-Schoenlein purpura (HSP) is the most common form of immune-mediated systemic vasculitis in children, which mainly affects the skin, joints, gastrointestinal tract and kidney [1]. The overall prognosis of HSP is favorable, but the long-term outcome is dependent on the degree of renal involvement [2-5]. The incidence of renal involvement varies from 20 to 100% [6-9]. Overall, an estimated 2% of children with HSP progress to renal failure and up to 20% of children with HSP nephritis (HSPN) treated in specialized centers require hemodialysis [6]. Mild HSPN generally does not require aggressive treatment due to a favorable course of the disease [5, 10]. However, long-term studies have shown that even mild renal symptoms at the onset of HSP could lead to an unfavorable prognosis after decades [3, 4]. Therefore, the patients with severe HSPN may require more aggressive therapies. Some authors suggested that treatment should be started early in the course of HSPN before glomerular crescents become fibrous [11].

Although evidence-based assessment of treatment options for children with IgA nephropathy has been studied [12, 13], there has been only one randomized controlled study in

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severe HSPN [14], and the treatment of severe HSPN still remains controversial.

In this review, we summarize the previous studies on the treatment of severe HSPN, although the efficacy of several drugs has mostly been shown in case series, and suggest a clinical approach to patients with severe HSPN.

Treatment of severe HSPN

1. Which patients belong to severe HSPN, should be biopsied, and should be treated intensively?

Severe HSPN generally includes nephrotic-range proteinuria (>40 mg/m^2/hr) or proteinuria >1 g/day, nephrotic syndrome, acute nephritic syndrome, and the classification of the International Study of Kidney Disease in Children (ISKDC) of more than grade IIIa (focal mesangial proliferation with <50% crescents) [4]. Therefore, blood pressure, urine output, 24 h urinary protein excretion, serum albumin, cholesterol, creatinine, creatinine clearance, and the presence of edema should be examined in patients with HSPN.

The indication of renal biopsy in children with HSPN still remains controversial. Renal biopsy is generally performed when a patient with HSPN shows proteinuria of more than 1 g/day [11, 15]. Nephrotic syndrome and acute nephritic syndrome are also the well accepted criteria of renal biopsy in HSPN. However, the indication of renal biopsy in HSPN patients with mild to moderate proteinuria (<1 g/day) should be further elucidated, although Halling et al. reported that the indications for early renal biopsy should be increased in these patients, because even HSPN patients with mild to moderate proteinuria showed severe morphological changes [16].

A recent study by Finland group [17] suggested an important issue on the treatment of HSPN patients with nephrotic-range proteinuria. In this study, the first renal biopsy did not predict the outcome of HSPN, since all the patients with the poorest outcome had only ISKDC II-III findings in their first biopsy. Therefore, they recommended that the treatment of HSPN patients should be based on the clinical presentation rather than on the biopsy findings. However, some authors reported that the best prognostic features of HSPN were histological, and the risk of chronic renal failure was high (47%) in HSPN children with crescents of more than half the glomeruli compared to adults [15]. Based on these studies, intensive therapy should be considered if a HSPN patient shows either severe renal symptoms or high histological classes with cellular/epithelial crescents on the renal biopsy.

2. The purpose of treatment: reduction of proteinuria or histological regression?

Clinical improvement, such as reduction of proteinuria, has been a main therapeutic aim of many renal diseases [18]. In HSPN, however, some long-term studies have shown that clinical recovery does not inevitably mean favorable long-term outcome [3, 4]. Therefore, we performed a study to elucidate the differences between clinical improvement and histological regression [19]. In this study, nineteen of the

20 patients with crescentic HSPN had a favorable outcome after immunosuppressive therapy, but histological regression was achieved in only 10 patients, confirming that clinical remission does not always mean histological improvement, and the histologic reversibility of crescentic HSPN is much less than clinical improvement. Therefore, it will be important to induce histological regression in addition to reduction of proteinuria in treating severe HSPN.

3. Outcome measurement: what is a favorable prognosis?

The clinical status of patients with HSPN has been classified as follows: State A. Normal: normal physical examination, urine, and renal function; State B. Minor urinary abnormalities: normal on physical examination with microscopic hematuria or proteinuria less than 40 mg/m^2/h; State C. Active renal disease: proteinuria of 40 mg/m^2/h or greater or hypertension, and GFR of 60 mL/min/1.73m^2 or greater; State D. Renal insufficiency: GFR less than 60 mL/min/1.73m^2 (including dialysis/transplant or death) [20]. However, the definition of a favorable prognosis has been variable according to the different studies. Some authors took clinical state A+B as a favorable prognosis [21], while others regarded only clinical state A as a favorable outcome [22]. What is a favorable prognosis? To elucidate this, we should think about the long-term outcome of HSPN rather than the short-term outcome [3, 4]. Goldstein et al. studied former HSP patients 23.4 years later and reported highly unpredictable outcomes, in that several patients with mild initial disease and apparent complete recovery showed chronic renal insufficiency after 2 decades [3]. Ronkainen et al. also reported that even patients with mild renal symptoms at the onset of HSP do carry a risk for severe long-term complications [4]. Algoet et al. performed a follow-up renal biopsy 2-9 years (median 5.5 years) after the HSP episode and found that renal histology was normal in only one of the 4 patients who had achieved complete clinical remission 5-9 years after the HSP onset [23]. Our previous report also showed that renal histologic findings after immunosuppressive therapy was abnormal in all HSPN patients regardless of clinical improvement, suggesting the kidneys were not completely healed even in patients with clinical remission [19]. These results suggest that more strict determination of favorable prognosis would be imperative.

4. What is intensive therapy and when should we start intensive therapy?

Intensive therapy includes intravenous high-dose methylprednisolone pulse, immunosuppressive drugs (e.g. cyclophosphamide, azathioprine, cyclosporin), fibrinolytic therapy (e.g. urokinase)/anticoagulants (e.g. heparin or warfarin)/antiplatelet agent (e.g. dipyridamole), plasma exchange, and a combination of these drugs [11, 14, 24-44].

Niaudet et al. suggested that immunosuppression like methylprednisolone pulse therapy (MPT) should be started early during the course of severe HSPN before the crescents

become fibrous, because scarring of the renal parenchyma as a sequela of previous extensive glomerular damage during the acute episode could have a risk of progression [11]. These results have been supported by several other studies [19, 25, 36]. Tanaka et al. showed the importance and efficacy of early treatment of severe proteinuric HSPN [25], and all nine patients with nephrotic-range proteinuria treated with prednisolone and oral cyclophosphamide within a month of HSP diagnosis showed improvement in symptoms and histological findings (From ISKDC IIIb or IVb to II) [25]. Our previous report also demonstrated that 6 patients with a very early stage of HSPN showing only nephrotic-range proteinuria without nephrotic syndrome treated with prednisolone and cyclosporin showed histological regression of ISKDC grade at the second biopsy [36]. However, these two studies could not prove the disadvantage of delayed treatment due to small case series without controls [25, 36]. Therefore, we performed another study [19] and showed that early treatment with immunosuppressants was an important factor to achieve histological regression by decreasing chronic renal injury. In this study, the chronicity index at the second biopsy correlated positively with the time immunosuppressive therapy was started. Ronkainen et al. also demonstrated that the only difference between four patients who achieved a stable remission after cyclosporin therapy and three patients who became cyclosporin dependent was that cyclosporin had been started significantly earlier in the former group than in the latter [34]. Therefore, early immunosuppressive therapy should be considered in children with severe HSPN.

5. The application of intensive therapy

1) Methylprednisolone pulse therapy (MPT)

MPT has been used as a sole agent [11] or in combination with other immunosuppressants in severe HSPN [26-30, 33-37, 43]. Niaudet et al. [11] have used MPT (3 consecutive days) followed by oral prednisone (3.5 months) in 38 patients with severe HSPN, 21 of whom had 50% or more glomeruli with crescents. After 1-16 years of follow-up, 27 children had clinically recovered, 3 showed minimal urinary abnormalities, 4 had persistent nephropathy, and 4 had progressed to end-stage renal failure. Although uncontrolled, this study suggests that MPT is effective in severe HSPN patients with the risk of renal progression, especially if started early during the course of the disease before the crescents become fibrous. The action mechanism of MPT is unclear, but Yamamoto et al. [47] demonstrated that a large dose of glucocorticoid ameliorated urinary protein excretion and crescent formation when started before the development of proteinuria in an experimental model of crescentic glomerulonephritis. Furthermore, a large dose of glucocorticoid ameliorated the clinical and histological abnormalities when given, even after the development of proteinuria and the diffuse formation of cellular crescents. Considering a short course (only 3 days) of treatment, simple method of administration, rare adverse effects, and unnecessary drug monitoring, MPT could be used as a safe and effective initial therapeutic regimen, and therefore should be applied

as early as possible in children with severe HSPN to decrease cellular crescents, urinary protein excretion, and chronic renal injury [11, 19].

2) Cyclophosphamide

Cyclophosphamide has also been used in combinations with prednisone or other regimens, such as MPT, urokinase, anticoagulants and antiplatelet agents [14, 24-27, 29]. Flynn et al. [24] and Tanaka et al. [25] suggested that oral cyclophosphamide therapy with steroids could significantly reduce proteinuria or induce histological regression in a case series, but Tarshish et al. [14] have recently reported the contrasting results of cyclophosphamide therapy in a randomized controlled study. The control and nontrial groups received supportive care alone, and the treatment group received supportive care plus cyclophosphamide for 42 days. No differences in outcome were found between the groups. These findings suggest that cyclophosphamide itself may not be effective in modifying the natural course of severe HSPN. However, several authors suggested that cyclophosphamide combined with other drugs, such as MPT, heparin/warfarin, dipyridamole, and urokinase had been very effective in rapidly progressive glomerulonephritis (RPGN) type of HSPN [26, 27, 29].

Therefore, cyclophosphamide could be used in combinations with other drugs in children with very severe HSPN, especially presenting with RPGN, considering the adverse effects of this cytotoxic drug, such as myelosuppression, cytopenia, infection, hemorrhagic cystitis, gonadal toxicity, and secondary cancer.

3) Azathioprine

Previous reports suggested that azathioprine combined with steroids might improve the clinical course of severe HSPN [30-33]. Bergstein et al. firstly reported the beneficial effect of azathioprine on severe HSN. Of 21 severe HSPN patients treated with azathioprine and steroids, 19 showed clinical improvement and 2 progressed to end-stage renal failure [30]. Foster et al. reported that azathioprine with prednisone was effective in improving clinical and histological findings at follow-up biopsy: 15 of the 17 patients had a favorable outcome, and the activity index decreased significantly without an increase of the chronicity index [31]. Especially, Singh et al. found that all 9 patients with acute nephritic syndrome achieved a stable remission following azathioprine and steroids therapy [32]. We also demonstrated the efficacy of azathioprine on severe HSPN by comparing 10 patients received azathioprine and steroids with 10 received steroids alone [33]. Therefore, the combination treatment of azathioprine and steroids may be beneficial in ameliorating histopathological features, and improving the clinical course of severe HSPN, especially presenting with acute nephritic syndrome.

4) Cyclosporin

Ronkainen et al. firstly reported the efficacy of cyclosporin in 7 children with severe HSPN [34]. In this study, all patients received additional angiotensin converting enzyme (ACE) inhibitor and one to three types of immunosuppressive treatment (methylprednisolone pulse,

azathioprine, and cyclophosphamide) had been tried in 5 of the 7 patients before cyclosporin therapy. All the patients responded to cyclosporin, but 4 patients achieved a stable remission and 3 became cyclosporin dependent. To elucidate the role of cyclosporin in the treatment of severe HSPN, we analyzed the efficacy of cyclosporin in 7 patients with nephrotic syndrome [35]. Among them, MPT was used in 2 patients and ACE inhibitor in 4 patients concurrently. After therapy, urinary protein excretion declined from a mean of 9.2 g/m^2/day to 0.3 g/m^2/day and severe hypoalbuminemia recovered from a mean of 2.1 g/dL to 4.6 g/dL. In these patients, the activity index decreased statistically at the second renal biopsies, but the grades of ISKDC did not improve and one patient had active renal disease and proteinuria of 1.2 g/m2/day at follow-up. Although this study showed the possible efficacy of cyclosporin in a subset of HSPN patients with nephrotic syndrome, there were some limitations since MPT or ACE inhibitor might have influenced the outcome of HSPN.

Therefore, we also evaluated the outcome of HSPN patients showing only nephrotic-range protienuria [36]. All the patients had a very early stage of HSPN without hypoalbuminemia, some of whom showed only borderline proteinuria and were treated only with cyclosporin and oral prednisolone without MPT or ACE inhibitor to exclude the effect of other drugs on proteinuria. In this study, proteinuria disappeared completely in 7 of the 8 patients, and only one patient showed minimal proteinuria with microscopic hematuria at the latest follow-up. In addition, histological regression was observed in all 6 patients who received a follow-up biopsy from ISKDC IIIa or IIIb to I or II, suggesting that very early intensive immunosuppression may induce the improvement of the ISKDC grade, which had not been observed in HSPN patients with nephrotic syndrome. Furthermore, we recently reported the successful use of cyclosporin in a severe HSN patient with chronically persistent nephrotic-range proteinuria, who failed to respond to methylprednisolone pulse and azathioprine therapy [37]. These results suggest that cyclosporin may have an important role in the treatment of severe HSPN. However, since the characteristic lesion of chronic cyclosporin toxicity was identified in one patient despite an appropriate plasma cyclosporin concentration [36], it would be necessary to monitor patients' renal function cautiously and use the lowest effective dose. In addition, it appears that cyclosporin is not compatible to treat severe HSPN patients presenting with acute nephritic syndrome, because we indirectly showed that 3 HSPN patients with acute nephritic syndrome treated with cyclosporin and steroids had active renal disease at the latest follow-up [38]. Therefore, cyclosporin should be avoided in HSN patients with acute nephritic features, considering it possible adverse effects, such as hypertension, hyperuricemia, hyperkalemia, nephrotoxicity, and neurotoxicity.

5) Fibrinolytic therapy: Urokinase

Watanabe et al. firstly showed the beneficial effect of urokinase on a small number of patients with severe HSPN [39], and Kawasaki et al. also demonstrated that urokinase com-

bined with methylprednisolone pulse or cyclophosphamide was very effective in severe HSPN patients with the grade of ISKDC of more than IV [28, 29]. They applied urokinase to these patients since glomerular fibrinogen deposits are frequently present in crescentic HSPN [28-39]. We found that the decrease of fibrinogen deposition was associated with histological regression of crescentic HSPN and the age at the onset of HSPN was correlated positively with the fibrinogen deposition at the second biopsy [19]. In this study, however, we could not show the exact role of fibrinogen deposition in the pathogenesis of crescentic HSPN. To elucidate this, we postulated that there would be some differences in crescent formation and glomerular fibrinogen deposition among HSPN patients, and fibrinolytic therapy should be done according to the characteristics of an individual patient since HSPN is a heterogenous disease with many histopathological presentations and crescents associated with HSPN are not always fibrinogen-dependent [40]. Therefore, we reclassified the patients with crescentic HSPN into two groups according to the subsequent course of fibrinogen deposits: group I (N=9) with no or decreased deposition and group II (N=12) with persistent or increased deposition [40]. Although other authors had treated the patients according to the fibrinogen deposits at the first biopsy, our results demonstrated the heterogenous serial changes of fibrinogen deposition between the first and second biopsy: 2 patients had no fibrinogen deposits throughout the course of the disease and 7 showed diminution or disappearance of crescents and fibrinogen deposits with only immunosuppressants in group I, whereas 3 patients who had shown no fibrinogen deposits at the first biopsy developed new fibrinogen deposits at the second biopsy, and 9 had persistent or increased fibrinogen deposits in spite of immunosuppressants in group II [40]. Therefore, we were interested in discriminating these two groups, and we found that an age more than 9 years was the only factor statistically significant related to the persistent or increased fibrinogen deposition. This study also demonstrated that changes in the percentage of crescents correlated positively with the intensity of fibrinogen deposits at the second biopsy [40]. In this point, fibrinolytic therapy could be a beneficial approach to ameliorate the progression of renal injury and histopathologic changes related to severe fibrinogen deposition in older children with crescentic HSPN. However, considering a possible risk of bleeding, urokinase should be restricted to the older HSPN children with the high grade of ISKDC.

6) Heparin/warfarin and dipyridamole

These drugs have been used in combination with other drugs, such as MPT, cyclophosphamide and urokinase, in patients with severe HSPN, presenting with RPGN [26-29, 43]. Oner et al. showed the beneficial effect of triple therapy (MPT, cyclophosphamide, dipyridamole) on 12 HSPN patients with RPGN [26], and Iijima et al. also demonstrated that multiple combined therapy (MPT, cyclophosphamide, heparin/warfarin, dipyridamole) was very effective in 14 HSPN patients showing severe glomerular changes (grade IV or V) [27]. Kawasaki et al. showed that methylprednisolone

urokinase pulse therapy (MPT, urokinase, heparin/warfarin, dipyridamole) was effective in not only reducing proteinuria but also decreasing the activity index by improving hypercoagulant state in 56 severe HSPN patients who had been diagnosed with at least type IIIb [28]. Although uncontrolled, these therapies could be used when the HSPN patients presented with RPGN, which might progress to end stage renal failure within a relatively short time.

7) Plasmapheresis

Plasmapheresis has been used in not only HSP showing severe mesenteric or cerebral vasculitis but also rapidly progressive HSPN [41-46]. Hattori et al. reported that plasmapheresis as the sole therapy was effective in improving the prognosis of patients with rapidly progressive HSPN, particularly if instituted early in the course of the disease [41]. Schärer et al. suggested that plasmapheresis might delay the rate of progression, but not prevent end stage renal failure in children with crescentic HSPN [42]. Plasmapheresis has been attempted to remove circulating humoral factors such as immune complexes, autoantibodies, immunoglobulins and mediators of inflammation in various diseases. Because IgA-mediated immune complexes are involved in the pathogenesis of HSPN [1], plasmapheresis could be beneficial in the treatment of rapidly progressive severe HSPN.

6. ACE inhibitor: is it beneficial in proteinuric HSN as in IgA nephropathy?

We already mentioned that the aim of treatment should be histological regression in addition to reduction of proteinuria in children with severe HSPN [19]. However, Coppo et al. recently reported that the risk for progression of HSPN was associated with increasing proteinuria levels during follow-up [48]. Therefore, proteinuria should also be regarded as an important therapeutic target. Although ACE inhibition has been established in the treatment of proteinuric patients with IgA nephropathy [49], there has been no controlled trial in HSPN patients with proteinuria. Camacho Diaz et al. reported that ACE inhibitors could be an effective alternative for reducing proteinuria in 9 children with prolonged nephropathy, including HSPN [50]. In this study, proteinuria was initially in the nephrotic range, but fell significantly after 6 months and at the end of the treatment without the decrease in glomerular filtration rate and adverse reactions in all patients. ACE inhibitors has also been used with other immunosuppressants safely [34, 35, 51] in children with severe HSPN. Therefore, ACE inhibitors could be used for renal protection in HSPN patients with severe proteinuria, because nephrotic syndrome at onset or increasing proteinuria during follow-up was associated with renal progression in HSPN [14, 21, 48].

7. Persistent proteinuria after initial intensive therapy: observation or further immunosuppression?

In addition to Coppo et al.'s study [48], Tarshish et al. pointed out an important issue on the course of disease in children with severe HSPN [14]. In this study, all patients with pro-

gression to end stage renal failure had nephrotic levels of proteinuria at onset, and only five of 28 patients with nephrotic levels of proteinuria and severe onset histopathology recovered fully. Persistence of urinary abnormalities for several years was one of the ominous signs. Therefore, if a patient shows persistent proteinuria after initial intensive therapy, we should pay more attention to the future outcome of this patient. In this situation, we would like to recommend performing a second renal biopsy to assess the histological effects of intensive therapy, the degree of pre-existing renal damage, and ongoing active or chronic changes [33]. If active histological lesions persist on the renal biopsy, additional intensive therapy should be considered, although some patients achieve the resolution of proteinuria several years after the end of immunosuppression [33, 35]. We recently demonstrated that chronically persistent severe HSPN could be successfully treated by additional intensive therapy such as cyclosporin or MPT by the Tune-Mendoza protocol [37, 52]. These two patients appeared azathioprine-resistant, but we speculate that azathioprine might have influenced the responsiveness of HSP kidney to additional immunosuppression. Therefore, every efforts should be focused on the histological regression, resolution of proteinuria, and control of hypertension in patients with severe HSPN.

Conclusions

Severe HSPN has a high risk of progression to end stage renal failure and recent studies emphasize the importance of early treatment in children with severe HSPN [11, 17, 19]. Considering the unfavorable long-term outcome even in HSPN patients with mild renal symptoms at onset [3, 4], the treatment of severe HSPN should be started early during the course of HSPN before the crescents become fibrous, as suggested by Niaudet et al. [11]. However, due to the rarity of randomized controlled studies in this field, the treatment of severe HSPN often depends on the individual case series. Therefore, multicenter collaborations may be necessary to establish the evidence-based treatment options for children with severe HSPN in the future, although it is very hard to conduct.

요 약

소아의 심한 헤노흐-쇤라인 자반증의 치료

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헤노흐-쇤라인 자반증의 전반적인 예후는 양호하나 심한 신염의 경우 말기신부전으로 진행될 위험이 높다. 최근 연구는 심한 헤노흐-쇤라인 자반증 신염을 가진 소아에서 조기 치료의 중요성을 강조하고 있으나 심한 자반증 신염의 치료는 맹검 대조 연구가 드물어 여전히 논쟁의 여지가 있다. 그럼에도, 정맥 고용량 메틸프레드니솔론 충격요법, 면역억제/세포독성 약제, 섬유소용해 치료, 항응고제, 항혈소판제, 혈장교환술같은 여러 강력한 치료가 심한 자반증 신염을 가진 소아에서 사용되어 왔다. 이 종설에서는 심한 자반증 신염을 가진 소아의 치료를 중점적으로 기술하였다.

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