영남의대학술지 제18권 제2호
Yeungnam Univ. J. of Med.
Vol. 18. No. 2. 246-252. Dec. 2001.

□ 원저 □

Treatment of Henoch-Schönlein Purpura with Intravenous Immunoglobulin

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- 요 약 -

고용량 스테로이드 충격 요법에 반응하지 않는 심한 복통과 신생검에서 50% 이상 반월체 형성이 되는 알레르기성 자반증 신염 환자의 치료를 위하여 고용량 정맥용 면역 글로불린을 투여하여 복부 증상이 조기 회복되었으며 이후 혈뇨와 단백뇨도 호전되었다. 그러므로 복부 증상과 신장 침범이 스테로이드 치료에 반응하지 않는 알레르기성 자반증 환자의 경우에 정맥용 면역 글로불린 치료가 고려되어야 할 것으로 사료된다.

Key Words: Henoch-Schönlein purpura, Nephrotic syndrome, Abdominal pain, Intravenous immunoglobulin

Introduction

Henoch-Schönlein purpura(HSP) is a systemic hypersensitivity vasculitis involving the skin, joints, kidneys, and gastrointestinal tract. The cause of HSP is unknown, but HSP typically follows an upper respiratory tract infection. This illness is more frequent in children than adults and overall incidence is estimated to be 9/100,000 population. In general, HSP in children is more benign and self-limited than adult. Adequate hydration, bland diet and pain control with acetaminophen are provided for self-limited complaints of arthralgia, fever and malaise. Avoidance of competitive activities and of maintaining the lower

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접수일 : 2001년 11월 15일, 게재승인일 : 2001년 12월 18일

extremities in persistent dependence may decrease local edema. Intestinal complications such as hemorrhage, obstruction and intussusception may be life threatening and managed with corticosteroids which often associated with dramatic improvement of gastrointestinal(GI) and CNS complications. Favorable anecdotal experiences of steroids to treat the patient with nephrotic syndrome contribute to continue its use. Rarely, these GI manifestations are intractable with corticosteroid therapy. High-dose intravenous immunoglobulin(IVIG) has been established to treat some autoimmune diseases(Berkman, et al., 1990). Heldrich and colleagues reported their experience using IVIG therapy successfully for a five-year-old girl with severe abdominal pain without nephritis secondary to HSP(Hedrich, et al., 1993). Thereafter a few successful experiences were reported using IVIG therapy for severe IgA nephropathy and HSP nephritis in adult(Rostoker, et al., 1994; Kusuda, et al., 1999). Here, we report the efficacy of IVIG in HSP with severe gastrointestinal manifestation and nephrotic syndrome, which was resistant to high-dose steroids therapy.

Case report

A six-year-old male was admitted to our department because of purpuric rash and severe abdominal pain. Twelve days prior to the admission, symptoms were arthralgia with periarticular swelling involving the right wrist and ankle, purpuric rashes over the both lower extremities and intermittent severe colicky abdominal pain without hematuria and proteinuria. Steroid (prednisolone 1 mg/kg/day) was given orally at another hospital. But these symptoms were aggravated and let him transferred to our hospital.

He was admitted to the pediatric unit in our hospital with intermittent severe abdominal pain. Physical examination revealed diffuse purpuric lesions in both lower extremities, both elbows and buttocks, and mild facial edema. His blood pressure was 100/60 mmHg; pulse rate was 90 beats per minute. Initial laboratory investigation showed: hemoglobin level 12.0 g/dL, leukocyte count 14,600 cells/㎣(with 71% polymorphonuclear leukocytes and 18% lymphocytes), platelet count 437,000 cells/㎣ and erythrocyte sedimentation rate 10 ㎜/hr. Other laboratory measures included serum IgA 318.1 mg/dL, ANA: negative, serum sodium level, 138 mEq/L; potassium level, 4.2 mEq/L; serum creatinine level, 0.5 mg/dL; blood urea nitrogen level, 11.0 mg/dL; serum total protein 7.3 g/dL; albumin 3.0 g/dL; total

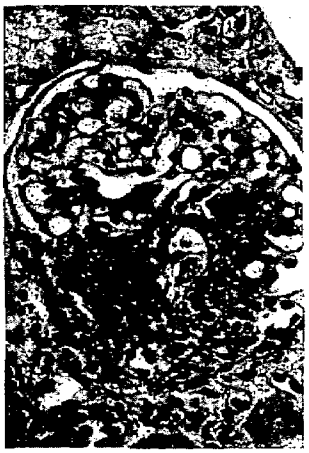

Fig. 1

Fig. 2

Fig. 3

Fig. 1. The glomerulus shows fibrocellular crescent formation on the lower half of capillary tuft and remaining area has mild mesangial cell proliferation(PAS, ×400).

Fig. 2. Electron micrograph. Arrow points dense deposits in mesangial and paramesangial area(×4,000).

Fig. 3. IgA is strong positive along the mesangial area by immunofluorescent examination(×200).

cholesterol 177 mg/dL and ASO level, 246 IU/mL. Hepatic transaminases were normal and urinalysis showed no hematuria or proteinuria. Occult blood in the stool was trace. Culture of throat was negative. Simple abdomen X-ray and abdomen and renal sonography revealed no abnormal findings.

On admission day, due to the impossibility of administering oral medication, he was receiving methylprednisolone(1.5 mg/kg/24 hrs) intravenously. Symptoms subsided gradually after 3 days of methylprednisolone administration, and steroid dose was reduced to 0.5 mg kg/24 hrs. Four days later, the patient experienced severe colicky abdominal pain but no more purpura. Simple abdomen showed focal edematous bowel gas pattern. But his severe colicky abdominal pain was not improved. High dose immunoglobulin was given intravenously(1 g/kg/24 hrs) for consecutive two days with continuous methylprednisolone therapy. Abdominal pain subsided remarkably. Eight days after administration of immunoglobulin, recurrence of severe abdominal pain and facial edema were developed. Subsequently, he had recognized melena and gross hematuria.

Laboratory data on this time were shown as follows: serum creatinine 0.7 mg/dL; hypoalbuminemia 2.7 g/dL; hypercholesterolemia 210 mg/dL; proteinuria 1.1 g/day. Urinalysis revealed numerous erythrocytes and granular casts, and 3+ protein on dipstick. Once more immunoglobulin was given intravenously(1 g/kg/24 hrs). And additional methylprednisolone pulse therapy at a dose of 20 mg/kg/24hrs for 3 successive days was done. Abdominal pain subsided but proteinuria and hematuria were consistent.

A percutaneous renal biopsy was performed on the 28th hospital day. The specimen contained about 10 glomeruli and showed diffuse mensangial cell proliferation with fibrocellular crescent formation, approximately 50%(Fig. 1). Electron microscopically, dense deposits were located at mesangium and paramesangial area(Fig. 2). Immunofluorescence study revealed strong positive staining for anti-IgA antibody along the paramesangial areas(Fig. 3). C3 was also positive but not stronger than IgA and others were negative for immunofluorescence. This biopsy findings were consistent with Henoch-Schnlein purpura nephritis, grade Ⅲb. On the 34th hospital day, due to partially improved proteinuria and hematuria and no further recurrence of abdominal pain and purpura, he was discharged. Steroid dosage was gradually reduced with mild proteinuria and microscopic hematuria. Proteinuria and hematuria disappeared after 4 months of IVIG and the remission state was achieved. On one and half-year follow-up, the patient is doing well with no proteinuria and microscopic hematuria and requiring no more medications.

Discussion

HSP is a vasculitis of undetermined etiology, but it may be the result of a defect in the regulation of IgA synthesis in response to circulating or mucosal antigenic stimulation. Entrap-ment of IgA immune complexes in postcapillary venules of the target organs leads to an inflammatory response mediated by macrophage infiltration and fibrin deposition(Fitzgerald, 2000). The gastrointestinal symptoms and signs result from the ensuing vasculitis, which causes ischemia, submucosal edema, and hemorrhage. Rare intestinal complications include pancreatitis, cholecystitis, intestinal perforation, intussusception that may be life-threatening. Renal involvement occurs in 25~50% of children. The occurrence of the acute nephrotic syndrome at the onset, persistent nephrotic syndrome with persisting hypertension or progressive decline in GFR, and diffuse proliferative glomerulonephritis with marked crescent formation

were indicators of a poor prognosis.

In general, an attempt to prevent gastrointestinal complication has led to the use of steroids in HSP who develop intermittent, colicky abdominal pain with melena successfully. Favorable anecdotal experiences of steroids to HSP with nephrotic syndrome contribute to continue its use. Patients with HSP accompanied by nephrotic or progressive renal failure have been treated with steroids or cytotoxic drugs, however, the low number of cases reported do not provide any firm conclusion. The present patient developed severe abdominal pain without nephrotic state at the onset. During admission, proteinuria and hematuria developed with generalized edema. Anyway, methylprednisolone pulse therapy did not suppress both the abdominal pain and the proteinuria in our case. Because of this, we elected to use intravenous gamma globulin in our patient.

The pathogenesis of HSP nephritis is unknown, but the cytokines(tumor necrosis factor and interleukin 6) have been implicated in active disease, and immune deposits in the mesangial lesions suggest an immune complex-mediated mesangial injury and proliferation. IVIG was chosen for this patient with the rationale that it has been shown to be effective in several immune-mediated diseases. Although the exact mechanism is unknown, it acts as an immunomediators, by the suppression of antibody production, Fe-receptor blockade, blockage of antiendothelial factors, modulation of inflammation, or neutralization of an unidentified infectious agent and anti-idiotypic reaction(Hamidou, et al., 1996).

Experience of IVIG in HSP is limited to a very few patients. Six cases of HSP including 2 children have been reported to be treated with IVIG. In two of the cases, severe abdominal symptoms without renal involvement subsided after IVIG. In the others, improvement of proteinuria was documented by IVIG without side effects. One patient developed a progressive deterioration in renal function with nephrotic syndrome, paradoxically. Therefore, we consider that IVIG therapy in HSP should be at least closely monitored, in spite of IVIG therapy has been used in several autoimmune diseases, such as IgA nephropathy, Kawasaki disease, and antineutrophil cytoplasmic antibody-positive vasculitis. Recently, occurrence of renal dysfunction in patients with pre-existing renal diseases was reported. IVIG increases plasma viscosity and consequently blood viscosity in vitro in a dose-dependent manner. The large fraction of sucrose isoosmotically active and causes erythrocyte shrinking and

therefore a fall in packed cell volume. In-vivo addition of IVIG increased plasma viscosity, blood viscosity at high and low shear rate, and erythrocyte aggregation. Furthermore, the potentially adverse effect of increased plasma viscosity may be aggravated by the usually rapid rise in platelet count in response to therapy. In patients at risk of cardiovascular disorders, the indication for IVIG should thus be assessed carefully and restricted to those with life-threatening bleeding (Schiefferli, et al., 1991; Reinhart and Berchtold, 1992; Blanco, et al., 1997).

In our case, there was no adverse effect of IVIG without anti-coagulant therapy. Although the delayed therapeutic effects of steroid pulse therapy should be considered, a dramatic improvement of proteinuria was observed by IVIG therapy in our case. We would propose that IVIG may be an effective therapy for HSP with severe abdominal pain and refractory nephrotic syndrome. Also, a long-term prospective study with a large number of cases might shed light on this controversy.

Abstract

We report the result of a high-dose intravenous immunoglobulin therapy in a Henoch-Schnlein purpura patient with severe abdominal pain and nephrotic syndrome who did not respond to methylprednisolone pulse therapy. Kidney biopsy showed diffuse mesangial cell proliferative glomerulonephritis with fibrocellular crescent formation in approximately 50% of glomeruli. Mesangium of all glomeruli were strong positive for IgA and C3 antibodies. High-dose intravenous immunoglobulin treatment was introduced and dramatic improvement of gastrointestinal symptom and proteinuria as well as hematuria was noted. Immunoglobulin administration should be considered in Henoch-Schnlein purpura patients with steroid-resistant intractable gastrointestinal manifestation and renal involvement.

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