การใช้ Intravenous immunoglobulin ในผู้ป่วย Systemic lupus erythematosus ที่มีภาวะ demyelinating polyneuropathy : รายงานผู้ป่วย 1 ราย และทบทวนวารสาร

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Intravenous Immunoglobulin (IV Ig) Treatment of Demyelinating Polyneuropathy in Patient with Systemic Lupus Erythematosus (SLE): A Case Report and Review of the Literatures.

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หลักการและเหตุผล: Demyelinating polyneuropathy เป็นภาวะที่พบไม่บ่อยในผู้ป่วยโรคเอสแอลอี (SLE) อาการแสดงของผู้ป่วยคือกล้ามเนื้ออ่อนแรงและชาคล้ายกับโรค Guillian-Barre syndrome (GBS) ปัจจุบันยังไม่มีการรักษาที่แน่นอนสำหรับภาวะนี้ในผู้ป่วยโรคเอสแอลอี การตอบสนองต่อ corticosteroids ให้ผลไม่แน่นอน

วัตถุประสงค์: เพื่อเสนอรายงานผู้ป่วย 1 ราย

ผลการศึกษา: ผู้ป่วยหญิงอายุ 40 ปี มีอาการปวดข้อและได้รับการวินิจฉัยเป็นโรคข้ออักเสบรูมาตอยด์ ผลการตรวจ Rheumatoid factor, ANA, anti-ds-DNA, anti-SSA และ anti-SSB ให้ผลบวก ผู้ป่วยได้รับการรักษาด้วย non steroidal anti-inflammatory drug (NSAID) และ methotrexate 3 เดือนต่อมาผู้ป่วยมีอาการแขนขาอ่อนแรง บวมที่หน้าและริมฝีปาก ปวดข้อ และชาเป็นๆ หายๆ บริเวณลำตัวด้านซ้ายมาเป็นเวลา 2 สัปดาห์ก่อนมาโรงพยาบาล การตรวจร่างกายพบว่ามีการอ่อนแรงของต้นแขนและขามากกว่าส่วนปลายแขนและขา และ deep tendon reflex ลดลง การตรวจทางห้องปฏิบัติการพบว่า ระดับของ anti-ds-DNA สูงขึ้น ระดับคอมพลีเมนต์ในเลือดลดต่ำลง และการตรวจ anticardiolipin antibodies ให้ผลบวก การตรวจน้ำไขสันหลังให้ผลปกติ (เม็ดเลือดขาว 3 ตัวต่อลูกบาศก์มิลลิลิตร ระดับน้ำตาล 77 มิลลิกรัมต่อเดซิลิตร และระดับโปรตีน 76 มิลลิกรัมต่อเดซิลิตร) การตรวจคลื่นไฟฟ้ากล้ามเนื้อและการนำกระแสไฟฟ้าของเส้นประสาทเข้าได้กับภาวะ diffuse demyelinating polyneuropathy ตรวจพบโปรตีนในปัสสาวะ

Background: Demyelinating polyneuropathy is an uncommon manifestation in SLE. Clinical manifestations include motor weakness, sensory loss and hyporeflexia resemble Guillian-Barre´ syndrome (GBS). Treatment is still not well document. Response to corticosteroids is inconsistent.

Objective: Herein is a case report of IV Ig treatment of polyneuropathy in patient with SLE.

Result: A 40 year-old African American woman with polyarthralgia was diagnosed having rheumatoid arthritis (RA). She had positive rheumatoid factor, positive ANA, positive anti-ds-DNA, positive anti-SSA and anti-SSB antibodies. She was treated with non-steroidal anti-inflammatory drug (NSAID) and methotrexate. Three months later, she presented with generalized weakness, swollen lips and face, polyarthralgia and intermittent left sided numbness for 2 weeks prior to being seen. Physical examination revealed quadriparesis predominately at the proximal groups and hyporeflexia. Laboratory findings showed elevated anti-ds-DNA, decreased serum compliment levels and positive anticardiolipin antibodies. CSF study showed normal profile with 3 WBC/mm^3, glucose of 77 mg/dl and protein of 76 mg/dl. Electromyographic (EMG) and nerve conduction test (NCT) showed diffuse demyeli-

2.26 กรัมต่อวัน ผู้ป่วยได้รับการวินิจฉัยโรคว่าเป็นโรคเอสแอลอี และได้รับการรักษาด้วย methylprednisolone 1 กรัมต่อวัน ทางหลอดเลือดดำเป็นเวลา 6 วัน ร่วมกับ azathioprine 100 มิลลิกรัมต่อวัน อาการผู้ป่วยยังไม่ดีขึ้น จึงได้เปลี่ยนการรักษาโดยให้ IV Ig 50 กรัมต่อวัน เป็นเวลา 2 วัน ผู้ป่วยมีอาการดีขึ้นอย่างรวดเร็ว 2 เดือนต่อมาได้ให้ IV Ig 50 กรัมต่อวันซ้ำอีกครั้งเป็นเวลา 2 วัน อาการของผู้ป่วยดีขึ้นเป็นลำดับ โดยไม่เกิดอาการข้างเคียงของการใช้ยา ผู้เขียนได้ทบทวนกลไกการออกฤทธิ์ ผลข้างเคียง และรายงานการใช้ IV Ig ในการรักษาผู้ป่วยโรคเอสแอลอีที่มีอาการทางระบบต่างๆ

สรุป: ได้รายงานผู้ป่วยเอสแอลอีที่มีภาวะ demyelinating polyneuropathy การรักษาโดย IV Ig ดูเหมือนจะมีประโยชน์ในการรักษาผู้ป่วยเอสแอลอีที่มีอาการและอาการแสดงในบางรูปแบบรวมถึงภาวะ demyelinating polyneuropathy ดังเช่นผู้ป่วยรายนี้ การรักษาโดย IV Ig ควรใช้ร่วมกับการรักษาโดยวิธีอื่น และควรใช้ด้วยความระมัดระวัง มีรายงานการเกิดภาวะไตวายเฉียบพลันหลังการใช้ IV Ig โดยเฉพาะผู้ป่วยสูงอายุและผู้ป่วยที่มีการทำงานของไตบกพร่อง

nating polyneuropathy. Renal function was normal but urinalysis showed 2.26 gm of protein in 24 hours. The diagnosis of SLE was made and she was treated with intravenous methylprednisolone (IV MP) 1 gm daily for 6 days and azathioprine (AZA) 100 mg/day. However the patient showed no improvement, thus IV Ig, 50 gm daily for 2 days was given. Rapid improvement was seen within one week. One month later, 2 days course of 50 gm of IV Ig was repeated with further improvement. There was no complication of IV Ig therapy in this patient. The mechanisms of action, adverse effects and clinical uses of IV Ig in various manifestations of SLE patients were also reviewed.

Conclusion: A case of demyelinating polyneuropathy in SLE patient was reported. IV Ig treatment appeared to be beneficial in certain manifestations of SLE including demyelinating polyneuropathy as described in this report. It should be used as an adjunct treatment with caution. Renal toxicity has been described especially in elderly patients and patient who has pre-existing renal disorder.

Key Words: IV Ig, SLE, Polyradiculopathy

ศรีนครินทร์เวชสาร 2541; 13(2), 106-111 • Srinagarind Med J 1998; 13(2), 106-111

CASE REPORT

In 1991, a 40 year-old African American with polyarthralgia and myalgia was previously diagnosed having rheumatoid arthritis (RA). She had positive rheumatoid factor (titer 1:1,280), positive ANA (titer 1:320, speckle pattern), positive anti-ds-DNA, positive anti-SSA and anti-SSB antibodies. The erythrocyte sedimentation rate was 126 mm/hr. She was treated with non-steroidal anti-inflammatory drug (NSAID) and methotrexate, 7.5 mg orally per week. Three months later, she presented with generalized weakness, swollen face and lips, polyarthralgia, and intermittent left sided numbness for 2 weeks prior to being seen. Physical examination revealed quadriparesis predominately at the proximal groups and hyporeflexia. Laboratory finding shows elevated anti-ds-DNA, decreased serum compliment levels with C_3 of 63.3 mg/dl (normal 83 - 177) and C_4 of <8 mg/dl (normal 15 -45). Anticardiolipin antibodies were positive. CSF study showed normal profile with 3 WBC/mm^3, glucose of 77 mg/dl and protein of 76 mg/dl. Electromyography (EMG) and nerve conduction test (NCT) showed diffuse demyelinating polyneuropathy. Renal function was normal but urinalysis showed 2.26 gm of protein in 24 hours. The diagnosis of SLE was made and the patient was treated with intravenous methylprednisolone (IV MP) 1 gm daily for 6 days including azathioprine (AZA), 100 mg. However the patient showed no improvement of weakness, thus IV Ig, 50 gm daily for 2 days was given. Rapid improvement of quadriparesis was seen. Patient was able to walk with minimal assistance within one week after IV Ig therapy. One month later, 2 days course of 50 gm of IV Ig was repeated with further improvement.

Patient was followed regularly at out-patient clinic, maintained with low dose prednisone, AZA and hydroxychloroquine. She developed diabetes mellitus and had frequent episodes of lupus flare up with polyarthralgia and myalgia. She also developed refractory hypertension. In 1994, the patient was found to have renal insufficiency with serum creatinine of 2.2 mg/dl with 24 hours urine protein greater than 3 gm. Kidney biopsy revealed WHO class V lupus nephritis with high chronicity index including extensive tubular atrophy and interstitial fibrosis. In 1995, patient developed end stage renal failure requiring long term hemodialysis.

DISCUSSION

Demyelinating polyneuropathy is an uncommon neurologic manifestation of SLE.[1-2] The pathogenesis is still not completely known. There is evidence for both cell-mediated and humoral immune processes in the pathogenesis of inflammatory demyelinating polyneuropathy. Cell-mediated mechanisms are suggested by increasing circulating activated T cells, lymphocytic infiltration of myelin and increased cell mediated immunity to myelin p2 protein. Humoral processes are suggested by a number of observations: (a) experimental induction of demyelination of animal nerves by serum of patients with Guillian-Barre´ syndrome (GBS) has been demonstrated; (b) patients with inflammatory demyelinating polyneuropathies have a number of anti-neuronal antibodies in the serum, notably to the antigens myelin protein p2 and cerebroside components; (c) plasma exchange and IV Ig have demonstrated to be benefit in the treatment of this condition. The other mechanisms which might explain the association between SLE and this manifestation: (a) autoantibodies which react with neural tissue may be produced in SLE patients; (b) immunological cross-reactivity may occur between autoantibody to nuclear antigens or cellular surface in SLE and antigens present on neural tissues i.e. antilymphocyte antibody; (c) vascular injury from deposition of immune complexes.[1,3] The treatment of demyelinating polyneuropathy in SLE patients is still not well documented. It includes corticosteroids, plasma exchange and IV Ig based on the trials of therapy carried out for GBS. Plasma exchange and IV Ig have been shown to be benefit in treatment of GBS and chronic inflammatory demyelinating polyneuropathy (CID).[1,3] The response of SLE associated polyneuropathy to corticosteroids seems to be inconsistent.[1-2]

In this report, we described the efficacy of IV Ig treatment in polyneuropathy in SLE patient. This patient presented with quadriparesis from acute demyelinating polyneuropathy which did not response to pulse IV MP therapy but IV Ig. There were eight patients reported of SLE-associated polyradiculoneuropathy in the literature. Seven received corticosteroids and four died [2]. Plasma exchange has shown to be effective in primary GBS but it has never been tried in SLE-associated polyradiculoneuropathy and is potentially dangerous especially in elderly patient with severe condition.[2] Lesprit et al also reported a case of prolonged remission of SLE-associated polyradiculoneuropathy after a single course of IV Ig therapy in the dose of 400 gm/kg for 5 days.[2] We decided to use IV Ig treatment in our patient. Although rapid improvement of neurological symptoms was seen but complete remission of SLE was not achieved after two courses of IV Ig therapy.

IV Ig has been using for treatment of various diseases e.g. immunodeficiency disorders and immunologic diseases including SLE.[2, 4-13] Reports on the efficacy of IV Ig treatment in SLE were summarized in **table 1**. Most reports showed favorable outcome but one patient with neonatal lupus syndrome and congenital heart block died.[2,4,6,8-12] The mechanism of action of IV Ig is not completely understood. It may have multiple modes of actions effecting the immune system in SLE patient as shown in **table 2**.

IV Ig treatment is rather safe. No complication was found in this patient. Serious side effects and complication of IV Ig treatment are rare[14] and was shown in **table 3**. The most serious side effects of IV Ig are anaphylactic reaction found particularly in patients with IgA deficiency and acute renal failure. To date, 35 patients were reported having acute renal failure as a complication of IV Ig therapy. All of these patients were adults and 56% were older than 65 years of age (range from 20 to 82 years old). More than 50% of these patients had pre-existing renal disease. Renal failure resolved within 2 weeks after discontinuation of IV Ig in 84% of cases (range 2 to 60 days). There was no apparent association between the dosage of IV Ig (dosage range from 0.35 to 1.0 gm/kg/d) and the occurrence of acute renal failure. The mechanism of renal toxicity is unknown.[15]

In summary, IV Ig treatment appeared to be beneficial in certain manifestations of SLE. It may be beneficial in treatment of demyelinating polyneuropathy in SLE patient. Further study of efficacy of IV Ig in this unusual manifestation of SLE is needed. However, it should be used as an adjunct treatment with caution because renal toxicity has been described especially in elderly patients and those who have pre-existing renal disorders.

Table 1 Case Reports of IV IgG Treatment in SLE Patients.

Manifeatation of SLE	No. of pts.	Dose and Duration	Outcome	Adverse effects	Ref.
Pure red cell aplasia	1	400 mg/kg x 5 d	Complete recovery	NR [a]	10
Thrombocytopenia	7	400 mg/kg x 5 d q 4 week for 12 mo.	Favorable out come in 5/7	2 cases [b]	6
Factor VIII inhibitor	2 [c]	400 mg/kg x 5 d [d]	Clinical improvement, ↓ of F VIII inhibitor	None	13
Refractory pleural effusion	1	400 mg/kg x 5 d q mo. for 5 mo.	Transient response, recurrent after stopping IV Ig. Rx	NR	8
Polyradiculoneuropathy, Thrombocytopenia	1	400 mg/kg x 5 d	Dramatic response	NR	2
Refractory myocarditis	1	400 mg/kg x 5 d	Recovery of CHF [e]	NR	9
Neonatal lupus, CHB[f]	1	1 gm/kg	Died	-	11
Immunological abnormality in 11/12, renal involvement in 5/12	12	400 mg/kg x 5 d q mo. last from 6 to 24 mo.	Clinical and serological improvement in 11/12	None	12
Lupus nephritis (5 class IV, 2 class V and 2 class IV and V)	9	400 mg/kg x 5 d	Improvement in renal function and serology, changes in histopathology [g]	Minimal [h]	4

[a] NR = not reported.
[b] One patient had headache and facial flushing and the other had low grade fever, headache and alternated felling hot and cold.
[c] One patient with SLE and the other with forme fruste SLE.
[d] One patient has been treated with IV Ig after plasmaphoresis every 3 weeks.
[e] CHF = congestive heart failure
[f] CHB = congenital heart block
[g] Good response with decrease proteinuria and serum creatinine, increase of serum compliment and changes in histopathology in 3/5 of WHO class IV lupus nephritis. Less effect seen in patients with WHO class V.
[h] Occationally patients had chill or twitching. There was no long-term immunological toxicity

Table 2 Mechanisms of Action of IV Ig.[5-7]

Fc receptor blockade of reticuloendothelial system and phagocytes.
Immunoregulation:
- Manipulation of the immune system by anti-idiotype antibodies.
- Decrease of number of activated T helper cells.
- Enhancement of T suppressor/cytotoxic cell function.
- Inhibition of B cell function and suppression of autoantibody synthesis.

Suppression of cytokine production.

Table 3 Adverse Effects and Complications of IV Ig therapy.[5, 14-15]

Fever, chill
Headache, aseptic meningitis
Myalgia, back pain
Nausea, emesis
Flushing, chest tightness, dyspnea, wheezing
Acute renal failure (elderly, pre-existing renal disease)
Anaphylactic reaction (patient with IgA deficiency)
Risk of viral infection (Hepatitis virus; non A - non B)
Hemolysis, thrombosis

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