



## Guillain-Barre Syndrome Associated with Cyclosporine A

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### Abstract

Guillain-Barre syndrome (GBS) is also known as an acute inflammatory demyelinating polyneuropathy (AIDP). It is an immune-mediated polyneuropathy commonly post-infectious in origin that presents with ascending weakness, loss of sensation and deep tendon reflexes resulting from demyelination of peripheral nerve. Drug-induced neuropathy has been describing before and remains a rare clinical entity. Development GBS after an episode of infections such as *Campylobacter Jejuni*, *Epstein Barr Virus*, and *Mycoplasma pneumonia* has been well described. However, GBS associated with Cyclosporine A (CsA) is rarely reported. Here we report a case of GBS developed two weeks after initiation of CsA in a patient with a known case of primary membranous nephropathy and responded well with cessation of the offending drug.

### Keywords

Guillain-Barre syndrome, Cycloporine A, Primary membranous nephropathy

### Introduction

Guillain-Barre syndrome (GBS) is the most common acute polyneuropathy and resembles acute inflammatory demyelinating polyneuropathy (AIDP). The incidence of typical Guillain-Barre syndrome has been reported ranging between one to two cases per 100 000 per year throughout the world [1]. It is commonly demyelinating or occasionally can be axonal and there have been major advances in understanding the mechanism of GBS. Antecedent *Campylobacter jejuni* infection occurs in about quarter of a patient with GBS [2]. The immunopathogenesis of GBS in post-infectious origin is due to the presence of an antibody that's against the peripheral nerve [3]. The diagnosis of GBS usually made from the clinical presentations consists of acute onset of paralysis that worsens over time, supported by absent of reflexes and can be confirmed from the neurophysiology study and cerebrospinal fluid examination. AIDP is the most widely recognized form of GBS but the variants are known as acute motor axonal neuropathy (AMAN), acute motor and sensory axonal neuropathy (AMSAN), Miller fisher syndrome are well established.

### Case Report

A 74-year-old lady was diagnosed to have type 2 diabetes mellitus, hypertension, dyslipidemia and gout for the past seven years. She also had ischemic heart disease in 1998 required percutaneous coronary stenting and remains asymptomatic of angina. She was referred

to our nephrology clinic for further investigations of progressive bilateral leg edema for 6 months. She had severe nephrotic syndrome with 24-hours urine protein was 6gm/day, serum albumin 16 g/l and preserved kidney function with a serum creatinine of 86  $\mu\text{mol/L}$  (estimated glomerular filtration rate (eGFR) of 56 ml/kg/1.73m<sup>2</sup>). Her connective tissue screen, consist of anti-nuclear antibody (ANA), anti-double-stranded DNA (dsDNA) were negative, normal C3 and C4 levels. Viral hepatitis B, C, and retroviral screen were negative. She was work-up extensively for myeloma kidneys and the results were negative as well. She underwent a renal biopsy and diagnosis of membranous nephropathy was made.

The possibility of secondary causes of membranous nephropathy was investigated thoroughly. She underwent computed tomography scan of the thorax, abdomen and pelvis (CT TAP), oesophago-duodenoscopy (OGDS), colonoscopy, mammogram and tumour marker screen namely alpha-fetoprotein ( $\alpha$ -FP), cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA) and the entire reports were normal. Ideally, detection of circulating antibodies against phospholipase A2 (PLA2R) will help to differentiate primary or secondary membranous nephropathy, however, this test is not available in our center and even throughout Malaysia. Thus, in the absence of secondary cause, she was subsequently diagnosed and treated for primary membranous nephropathy (PMN).

A period of observation for 6 months with optimized antiproteinuric medication (losartan 100mg daily) failed to improve her 24-hours urine protein excretion and it was rather increased to 10.3 gm/day. Thus, she was started on pulse dose of intravenous methylprednisolone 150 mg daily for 3 days when the followed by oral prednisolone. Intermittent two weekly doses of intravenous cyclophosphamide (IV CYC) was initiated; however her treatment was interrupted as she had multiple infections with two episodes of severe pneumonia and urinary tract infection that require hospitalization. She had another CT Thorax during the admission that proved lung consolidation, however, she was also found to have right descending artery pulmonary embolism needing anticoagulant treatment with subcutaneous enoxaparin. This event was likely due to her heavy proteinuria with low serum albumin. Despite 3.0gm cumulative dose of IV CYC over a period of 6 months, her 24-hours urine protein was failed to achieve below nephrotic range, therefore, the IV CYC was discontinued and Cyclosporine (CsA) was started at a dose of 75 mg twice daily with her body weight was 72 kg. Her oral

prednisolone was continued. Her serum creatinine upon initiation of CsA was 98  $\mu\text{mol/L}$  with eGFR of 50  $\text{mls/kg/1.73m}^2$ .

Two weeks later, she complains of insidious onset lower limb weakness associated with difficulty in walking, instability, recurrent fall and hands tremor, followed by upper limb weakness 3 days after that. There was no preceding symptoms of fever, upper or lower respiratory tract infection symptoms, abdominal pain, diarrhea or altered bowel habit and vomiting to suggest gastrointestinal tract (GIT) infection. She was compliant to the CsA. She was not on any other medications or supplements except the treatment prescribed from our clinic. Her blood pressure (BP) was 150/80 mmHg with pulse rate 80 beats per minute. Oxygen saturation was 98% on room air and was not tachypnoeic. She had features of proximal neuropathy with her bilateral lower limbs (LL) proximal muscles power of 2/5 at thighs, 3/5 knees and 5/5 distally over her ankles. All the LL reflexes were absent. However, there was no loss of sensation. Examination of the upper limbs was unremarkable. Other physical examinations were normal and no concurrent infections elicited.

Her blood investigations showed serum creatinine was 81  $\mu\text{mol/L}$ , albumin 31  $\text{mmol/L}$ , corrected calcium 2.39  $\text{mmol/L}$  and phosphate 1.18  $\text{mmol/L}$ , erythrocyte sedimentation rate (ESR) was 59  $\text{mm/hr}$ . Her hemoglobin was 12.8  $\text{g/dL}$ , white cell count of  $9.3 \times 10^9 \text{ g/dL}$ . Her diabetes control was good with glycosylated hemoglobin (HbA1c) ranging between 5.1%-5.7%. Her 24-hours urine protein was 13  $\text{g/day}$ . Repeat Hepatitis B, C and retroviral screen, tumor markers (CEA, CA-125, CA 19-9,  $\alpha$ -FP) and connective tissue disease screen (ANA, dsDNA) were all negative. She was subjected for a chest x - ray, CT thorax, abdomen and pelvis to rule out neoplasia and the results were normal. Electrocardiogram (ECG) did not show any acute ischemic changes or any cardiac arrhythmia. Other viral markers including Epstein-Bar virus (EBV), Cytomegalovirus (CMV) and *Mycoplasma* were negative. Cyclosporine blood level was not toxic at 33  $\text{ng/ml}$ . Stool specimen for *Campylobacter jejuni* test was not sent as she does not have any GIT symptoms and clinically not suggestive of this infection.

Lumbar puncture showed albumino-cytologic dissociation with a protein of 778  $\text{mg/L}$  (150-450  $\text{mg/L}$ ) and no other features to suggest infections. The motor nerve conduction studies (NCS) over the common peroneal nerves showed the distal motor latency (DML) and motor conduction velocity (MCV) were normal, the compound muscle action potential (CMAP) amplitude was reduced and the F-wave latency was absent. Whereas the tibia nerves conduction studies showed the DML was prolonged, the CMAP amplitude was reduced, the MCV was normal and the F-wave latency was prolonged. Sensory nerve conduction study over the sural nerve showed the distal sensory latency (DSL) and the sensory nerve action potential (SNAP) amplitude were normal. These findings were in keeping with a predominantly axonal motor polyneuropathy (AMAN) variant of GBS.

Based on the available investigations, the temporal relationship with the initiation of CsA, and no other possible causes of GBS, a diagnosis of GBS associated with CsA was made. The CsA stopped upon admission and she was treated with intravenous immunoglobulin (IVIG) 0.4  $\text{mg/kg}$  (25  $\text{mg}$ ) daily for 5 days. She slowly regained her muscles power of the LL to 3/5 to 4/5 distally. All her LL reflexes were improved to 1+. Since she responded to IVIG, plasmapheresis was not offered to her and she continued her physiotherapy as out-patient. However, she was not subjected for a repeat NCS. In term of further management for her PMN, she was started on Mycophenolate mofetil (MMF) and the dose was up-titrated to the best-tolerated dose of 500  $\text{mg}$  twice daily and continued with a tapering dose of oral prednisolone. She manages to achieve partial remission after 3 months of MMF with 24-hours urine protein excretion below nephrotic range and stable at 2-3  $\text{gm}$  per day and her serum albumin was improved to 35-38  $\text{gm/dl}$  with a stable serum creatinine of 100  $\mu\text{mol/L}$ .

## Discussion

CsA has been widely used as the immunosuppressive agent in human recipients of kidney, liver, heart, pancreas, lung and bone

marrow transplantations. It has also been extensively used in the treatment of autoimmune diseases such as in primary biliary cirrhosis, psoriasis, systemic lupus erythematosus and rheumatoid arthritis. Each of these conditions has its own protocols for doses, frequency, target therapeutic levels as well as the concomitant use of other immunosuppressive agents. CsA is calcineurin inhibitor that has immunologic properties that made it attractive as immunosuppressive medications. Calcineurin is a calcium/calmodulin -dependent serine threonine protein phosphatase and inhibition of calcineurin by CsA occurs through the binding to the immunophilin and cyclophilin. The subsequent process is mediated through interleukin-2 that eventually will prevent T cell activations and the immune response [4]. In a normal hepatic and renal function, metabolism of CsA is primarily hepatic with a half-life of 6.4-8.7 hours with less than 1% appearing in the urine or feces and it will also go through metabolism by the cytochrome P450 system. CsA metabolites are eliminated in the bile with less than 5% excreted in the urine [4].

CsA is well known for its nephrotoxic side effects [4]. Other common side effects include gingival hyperplasia, hirsutism, glucose intolerance, and hypertension. It is also demonstrated that usage of CsA increases the risk of neurotoxicity, infection and malignancy such as lympho-proliferative disorder. CsA induces neurological side effects can occur up to 40% of patients [5]. The most common neurotoxicity effects are tremor that can be mild to severe. Mild tremor may resolve spontaneously despite continuing the treatment. Rare side effects of neurotoxicity are a headache, seizures, visual abnormalities, peripheral neuropathy and Guillain-Barre Syndrome (GBS) [5]. Neurotoxicity more frequently occurs with high CsA level, however despite within or below therapeutic range these symptoms may happen and dose reduction or withdrawal is warranted and usually results in resolution of neurological symptoms. In this case, she developed mild tremor that resolves upon withdrawing the drugs however her lower limb weaknesses improvement was delayed that require further management. She does not have other features of adverse events from the CsA used.

GBS or AIDP is an immune-mediated post-infectious polyneuropathy that presents with ascending weakness, loss of deep tendon reflexes and sensation resulting from demyelination of peripheral nerve. Approximately two-thirds of patients with GBS give a history of an antecedent respiratory tract or gastrointestinal infection [6]. It is commonly preceded by *Campylobacter jejuni* infection, however, EBV, CMV, *Mycoplasma*, *Varicella*, retroviral infection, influenza virus also has been reported as an infective cause prior to the development of GBS [7-9]. The mechanism in post-infectious GBS is likely due to immune response towards the infecting organism that cross-react with the ganglioside surface of the neural tissue that will result in acute demyelinating neuropathy [6].

Rare causes of GBS are related to drugs [10]. Drugs such as oxaliplatin and infliximab were reported before [11,12]. CsA associated with GBS is rare and to our knowledge, there are not many case reports on it [13,14]. Amongst the case reports which have been published are of patients who were on CsA post-transplant namely lung, renal and stem cell transplant [13,14]. In one report of a lung transplant patient, CsA induced GBS improved after CsA was switched to tacrolimus and treated with plasmapheresis [13]. Three renal transplant patients who developed CsA neurotoxicity of which one of them was confirmed to be GBS post investigations [14]. The mechanism of drugs induced GBS is believed due to the neurotoxic effects of the drugs that cause damage or apoptosis to the ganglioside of the neurons [15].

Other possible causes of GBS are an autoimmune disease and malignancy. There were reported cases of GBS that associated with lymphoma, ulcerative colitis and also multiple sclerosis [16]. The mainstay of immune-pathologic mechanism, in this case, is also due to destructions of nerve from the circulating immunologic process.

GBS is rarely associated with nephrotic syndrome and the available reported cases of GBS and membranous nephropathy

describes that they occurred simultaneously with the onset of the membranous nephropathy [17,18]. Emsley *et al.* in 2002 published a case of membranous nephropathy that occurred concurrently with sub-acute inflammatory demyelinating polyradiculoneuropathy in a patient with progressive multiple sclerosis [19]. The pathologic mechanism described in both cases was in relation to the antibody-antigen complexes that can deposit both in the glomeruli and nerves and further causes destruction and damage. These immune complexes were responsible for both presentations [18,19]. However the current illustrated case report is a case of GBS that occurred immediately after the introduction of CsA despite PMN remains to unsettle, yet the GBS occurred 12 months later and her symptoms improving with cessation of CsA.

The mainstay of treatment of GBS is related to the likely offending cause. Treatment or removal of the precipitating events is deemed important. GBS patients are treated with a course of immune globulin or plasma exchange and studies have shown they are equally effective [20,21]. In described case, she received a five days course of 0.4 gm/kg/day immune globulin G and she showed gradually neurological improvement. In conclusion, there is still a paucity of information to relate the immediate causal relationship in this case, however, based on the history, timing and exclusion of other possible cause, we believe this case is one of the rare cases of CsA associated with GBS.

## Acknowledgement

We would like to thank Associate Professor Dr. Rozita Mohd, Consultant Nephrologist UKMMC for her guidance in the preparation of this case report, Professor Dr. Abd Halim Abd Gafor (Senior Consultant Nephrologist), and Dr. Kong Wei Yen (Head of Nephrology Unit) UKMMC for their continuous support.

## References

1. Yuki N, Hartung HP (2012) Guillain-Barré syndrome. *N Engl J Med* 366: 2294-2304.
2. Rees JH, Soudain SE, Gregson NA, Hughes RA (1995) *Campylobacter jejuni* infection and Guillain-Barré syndrome. *N Engl J Med* 333: 1374-1379.
3. Rees JH, Gregson NA, Hughes RA (1995) Anti-ganglioside antibodies in patients with Guillain-Barré syndrome and *Campylobacter jejuni* infection. *J Infect Dis* 172: 605-606.
4. Tedesco D, Haragsim L (2012) Cyclosporine: a review. *J Transplant* 2012: 230386.
5. Gijtenbeek JM, van den Bent MJ, Vecht CJ (1999) Cyclosporine neurotoxicity: a review. *J Neurol* 246: 339-346.
6. Hahn AF (1998) Guillain-Barré syndrome. *Lancet* 352: 635-641.
7. Bitan M, Or R, Shapira MY, Mador N, Resnick IB, et al. (2004) Early-onset Guillain-Barre syndrome associated with reactivation of Epstein-Barr virus infection after nonmyeloablative stem cell transplantation. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 39: 1076-1078.
8. Orlikowski D, Porcher R, Sivadon-Tardy V, Quincampoix JC, Raphael JC, et al. (2011) Guillain-Barre syndrome following primary cytomegalovirus infection: a prospective cohort study. *Clin Infect Dis* 52: 837-844.
9. Winer JB, Hughes RA, Anderson MJ, Jones DM, Kangro H, et al. (1988) A prospective study of acute idiopathic neuropathy. II. Antecedent events. *J Neurol Neurosurg Psychiatry* 51: 613-618.
10. Awong IE, Dandurand KR, Keeys CA, Maung-Gyi FA (1996) Drug-associated Guillain-Barré syndrome: a literature review. *Ann Pharmacother* 30: 173-180.
11. Shin IS, Baer AN, Kwon HJ, Papadopoulos EJ, Siegel JN (2006) Guillain-Barre and Miller Fisher syndromes occurring with tumor necrosis factor alpha antagonist therapy. *Arthritis and rheumatism* 54: 1429-1434.
12. Christodoulou C, Anastasopoulos D, Visvikis A, Mellou S, Detsi I, et al. (2004) Guillain-Barre syndrome in a patient with metastatic colon cancer receiving oxaliplatin-based chemotherapy. *Anti-cancer drugs* 15: 997-999.
13. Falk JA, Cordova FC, Popescu A, Tatarian G, Criner GJ (2006) Treatment of Guillain-Barre syndrome induced by cyclosporine in a lung transplant patient. *J Heart Lung Transplant* 25: 140-143.
14. Palmer BF, Toto RD (1991) Severe neurologic toxicity induced by cyclosporine A in three renal transplant patients. *Am J Kidney Dis* 18: 116-121.
15. Peltier AC, Russell JW (2002) Recent advances in drug-induced neuropathies. *Curr Opin Neurol* 15: 633-638.
16. Zimmerman J, Steiner I, Gavish D, Argov Z (1985) Guillain-Barre syndrome: a possible extraintestinal manifestation of ulcerative colitis. *J Clin Gastroenterol* 7: 301-303.
17. Froelich CJ, Searles RP, Davis LE, Goodwin JS (1980) A case of Guillain-Barré syndrome with immunologic abnormalities. *Ann Intern Med* 93: 563-565.
18. Talamo TS, Borochoviz D (1982) Membranous glomerulonephritis associated with the Guillain-Barre syndrome. *Am J Clin Pathol* 78: 563-566.
19. Emsley HC, Molloy J (2002) Inflammatory demyelinating polyradiculoneuropathy associated with membranous glomerulonephritis and thrombocytopenia. *Clinical neurology and neurosurgery* 105: 23-26.
20. van der Meche FG, Schmitz PI (1992) A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barre syndrome. Dutch Guillain-Barre Study Group. *N Engl J Med* 326: 1123-1129.
21. Sharief MK, Ingram DA, Swash M, Thompson EJ (1999) I.v. immunoglobulin reduces circulating proinflammatory cytokines in Guillain-Barre syndrome. *Neurology* 52: 1833-1838.