

## Neutropenia Following Intravenous Immunoglobulin Administration in a Patient with Multifocal Motor Neuropathy with Conduction Block

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### Abstract

Intravenous immunoglobulin (IVIG) is the treatment of choice in patients with multifocal motor neuropathy with conduction block (MMNCB). Although IVIG is considered generally safe, neutropenia following IVIG infusion has been recognized as a rare hematologic side effect. Herein we report a patient with MMNCB who developed severe neutropenia following IVIG administration.

A 41 year old woman presented with progressive weakness of her left lower extremity with frequent muscle cramps. Nerve conduction study revealed marked conduction blocks on right ulnar and right tibial nerves. Serum IgM anti-GM1 antibody was detected. Neutrophil count decreased from day 2 and recovered after 2 weeks following IVIG infusion. To our knowledge, neutropenia following IVIG infusion in MMNCB has never been discussed apart, although it can be an important clinical issue especially for patients with MMNCB.

**Keywords:** Multifocal motor neuropathy with conduction block; Neutropenia; Intravenous immunoglobulin

### Introduction

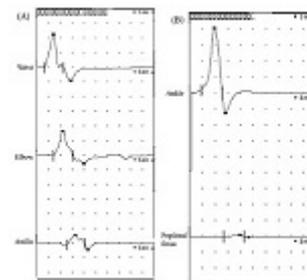
Multifocal motor neuropathy with conduction block (MMNCB) is a rare chronic immune mediated polyneuropathy which prevalence is known to be less than 1 per 100000 [1]. Although rare, if recognized early and properly managed, MMNCB is a treatable condition. MMNCB should be distinguished from other chronic acquired demyelinating polyneuropathy, especially in that MMNCB is resistant to corticosteroid and plasmapheresis [2]. To date, intravenous immunoglobulin (IVIG) administration is the mainstay of MMNCB therapy owing to its excellent safety profile as well as its clinical efficacy [3,4].

Intravenous immunoglobulin is generally considered safe [5], despite hematologic toxicities were recognized in various clinical applications, such as idiopathic thrombocytopenia purpura, systemic lupus erythematosus, pemphigus vulgaris, Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), polymyositis [6]. To our knowledge, leukopenia following IVIG administration in MMNCB has never been discussed apart, although it can be an important clinical issue especially for patients with MMNCB. We report herein a patient with MMNCB who developed leukopenia following IVIG infusion.

### Case Report

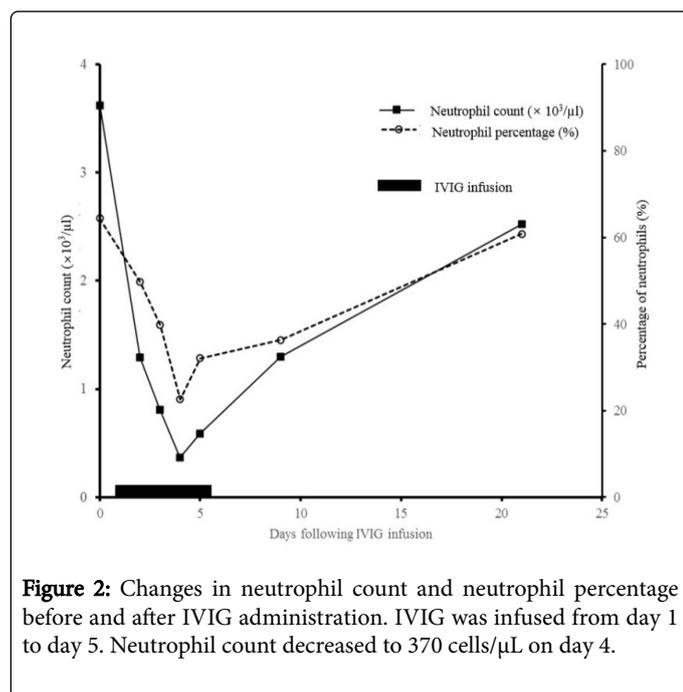
A 41 year old woman visited our hospital complaining of insidious weakness in her left leg, which was worsening from 6 months ago. She had mild difficulty lifting up the left ankle, but it did not interfere with her daily activities. From 2 months before admission, she experienced frequent muscle cramps at night, and the frequency of nocturnal cramps increased over time. The patient denied any sensory symptoms.

Her previous medical history was unremarkable. On neurological examination, motor weakness was confined to her left leg, especially dorsiflexion of great toe and ankle showed Medical Research Council (MRC) grade 4+. Steppage gait was noticed while walking. Sensory examination to all modalities was normal. Deep tendon reflexes including left knee jerk were all within normal limits. Nerve conduction study revealed marked conduction blocks on right ulnar and right tibial nerves (Figure 1), with slowing of motor conduction velocities on left median, right ulnar, left peroneal nerves. Laboratory investigations for rheumatoid factor, antinuclear antibody, anti-Ro/La, anti-neutrophil cytoplasmic antibody, anti-myelin associated glycoprotein antibody, vitamin B12 level, protein electrophoresis and immunofixation electrophoresis showed negative results. Cerebrospinal fluid analysis showed normal protein level without pleocytosis.



**Figure 1:** Nerve conduction study of the patient at presentation. Note the prominent motor conduction block of the right ulnar nerve between elbow and axilla (A) and of the right tibial nerve between ankle and popliteal fossa (B).

Under the diagnosis of MMNCB, the administration of IVIG was initiated (0.4 g/Kg/day for 5 days). White blood cell count began to decrease from day 2 and showed nadir on day 4, reaching absolute neutrophil count of 370 cells/ $\mu$ L. The occurrence of leukopenia was thought to be due to neutropenia, since neutrophil count decreased most prominently, accounting for 22 percent of total leukocytes during nadir (Figure 2). White blood cell count recovered to normal range 2 weeks after completion of IVIG infusion. Serum IgM anti-GM1 antibody was detected at high titer (>100% by enzyme-linked immunosorbent assay; Bühlmann Laboratories, Switzerland), confirming the diagnosis in our patient.



**Figure 2:** Changes in neutrophil count and neutrophil percentage before and after IVIG administration. IVIG was infused from day 1 to day 5. Neutrophil count decreased to 370 cells/ $\mu$ L on day 4.

## Discussion

Since the introduction of IVIG therapy in various immunological diseases, neutropenia was reported as a rare adverse event. Neutropenia following IVIG was initially recognized in patients with idiopathic thrombocytopenia purpura [7,8]. Ben-Chetrit et al. [9] reported a patient with active systemic lupus erythematosus who received two courses of IVIG infusion. Marked neutropenia developed repeatedly after each IVIG course, confirming the association between IVIG infusion and neutropenic event. In the present case, neutropenia developed on day 2 after initiation of infusion and reached nadir on day 4. In line with previous reports [8,10], leukocyte counts of our patient returned to baseline after 2 weeks without any complication.

The mechanism of neutropenia following IVIG remains to be elucidated. Tam et al. [11] reported a child with Guillain-Barre syndrome, in whom the authors revealed the presence of anti-neutrophil antibodies. Some authors suggested roles of atypical anti-neutrophil cytoplasmic antibodies (ANCA) [12,13]. IgG aggregates with immune-complex-like activity was suggested as the cause of transient neutropenia by some researchers [9,14]. Matsuda et al. [10] focused on two factors located in the surface of neutrophils: a complement receptor CD11b and an Fc gamma receptor CD16. Of the two surface antigens, only the level of expression of CD11b was found to be decreased after IVIG. The authors concluded that circulating

neutrophils may adhere to vascular wall with the involvement of CD11b. More recently, von Gunten et al. [15,16] demonstrated that neutropenia was mediated by sialic acid-binding immunoglobulin-like lectin 9 (siglec-9) expressed on neutrophils. IVIG preparations may contain natural autoantibodies to siglec-9 and these autoantibodies can cause neutropenia in both caspase-dependent and independent manner.

The side effect of IVIG in MMNCB, including our case, should not be considered as similar to that seen in other neurological disorders. For instance, IVIG is widely used in GBS patients, but it is not necessary to continue IVIG administration despite side effect such as IVIG-induced neutropenia, since GBS usually does not recur and there are other treatments as plasmapheresis. In CIDP or polymyositis, alternative therapies such as corticosteroid or other immunosuppressive agents are still available. IVIG therapy is unique for MMNCB patients with no suitable alternative, since corticosteroids or plasmapheresis can lead to worsening of the disease and immunosuppressive agent like cyclophosphamide is limited owing to its cumulative toxicity [3]. Furthermore, long-term regular maintenance dosing of IVIG is required in most cases of MMNCB [2]. We found no articles discussing the long-term safety of repeated IVIG administration in patients with IVIG-induced neutropenia. If neutropenia occurs repeatedly, there is always possibility of exacerbating or causing sepsis, and some authors have expressed concerns about using IVIG in these situations [17].

To date, two approaches have been proposed to prevent IVIG-induced neutropenia. First, Matsuda et al. revealed that co-administration of corticosteroids prevented neutropenia following IVIG infusion [10], but that may not be appropriate for patients with MMNCB. Second, subcutaneous immunoglobulin (SCIG) may be an alternative [18,19]. Hadden et al. briefly described the occurrence of IVIG-induced neutropenia in three patients with MMNCB, which resolved after switching to SCIG [20]. We have not been able to administer SCIG in our case because it is not available in Korea. But it seems quite promising for MMNCB patients with previous history of IVIG-induced neutropenia if available.

Neutropenia following IVIG administration has been considered to be transient and self-limited. However, it may be an important clinical issue in MMNCB because long-term IVIG infusions are often required. Further studies on the mechanism of IVIG-induced neutropenia are required to manage patients with MMNCB properly.

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