Ultra-high dose of intravenous immunoglobulin restores strength and motor function in a patient with refractory multifocal motor neuropathy

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Introduction. Multifocal motor neuropathy (MMN) is a chronic progressive immune-mediated neuropathy, predominantly involving upper limbs asymmetrically with electrophysiologic evidence of motor conduction block. The treatment of choice is immunoglobulin (Ig). Nevertheless, some patients may become resistant to treatment. We describe a patient with history of MMN who became resistant to gammaglobulin treatment but markedly improved using ultra-high doses of intravenous immunoglobulin.

Case report. A 36-year-old woman with diagnosis of MMN. After 5 years of clinical stability under subcutaneous Ig (2g/kg/month) the patient developed bilateral weakness involving both hands. Treatment was switched to intravenous Ig 2g/kg/month, nevertheless, she progressed and became totally dependent for activities of daily living. We started ultra-high dose intravenous immunoglobulin 5 g/kg/month, with good response. She became independent for activities of daily living and returned to work. The only treatment related adverse event was headache during infusion.

Conclusion. Ultra-high dose intravenous Ig seems to be a useful therapy in aggressive MMN with severe disability despite conventional treatment. A low cardiovascular risk score (QRISK2 less than 10%) and a daily intravenous Ig lower than 35 g reduce the risk of severe complications related to intravenous Ig.

Key words. Immune-mediated. Immunoglobulin. Inflammatory. Multifocal motor neuropathy. Polyneuropathy. Refractory.

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Introduction

Multifocal motor neuropathy (MMN) is a rare and chronic progressive immune-mediated neuropathy, with a prevalence estimated at 0.6 to 2 per 100,000 population. Classically presents with a progressive, predominantly distal, asymmetric weakness associated to electrophysiological evidence of multifocal motor conduction block.

Anti-GM1 IgM antibodies are identified in at least 40% of patients [1,2]. The treatment of choice is immunoglobulin (Ig) [3]. Most patients require maintenance with intravenous Ig or subcutaneous Ig to prevent clinical worsening. Nevertheless, patients with MMN may present worsening of muscle strength associated to axonal damage over the years despite maintenance treatment with immunoglobulin [4]. In patients that do not respond to intravenous Ig there is lack of good clinical evidence in favor of the use of immunosuppressants such as mycophenolate, steroids, rituximab or eculizumab. Cyclophosphamide may be an alternative option, but with marked adverse effects [3].

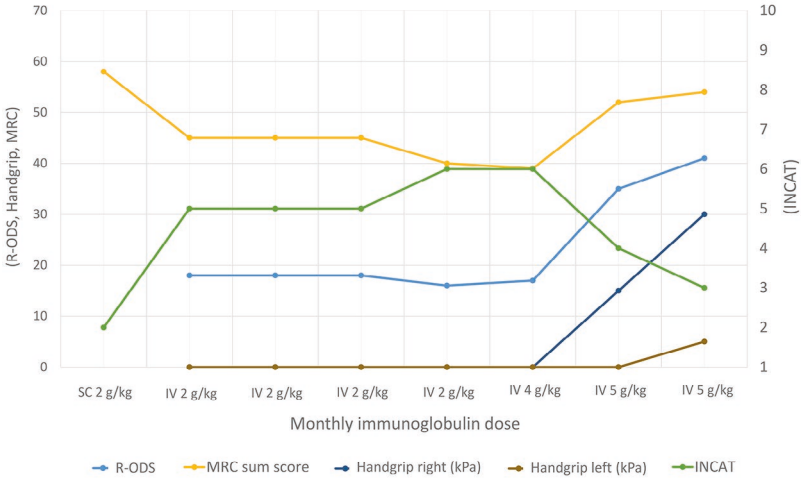
We describe one patient with MMN who became refractory to standard treatment with intravenous Ig but improved markedly using ultra-high dose of intravenous Ig.

Case report

A 36-year-old woman presented 6 years ago with several months of progressive bilateral asymmetric hand weakness, wasting and cramps, right steppage gait and normal sensory examination –Inflammatory Neuropathy Cause and Treatment (INCAT): 4; and Medical Research Council Global Scale (MRC) sum score: 58–. Motor conduction block was identified in the left median nerve 8 cm proximal to the wrist and the ulnar nerve bilaterally distal to the elbow. Anti-GM1 IgM antibody was positive.

With the diagnosis of definite MMN [2] she received intravenous Ig 2 g/kg/month (100 g) for two consecutive months. Her strength improved (INCAT: 2) and she was switched to subcutaneous Ig 2 g/kg/month (100 g) remaining clinically stable. Sev-

Figure. Strength and functional status over time.



INCAT: Inflammatory Neuropathy Cause and Treatment; IV: intravenous; MRC: Medical Research Council Global Scale; R-ODS: Rasch-built Overall Disability Scale; SC: subcutaneous.

eral attempts to reduce subcutaneous Ig regime led to worsening of strength.

After five years of follow up, and despite a stable subcutaneous Ig dose, she worsened and developed marked weakness in both hands without sensory symptoms. She became severely disabled and fully dependent for activities of daily living like dressing, washing, feeding herself and was unable to care for her daughter. (INCAT: 5; MRC sum score: 40; Handgrip Martin Vigorimeter left: 0 kPa, and right: 0 kPa; Rasch-built Overall Disability Scale: 16). She was switched back to intravenous Ig 2 g/kg/month for four months without improvement. Neither prednisone 1 mg/kg during six weeks nor rituximab 375 mg/m^2 in four consecutive weeks were effective.

Based on a recent report [5] we started ultra-high dose of intravenous Ig 4 g/kg/month (200 g) followed by 5 g/kg/month for two months (250 g) fractionated in two cycles every 15 days. Her cardiovascular risk score (QRISK2) was low (6%) [6], and daily intravenous Ig dose never exceeded 35 g/day. The patient progressively improved (MRC sum score: 54; Handgrip left: 5 kPa, and right: 30 kPa; Rasch-built Overall Disability Scale: 41; and INCAT: 3) (Figure).

Patient became independent for activities of daily living and returned to work. The only intravenous Ig-related adverse event was headache during infusion.

Discussion

Our patient with MMN became resistant to standard doses of Ig after five years of stability but she recovered markedly using ultra-high dose of intravenous Ig.

In a recent report six patients, three of them diagnosed with chronic inflammatory demyelinating polyneuropathy and three of them with MMN, initially responsive to immunoglobulin became resistant to standard intravenous Ig doses as well as to other immunosuppressants, presented a marked improvement with ultra-high dose of intravenous Ig [5].

Because there is a risk of serious adverse events related to the use of both standard and high intravenous Ig dosages [5-7], a low QRISK2 score (less than 10%) and a daily intravenous Ig dose lower than 35 g have been suggested to help prevent severe complications [6].

Ultra-high dose of intravenous Ig should be considered as a useful therapeutic alternative for patients with MMN who become refractory to standard Ig doses.

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Dosis ultraaltas de inmunoglobulina endovenosa mejoran la fuerza y la funcionalidad motora en una paciente con neuropatía motora multifocal refractaria

Introducción. La neuropatía motora multifocal (NMM) es una enfermedad crónica, progresiva e inmunomediada que afecta predominantemente a los miembros superiores de forma asimétrica. En los estudios electrofisiológicos se evidencian bloqueos en la conducción motora, y el tratamiento de elección es la inmunoglobulina humana (Ig); sin embargo, algunos pacientes pueden desarrollar refractariedad a este tratamiento. Describimos el caso de una paciente con diagnóstico de NMM que desarrolló refractariedad a la gammaglobulina y que mejoró marcadamente con dosis ultraaltas de esta misma medicación.

Caso clínico. Mujer de 36 años, con diagnóstico de NMM, que, después de cinco años de estabilidad clínica bajo tratamiento con Ig subcutánea en dosis de 2 g/kg/mes, evolucionó con grave debilidad en ambas manos, por lo que se decidió cambiar el tratamiento a Ig endovenosa. No obstante, progresó hasta quedar incapacitada para realizar actividades básicas de la vida diaria. Iniciamos tratamiento con Ig endovenosa en dosis ultraaltas (5 g/kg/mes) con buena respuesta, logrando independencia funcional en las actividades de la vida diaria y que regresara al trabajo. El único evento adverso relacionado con la Ig endovenosa en dosis ultraaltas fue la presencia de cefalea durante la infusión.

Conclusión. La Ig endovenosa en dosis ultraaltas parece ser un tratamiento efectivo para pacientes con NMM y grave discapacidad no respondedores a dosis convencionales. Un bajo índice de riesgo cardiovascular (QRISK2 menor que 10%) y una dosis diaria de Ig endovenosa menor de 35 g reducen el riesgo de complicaciones graves relacionadas con el uso de esta medicación.

Palabras clave. Inflamatoria. Inmunoglobulina. Inmunomediada. Neuropatía motora multifocal. Polineuropatía. Refractaria.