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Clinical Practice Guidelines

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Recommendations for the diagnosis and treatment of multifocal motor neuropathy

Recomendaciones sobre el diagnóstico y tratamiento de la neuropatía motora multifocal

Abstract

Introduction. Multifocal motor neuropathy (NMM) is a rare disease characterized by progressive, distal and asymmetrical weakness in extremities, without sensitivity alterations. This autoimmune disease affects the peripheral nerves, causing demyelination, usually with documentable nerve conduction block by electroneurography.

Objective. To develop a guideline on definition, diagnosis and treatment of the MMN by using the best existing scientific evidence and when not available, expert consensus.

Methods. A group of neurologists from different institutions representing the Mexican sanitary system and pertaining to the Study Group of Neuromuscular Diseases of the Mexican Academy of Neurology met and carried out a MEDLINE and Cochrane systematic search, selecting the best available evidence on diagnosis and treatment and qualifying the recommendations according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. The recommendations are organized into short statements supported by a brief dissertation on the scientific evidence supporting the statements.

Recommendations. This panel recommends testing and diagnostic criteria proposed by the EFNS/PNS (European Federation of Neurological Societies / Peripheral Nerve Society) with minor modifications that are described in the present document. The panel recommends human intravenous or subcutaneous immunoglobulin in the treatment of MMN. Treatment with cyclophosphamide is only recommended as an add-on to immunoglobulin therapy and not as monotherapy. Eculizumab could potentially offer benefits as add-on therapy, but more studies are needed. Rituximab has shown no benefit in studies of greater scientific rigor. Other immunosuppressive or

immunomodulatory agents such as methotrexate, azathioprine, cyclosporine or mofetil mycophenolate have not been shown benefits as monotherapy or add-on therapy, and thus, this panel does not recommended their use in patients with MMN. Plasma exchange offers no benefit and may be associated with clinical deterioration, and therefore its use is contraindicated in patients with MMN.

Keywords

Definition, diagnosis, management, multifocal motor neuropathy, treatment.

Resumen

Introducción. La neuropatía motora multifocal (NMM) es una enfermedad rara que se caracteriza por debilidad progresiva y asimétrica de predominio distal en las extremidades, sin alteraciones de la sensibilidad. Esta enfermedad autoinmune afecta a los nervios periféricos, lo que provoca desmielinización, usualmente con bloqueo de la conducción nerviosa documentable por electroneurografía.

Objetivo. Elaborar una guía sobre definición, diagnóstico y tratamiento de la NMM utilizando la mejor evidencia científica existente y cuando no esté disponible, el consenso de expertos.

Métodos. Un grupo de neurólogos de diferentes instituciones que representan al sistema sanitario mexicano y pertenecientes al grupo de estudio de Enfermedades Neuromusculares de la Academia Mexicana de Neurología, realizaron una búsqueda en MEDLINE y revisiones sistemáticas Cochrane sobre diagnóstico y tratamiento de la NMM, seleccionando la mejor evidencia disponible clasificando la recomendación de acuerdo al sistema GRADE (Grading of Recommendations Assessment, Development and Evaluation). Las recomendaciones se organizan en enunciados breves y una breve disertación sobre la evidencia científica de la que derivaron.

Recomendaciones. Este panel recomienda utilizar las pruebas y criterios diagnósticos propuestos por la EFNS/PNS (European Federation of Neurological Societies/ Peripheral Nerve Society), mismos que son expuestos en este documento con leves modificaciones. El panel recomienda la inmunoglobulina humana intravenosa o subcutánea en el tratamiento de la NMM. El tratamiento con ciclofosfamida sólo es recomendado como terapia de adición a la inmunoglobulina y no como monoterapia de inicio o sustitución. Potencialmente eculizumab podría ofrecer beneficios

Palabras clave

Definición, diagnóstico, manejo, neuropatía motora multifocal, tratamiento.

como terapia de adición, pero se requiere de más estudios. Rituximab no ha mostrado beneficio en estudios de mayor rigor científico. Otros inmunosupresores o inmunomoduladores tales como metotrexate, azatioprina, ciclosporina o micofenolato de mofetilo no han mostrado beneficios como terapia de adición o en monoterapia, por lo que este panel no recomienda su uso en la NMM. El recambio plasmático no ofrece beneficios y podría asociarse a deterioro clínico, por lo que su uso está contraindicado en pacientes con NMM.

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Introduction

Multifocal motor neuropathy (MMN), a disease first described in 1986 by Chad *et al*. and a little later by Roth *et al*.,[1,2] is characterized by progressive and asymmetric weakness, predominantly in the distal extremities, without alterations in sensitivity.[3] It is a rare disease, with a prevalence of 0.2 to 2 per 100,000 people.[4-6] Of autoimmune etiopathogenesis, it affects the peripheral nerves causing demyelination, usually with nerve conduction block (NCB) which can be documented by electroneurography.[7] The presence of IgM anti-GM1 antibodies has been reported in 50% of cases.[8] MMN is not considered a variant of chronic inflammatory demyelinating polyneuropathy (CIDP), although it shares some clinical characteristics and immunopathogenesis.

Since the description of this disease in 1986, several diagnostic criteria have been proposed due to the difficulty establishing its diagnosis and differentiating it clinically from conditions that affect the lower motor neurons, particularly amyotrophic lateral sclerosis (ALS) and immune-mediated polyradiculoneuropathies.[9,10]

The presence of NCB in electroneurography has been the marker of this disease. NCB is defined as a drop in amplitude and the proximal area in relation to the distal area of the nerve studied, in the absence of temporal dispersion and outside the common sites of nerve compression.[11] Its absence, either due to difficulty demonstrating the location of the NCB and/or the lack of sensitivity of routine neuroconduction studies, does not rule it out either.[11-13] The percentage of drop in amplitude and area of nerve conduction that should be considered as a critical threshold for the diagnosis of MMN is a subject that is still under debate.

MMN has limited options for pharmacological treatment. Up to 80% of patients respond to therapy with human immunoglobulin.[11,12,14-18] There are case series and nonrandomized clinical trials that describe variable benefits of other immunomodulatory and immunosuppressive agents such as methotrexate, mycophenolate mofetil, cyclophosphamide, cyclosporine, azathioprine, interferon beta-1a, and rituximab; but with limited results.[3]

Given the uncertainty and scarcity of information regarding this rare disease, this working group has considered it necessary to review the best available scientific information with the purpose of formulating recommendations that can guide the clinician in the diagnosis and treatment of MMN. It is important to note that a clinical practice guide is not a substitute for the best clinical judgment. Not all possible clinical scenarios get to be observed in a clinical trial or observational study, and therefore, also do not get reported in a guide.

Methods

A working group formed by clinical neurologists with knowledge and interest in neuromuscular diseases was convened. Questions and topics about the diagnosis and treatment of MMN were proposed, leading to a consensus for a work schedule to be tackled in a 12-hour face-to-face session distributed throughout a day and a half. Prior to the face-to-face meeting, the topics and clinical questions were circulated among the participating clinical panelists to be developed and answered in two working groups. The members of the working groups systematically formulated the answers to the questions according to the recommendations of the GRADE system (Grading of Recommendations Assessment, Development and Evaluation) (Table 1).[19-21] This system consists mainly of a series of steps to organize the answers to clinical questions of interest, particularly regarding diagnosis and treatment. It focuses principally, but not exclusively, on qualifying the quality of the evidence and formulating a recommendation structured in a succinct statement, which is properly the answer to the clinical question posed. The working group agreed to use the GRADE system in order to systematize

the development of the document and evaluate the evidence in order to offer the user of the guide certainty about the knowledge that supports each recommendation. However, the group is aware that no system for classifying evidence is perfect and that none has been scientifically and properly proven as better to support using over the other systems. This method has been chosen, however, because it is widely used today and because its strength lies in providing texts that are easy to understand without excessive use of technicalities. The working group formulated recommendations for clinical practice based on evidence that provides a systematic review, with which semi-axiomatic principles on health care were formulated, considering equally the judgments about the perceived risk-benefit ratio and costs of interventions as well as the values and preferences of patients.

MEDLINE was searched for articles on MMN with specific keywords and MeSH terms in the English language related to study design, treatment, and disease, as follows:

#1. Multifocal motor neuropathy
#2. Conduction block
#3. MMN
#4. Diagnosis
#5. Treatment
#6. Therapy
#7. Trial
#8. Clinical trial
#9. Controlled trial
#10. Randomized clinical trial
#11. Guideline
#12. Open label study
#13. Observational study
#14. #1 AND #2
#15. #2 AND #3
#16. #1 AND #4
#17. #3 AND #4
#18. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#19. #8 OR #9 OR #10 OR #11 OR #12
#20. #13 OR #14 OR #15
#21. #16 AND #17 AND #18

No date restrictions were applied to the searches. Additionally, reference lists of the selected relevant articles were searched manually. The evidence and recommendations were classified according to the GRADE system (Table 1). When only very low quality evidence was found (opinions from other expert panels, clinical anecdotes, or the working group's own experience), an attempt was made to reach a consensus by the team and, therefore, the recommendations are classified as "good practice points."

The statements were reviewed one by one by all members of the working group and were compiled into a single document that was then reviewed iteratively until consensus was reached. Once consensus was reached on the final version of the document, it was prepared with the format required by the standards for journal authors, and the last version was distributed via email for the review and approval of the group members. The references and the complete texts were deposited in a specially created web repository, which can be freely consulted by readers. (*http://editor.manuscript-manager.com.mx/GPC_NMM*).

Table 1. Description of the GRADE rating system (Grading of Recommendations Assessment, Development and Evaluation) for the classification of scientific evidence available to answer clinical questions relevant to diagnosis and treatment.

Strength of the recommendation	Implications
1 (strong)	Strong recommendation. The benefits of the action clearly outweigh the disadvantages. This is independent of the quality of the evidence that supports this recommendation.
2 (weak)	Weak recommendation. The benefits of the action are similar to the disadvantages. This is independent of the quality of the evidence that supports this recommendation.
Quality of evidence	**Implicaciones**
A (high)	It is unlikely that future studies will change the degree of confidence in the results or the data that is already available (i.e., no more studies are needed).
B (moderate)	It is likely that new studies will change the degree of confidence in the data that make up the recommendation.
C (low)	It is highly probable that new studies change the degree of confidence in the data that make up the recommendation (i.e., more studies are recommended).
D (very low)	Any estimate of the benefit/harm of an intervention or action is very uncertain (i.e., studies are necessary).
Good practice point	Only the opinions of other expert panels, clinical anecdotes, or the experience of the working group are available. In this type of recommendation, the working group offers its opinion without qualifying the level of evidence (since it is non-existent) or the strength of the recommendation. Nor is it inclined to propose that scientific studies are needed to clarify this recommendation, although it does not oppose the realization of them.

Results

Diagnosis

This panel recommends the use of the clinical and electrophysiological EFNS/PNS diagnostic criteria, classifying the cases as definite, probable, or possible MMN, according to the level of certainty reached by applying the criteria. (Strong recommendation, high quality of evidence: 1A)

The typical patient with MMN presents with progressive or escalating chronic weakness of the upper limbs, predominantly distal and asymmetric, without sensory or upper motor neuron (first motor neuron) alterations.[11-13] The different diagnostic criteria proposed internationally share the following characteristics: predominantly distal weakness, asymmetric and of slow progression, without objective evidence of sensory alteration and with distribution in two or more nerves, as well as the absence of upper motor neuron signs (Table 2). Some clinical signs of lower motor neuron (second motor neuron) such as muscle atrophy, cramps, and fasciculations make it difficult to distinguish from motor neuronopathy (i.e., ALS and other variants of motor neuron disease), which makes it essential that the clinical criteria always include electrodiagnostic studies to document (Table 3).

Table 2. Criteria for the clinical diagnosis of multifocal motor neuropathy (MMN).

Major clinical criteria[a]
1. Weakness of the extremities that progresses slowly or escalating, in a focal and asymmetric way, affecting at least the distribution of two motor nerves for more than 30 days.[b]
2. Absence of objective sensory alterations, except for slight abnormalities in the perception of vibrations in the lower extremities.
Criteria that support diagnosis
3. Prevalence in upper limbs.
4. Muscle stretch reflexes diminished or absent in the affected sites.
5. Absence of alteration of the cranial nerves.
6. Cramps and fasciculations in the affected sites.
Criteria that exclude the diagnosis
7. Signs of upper motor neuron.
8. Signs of bulbar involvement.
9. Marked sensory condition.[c]
10. Diffuse and symmetric weakness in the first weeks after onset of disease.
11. Hyperproteinorrachia > 100 mg/dL.

[a] Both must be present (see table 4 for diagnostic integration).
[b] If the signs and symptoms are present only in the distribution of one nerve, the diagnosis of possible MMN can be carried out.
[c] Sensory alterations more marked than a slight hipopalestesia in the distal portion of the lower extremities.

Table 3. Criteria for neurophysiological diagnosis in multifocal motor neuropathy (MMN).

1. Nerve conduction block definite
Negative peak area reduction of the proximal compound muscle action potential by 50% against the distal, independently of the stimulated nerve (median, ulnar, or peroneal).
2. Nerve conduction block probable
Negative peak area reduction of the proximal compound muscle action potential by 30% against the distal in an upper extremity, with an increase ≤30% in the duration of the negative peak of the proximal compound muscle action potential in relation to the distal.
Or:
Negative peak area reduction of the proximal compound muscle action potential by 50% versus the distal one in an upper extremity, with an increase >30% in the duration of the negative peak of the proximal compound muscle action potential in relation to the distal.
3. Normal sensory nerve conduction studies in segments of the upper extremity that present nerve conduction block

It has been documented there is a mild to moderate increase in creatine kinase levels in MMN that usually affects slightly more than half of patients and is usually no more than two to three times the upper limit of normality of this biomarker.[22] In the CSF analysis, the presence of hyperproteinorrachia lower than 100 mg/dL is observed in a third of the cases, with values usually around 80 mg/dL. Hyperproteinorrachia higher than 100 mg/dL does not exclude MMN, but it suggests there should be a differential diagnosis or the concomitance with another nosological process. In serum protein electrophoresis and immunofixation, the presence of monoclonal and polyclonal gammopathy has been documented, with IgM gammopathy in 20% of cases. The most typical finding in MMN is the presence of high levels of IgM anti-GM1 antibodies; however, it is possible to find low titers of antibodies against other gangliosides such as GM2, GD1a, and GD1b (Table 4). There are differences in the prevalence of anti-GM1 antibodies, with frequencies that fluctuate from 30% to 80% of cases.[23,24] If present, titers of these antibodies are usually above 10 times the normal value. Lower levels are nonspecific and can be found in other dysimmune neuropathies and in motor neuron disease. The latter has been misinterpreted and it is not uncommon to find centers that almost routinely request anti-GM1 levels from patients if they suspect ALS. This practice is incorrect and may result in patients with MMN (a treatable entity) to be misdiagnosed with ALS (an orphan entity).

In nuclear magnetic resonance (NMR) imaging of the brachial plexus it has been possible to observe the presence of abnormalities in the nerve trunks characterized by a hyperintense signal in the T2-weighted sequence and reinforcement in T1 after gadolinium administration.[25-27] Unlike CIDP, an asymmetric pattern of these alterations is common in MMN.[25] Ultrasound of the peripheral nerve and at the level of the cervical roots is related to an increase in the transversal area of the nerve (i.e., focal thickening) in areas not susceptible to entrapment.[28-30] High-resolution peripheral nerve ultrasound may be particularly useful in cases that do not show NCB in electroneurography, supporting the notion that no evidence of NCB does not mean that it's not there (i.e., the absence of evidence is not evidence of absence). The role of nerve imaging is still to be defined.[29]

Nerve biopsy is rarely useful in diagnosis. Pathological studies are often normal or may show axonal degeneration or mild demyelination. In motor nerve biopsy, demyelination can be observed with onion bulb pattern (demyelination-remyelination). Other findings described include endoneurial edema, mononuclear cell infiltration, myelinated fiber population reduction, and multifocal degeneration.[3,7]

With the diagnostic resources described above, three levels of certainty have been categorized (Table 5). Thus, with the integration of the clinical judgment, the information provided by the electroneurography, and the other diagnostic aids, it is possible to define a case of MMN and, above all, to reasonably distinguish it from other entities.

Traditionally, the typical case of MMN was a patient with progressive and asymmetrical limb weakness, predominantly distal in the distribution of at least two motor nerves, without sensory alterations, with demyelination data in electroneurography, and with demonstrable conduction block in at least one nerve. Now, three levels of certainty have been organized for the diagnosis of MMN as definite, probable, and possible. This has allowed to classify more patients eligible for treatment and to distinguish them from other conditions, such as the motor neuron diseases group.

Differential diagnosis

Given the asymmetrical weakness characteristic of MMN, which mainly involves the distal muscle groups, it is important to first consider within the differential diagnosis the pathological entities included within the heterogeneous spectrum of hereditary or acquired motor neuron diseases such as classic ALS, progressive muscular atrophy, and spinal muscular atrophy, among others

Table 4. Auxiliary diagnostic criteria in multifocal motor neuropathy (MMN).

Auxiliary criterion
1. Elevation of IgM anti-GM1 antibodies.
2. Increase in cerebrospinal fluid proteins (increase not higher than 100 mg/L).
3. Magnetic resonance imaging of the brachial plexus with T2 hyperintensity.
4. Objective improvement after treatment with immunoglobulin.

Table 5. Integration of clinical and paraclinical evidence into diagnostic categories of multifocal motor neuropathy (MMN).

Multifocal motor neuropathy definite
Clinical criteria 1 and 2 from Table 2, without clinical exclusion criteria 7-11 and the presence of electrophysiological criteria 1 and 3 from Table 3 in at least one nerve.
Multifocal motor neuropathy probable
Clinical criteria 1 and 2 from Table 2, without clinical exclusion criteria 7-11 and the presence of electrophysiological criteria 2 and 3 from Table 3 in at least two nerves.
Clinical criteria 1 and 2 from Table 2, without clinical exclusion criteria 7-11 and electrophysiological criteria 2 and 3 from Table 3 in one nerve and at least two support criteria from Table 4.
Multifocal motor neuropathy possible
Clinical criteria 1 and 2 from Table 2 without clinical exclusion criteria 7-11, with normal sensory nerve conduction studies and support criteria 4 from Table 4.
Clinical criterion 1 in a single nerve and criterion 2 in Table 2 without clinical exclusion criteria 7-11, with electrophysiological criteria 1 or with electrophysiological criteria 2 and 3 from Table 3 in one nerve.

(Table 6). MMN can mimic the early symptoms of ALS or its variants,[31] particularly in cases of neuronopathy with predominantly lower motor neuron type presentation. However, the presence of hyperreflexia, spasticity, extensor plantar response, pseudobulbar affect, and respiratory compromise should suggest neuronopathy instead of neuropathy. Only isolated cases of hyperreflexia have been reported in MMN, so this should in no way be understood as a typical scenario.[32] Respiratory distress due to phrenic nerve paralysis[33] as well as hypoglossal nerve palsy have also been reported very infrequently.[34] It is important to emphasize that the presence of these signs should discard other entities and only when they are discarded can the MMN diagnosis be considered, but only if the neurophysiology studies are compatible. Too many exceptions to the typical clinical presentation in rare diseases usually results in a different diagnosis when an appropriate approach of the differential is made. The differential diagnosis with lower motor neuron diseases can become complex, particularly in advanced stages and without specific treatment. In these cases, a nerve conduction study that shows signs of demyelination with or without NCB outside of nerve compression sites is highly suggestive of MMN.[11,12] On the other hand, when there is evidence of axonal involvement in the electrodiagnostic studies, this could suggest motor neuron disease. The asymmetric character of the clinical manifestations and the electrophysiological alterations that is limited to territories corresponding to individual nerve trunks, rather than to a myotomic distribution, should maintain the suspicion of MMN, although the asymmetry may be less evident with the chronic course of the illness.[3,7] Clinically, it has been suggested that the asymmetric weakness of the common extensor

digitorum muscle is a typical but not necessarily pathognomonic pattern of MMN.[13]

Autoimmune polyradiculoneuropathies, especially the asymmetric form of CIDP, the Lewis-Sumner syndrome also known as multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy, as well as the purely motor variant of CIDP, constitute another group of entities that in the clinical context and in the presence of NCB may pose a challenge in the differential diagnosis with MMN. During the course of the disease, approximately 20% of patients with MMN develop sensitive alterations; however, these are not a predominant complaint and it is not an initial symptom, unlike MADSAM.[35-37] The main sensory disturbances are mild and in the perception of vibration, and apalestesia or positive sensory symptoms such as pain are rare, although some patients may report paraesthesia. On the other hand, the pure motor variant of CIDP also tends to present itself with a symmetric pattern of weakness. In these cases of difficult differential diagnosis, the finding of high titers of IgM anti-GM1 antibodies, as well as the absence of hyperproteinorrachia (or a slight increase in proteins) can help establish the diagnosis of MMN.[35,38] Another notable difference from other immune-mediated neuropathies is the lack of clinical response to steroid management and/or plasma exchange that characterizes patients with MMN. So far it is unknown whether MMN and MADSAM are part of the clinical spectrum of the same disease.

The differential diagnosis includes other pathological entities such as neuropathies due to entrapment and hereditary neuropathy liable to pressure paralysis.[7,38] Both of these usually coexist with sensory manifestations, Tinel's sign, and conduction abnormalities in compression sites, unlike MMN.[35]

Table 6. Main differential diagnoses of multifocal motor neuropathy (MMN).

	MMN	CIDP	Lewis-Sumner syndrome	ALS	Lower motor neuron disease
Clinical features					
Typical distribution of weakness	Asymmetric	Symmetric	Asymmetric	Asymmetric	Asymmetric
Course of the disease	Slowly progressive	Progressive or recurrent	Progressive or recurrent	Quickly progressive	Slow or rapidly progressive
Prominent sensory symptoms	No	Yes	Yes	No	No
Muscle stretch reflex	Normal or decreased in paretic muscles	Generalized hyporeflexia or areflexia	Decreased in paretic muscles	Increased or decreased in paretic muscles	Decreased in paretic muscles
Paraclinical characteristics					
Marked hyperproteinorrachia	No	Yes	Rare	No	No
High titers of IgM anti-GM1 antibodies	Common	Rare	Rare	Rare	Rare
Focal thickening outside of compression sites in peripheral nerves that can be examined by ultrasound	Present	Present	Present	Absent	Absent
Abnormal sign in magnetic resonance of the brachial plexus	Asymmetric	Symmetric	Asymmetric	No	No
Response to intravenous immunoglobulin	Yes	Yes	Yes	No	No
Response to steroids	No	Yes	Yes	No	No

Treatment

Intravenous immunoglobulin

In adults with MMN, this panel recommends the use of intravenous human immunoglobulin as first-line therapy to improve symptoms related to muscle weakness with possible decline in disability. (Strong recommendation, moderate quality of evidence, 1B)

LMMN has limited options for pharmacological treatment, although up to 80% of patients respond to polyvalent human immunoglobulin therapy. There are case series and nonrandomized clinical trials demonstrating variable benefits of other immunomodulatory and immunosuppressive agents such as mycophenolate mofetil, cyclophosphamide, cyclosporine, azathioprine, interferon beta-1a, and rituximab, although with questionable results.[30] Unlike other immune-mediated neuropathies such as CIDP, there is no benefit in MMN with the use of steroids.[39]

Though there is no general consensus, intravenous immunoglobulin therapy (IVIG) is typically divided into two types: induction and maintenance. IVIG induction therapy for patients with MMN is initiated at a standard dose of 2 g/kg of body weight in 2 to 5 consecutive days, followed by individually tailored maintenance infusions ranging from 0.4 g/kg once a week at 1-2 g/kg every 2-8 weeks for 6 months. The infusion rate regularly ranges from 150 to 200 ml/hour. The duration of therapy depends on the patient's clinical response.[39]

There have been no clinical trials comparing the efficacy and safety of lyophilized immunoglobulin versus the liquid presentation. Nor have the different maintenance schemes been compared. There are four randomized controlled clinical trials with a total of 45 patients gathered in a Cochrane systematic review treated with IVIG versus placebo.[40] For the outcome of muscle strength improvement, it was concluded that IVIG is superior to placebo, with two as the necessary number to treat to observe a patient experience improvement in strength. A third of the patients had remission for more than 12 months. Half of them required repeated infusions, and half of them received additional immunosuppressive therapy. Possibly due to the development of axonal degeneration, the clinical benefit of IVIG may decline over time even when the dose is increased.[39] In another retrospective study, it was observed that in treatments with high doses of 1.6-2.0 g/Kg during 4 to 5 days, IVIG promoted reinnervation and prevented axonal degeneration for up to 12 years or more.[41] A prospective study of 37 patients with MMN and treated with immunoglobulin found that the non-responders had a greater decrease in the distal mean amplitudes in the neuroconduction studies than in the responders, possibly due to the presence of axonal degeneration, so it is possible that neurophysiological diagnostic criteria have a predictive value of response to IVIG, although this should be further examined in the future.[42] Another double-blind placebo-controlled study included 19 patients who were grouped into those who had never received IVIG, and those who had previously received treatment and symptoms recurred. A therapeutic benefit was demonstrated, taking as a primary point the evaluation of muscle strength.[43] Treatment with IVIG does not modify the anti-GM1 antibody titers even in the presence of clinical benefit, so its determination has no role in monitoring the clinical response. In a study of 24 patients with MMN treated with immunoglobulin, it was found that patients with little or no atrophy presented a greater and more sustained therapeutic response than those with evident muscular atrophy.[44] The maximum duration of the clinical benefit of an isolated cycle of infusion with IVIG was evaluated and it was determined that it rarely lasts more than three months, so the majority of patients depend on monthly infusions and others even need them weekly.[45]

Since it has recently been shown that an increase in IgG levels after administering IVIG in patients with Guillain-Barré syndrome has been associated with response to treatment, this notion is being explored in patients with MMN treated with IVIG. In one study, 23 patients with MMN were recruited and 17 of them had a good clinical response that was associated with high levels of total serum IgG compared to non-responders, so pharmacokinetic

variations could be associated with clinical response in patients with MMN.[46]

Subcutaneous immunoglobulin

In adults with MMN, this panel recommends the use of subcutaneous human immunoglobulin as an alternative to intravenous in maintenance therapy to improve symptoms related to muscle weakness. (Strong recommendation, low quality of evidence, 1C)

Scientific information about subcutaneous immunoglobulin in the treatment of MMN is still extremely scarce and focused on maintenance treatment, not as induction therapy.[47-49] Subcutaneous immunoglobulin infusion has been shown to be safe, feasible, and as effective as traditional intravenous infusion.[50] The advantage of this modality is that it can be administered at home by the patients, after initial training. Potential disadvantages include pain and reactions at the infusion site, since its volume is relatively high compared to other subcutaneous administration therapies. Self-administration at home and the prevention of lost work time reduces direct and indirect costs. Systemic adverse events occur in less than 1% of cases. Another advantage is that this immunoglobulin administration method produces stable concentrations of IgG. The subcutaneous dose should be the same as the intravenous dose, weekly or twice a week, depending on the size of the dose.[49]

Cyclophosphamide

For adults with MMN, this panel does not recommend the use of cyclophosphamide as first-line therapy. Due to the potentially serious effects, treatment should be reserved for patients with severe and progressive conditions who do not respond to IVIG or have a dependency to it. (Weak recommendation, low quality of evidence: 2C)

Pestronk *et al*. were the first to describe that MMN is very frequently associated with high levels of anti-ganglioside GM1 antibodies in serum and that it usually responds effectively to treatment with high doses of cyclophosphamide.[51] Treatment with cyclophosphamide as a second-line treatment after failure with IVIG has been associated with improvement of muscle strength, in most cases within the first two to six months after starting treatment.[51,52] A sustained improvement can be observed after its suspension and in some cases remission of up to two years, although there have been reports of worsening after its suspension and other cases without appreciable clinical improvement. Treatment with cyclophosphamide has been related to a decrease in IgM anti-GM1 levels and improvement of NCB. However, its use has been limited by its potentially serious adverse effects, with descriptions of fatal cases and abandonment of treatment, which makes its long-term use unfeasible.[51-53]

Eculizumab

For adults with MMN, this panel does not recommend the use of eculizumab as first-line therapy. (Strong recommendation, low quality of evidence: 2C). As adjunctive therapy to immunoglobulin, the available information is still insufficient to recommend the use of eculizumab. (Weak recommendation, low quality of evidence: 2C)

Given that in the pathogenesis of MMN the damage to the peripheral nerve potentially exerted by antiganglioside autoantibodies is mediated by complement, the inhibition of this mechanism could have a clinical effect in patients with MMN. Eculizumab is a monoclonal antibody that blocks complement factor C5, which prevents the terminal activation of the complement cascade and the membrane lysis imposed by the membrane attack complex.[3,30,51] In an open clinical trial of proof of concept in 13 patients with MMN receiving concomitant IVIG, a small but appreciable strength improvement was observed after 14 weeks of treatment with eculizumab. An improvement in neurophysiological characteristics was also observed with a minimum of adverse effects.[54] This clinical trial presents a tempting challenge for the use of complement inhibitors in MMN.

Rituximab

For adults with MMN, this panel does not recommend the use of rituximab as first-line therapy or as adjunctive therapy to immunoglobulin. (Strong recommendation, low quality of evidence: 2C)

Since MMN is an autoimmune disease mediated by autoantibodies, it rather requires testing anti-CD20 therapy in order to decrease the population of plasma cells and thereby the production of said antibodies. Although in a few cases a potential benefit of rituximab has been suggested as an added therapy to IVIG[55] or change in monotherapy[56] in patients with refractory disease, a small open-label study failed to show that adding rituximab to the therapy results in clinical or neurophysiological improvement.[57] Therefore, up to now, it is not recommended to offer this therapy to patients with MMN, given its scarce or nil benefit in contrast to its high cost and potential adverse effects.

Mycophenolate mofetil

For adults with MMN, this panel does not suggest the use of mycophenolate mofetil as monotherapy or adjunctive therapy to intravenous immunoglobulin for the improvement and stabilization of motor disability with reduction of dose and/or frequency of administration of IVIG. (Weak recommendation, moderate quality of evidence: 2B)

Although mycophenolate mofetil has been used anecdotally in the immunosuppressive treatment of MMN associated with IVIG, its role has only been evaluated in a clinical trial that was negative. Mycophenolate mofetil was not associated with improvement of strength, functionality, or a reduction of IVIG dose.[52] Given that this immunosuppressant acts mainly as a steroid saver in other autoimmune diseases, and given that steroids have no clinical role in MMN management, this may help to explain why mycophenolate mofetil offers no advantage in the management of MMN.

Azathioprine, cyclosporine, and methotrexate

For adults with MMN, this panel does not recommend the use of immunosuppressants such as azathioprine, cyclosporine, and methotrexate in monotherapy or adjunctive therapy to intravenous immunoglobulin, for the improvement and stabilization of functional status with reduction of dose and/or frequency of administration of IVIG. (Weak recommendation, low quality of evidence: 2C)

In MMN, the efficacy of intravenous immunoglobulin and cyclophosphamide has been observed, however, the transitory effect of the former and the toxicity of the latter have forced a search for alternative therapies. At the moment there are few studies. Most of them are a series of cases and reports of isolated patients, but few are controlled and randomized trials involving other immunosuppressive agents such as azathioprine, methotrexate, or cyclosporin.[51,52] These drugs have been used mostly as adjunctive therapies in order to reduce the dose and/or frequency with which intravenous immunoglobulin is administered in patients with management failure or who depend on IVIG frequently, and have rarely been used as initial therapy. The results have been inconsistent. There were isolated cases of motor disability improvement with cyclosporine and azathioprine, the latter as adjunctive therapy with steroids, resulting in important doubts about the appropriate diagnosis of the patients who received it or the scientific rigor employed. The administration of methotrexate in a single uncontrolled trial allowed the reduction of the dose and, in one case, the suspension of intravenous immunoglobulin; however, in most cases, its administration was suspended due to the appearance of adverse effects.[51,52]

Steroids

For adults with MMN, this panel does not recommend the use of steroids for the improvement of disability related to the disease. (Strong recommendation, very low quality of evidence: 1D

The treatment with steroids for patients with MMN has been tried for decades, whenever the advance in knowledge of its etiopathogenesis has allowed establishing dysimmunity as a fundamental process.58,59 This management, however, comes from experiences in few patients or anecdotes, which, in the best of cases, allowed us to establish that the use of steroids in their various pharmacological forms do not offer any appreciable clinical benefit, with an increased risk of clinical worsening.60,61 This fact has contributed to establishing essential etiopathogenic differences with CIDP. Consequently, this panel has agreed that the use of steroids in MMN is contraindicated.

Plasma exchange

For adults with MMN, this panel does not recommend the use of plasma exchange for the improvement of disability related to the disease. (Strong recommendation, very low quality of evidence: 1D)

There are fundamental differences between the procedure known as plasmapheresis and plasma exchange. The procedure by which a relatively large volume of blood plasma is extracted and replaced with a similar volume is known as plasma exchange.[62,63] This procedure has been studied poorly in patients with MMN, but from the little evidence available it can be concluded that plasma exchange does not offer any tangible benefit in the functional improvement of patients with MMN.[63-67] Furthermore, there is evidence derived from small observational studies or case reports that suggest that this intervention could be associated with a greater probability of adverse outcomes.[65] Therefore, the working group does not recommend that patients with MMN be treated with plasma exchange, since this therapeutic option has not shown benefits and could be associated with a worse outcome.

Context of this guide

As far as we know, this document represents the first clinical practice guide on the diagnosis and treatment of MMN using a system evaluating the quality of evidence and strength of recommendation, with the participation of members of various Mexican institutions. Although the evidence supporting previous international guidelines is analyzed and minor modifications are made regarding the diagnostic criteria, in its text it gathers, orders, summarizes, and combines the best available evidence in a clear and simple format in order to reduce the variability of clinical practice in the management of MMN. Its original design similarly weighs the diagnosis and treatment, fostering in one way the encounter between research and clinical practice by stating the quality of the available evidence and, in another way, improving the quality of health service management. Efforts have been made to minimize the controversy, guaranteeing as much as possible the diagnostic criteria of MMN to avoid confusion among readers and because we genuinely found few reasons to propose changes to international recommendations on the diagnosis of this entity. The most notable changes in this document that contrast with previous international recommendations are with respect to treatment, clarifying whether there is clear evidence regarding the use of second-line pharmacological therapies.

Research recommendations

This panel identified the need to research the use of combination therapy to optimize the management of MMN. Additionally, with advances in the understanding of the pathogenesis of this entity, it would be possible to propose specific therapies to target a key phenomenon in the development and progression of this autoimmune disease. More studies are required in extreme age groups, although there are few cases, in addition to markers of response to treatment and progression of the disease. In addition, the high variability of treatments, doses, schedules, and administration pathways makes standardization and comparison with different therapeutic maneuvers complex and laborious, partly explained by the heterogeneity of the disease. The role of rescue therapies and second-line therapies should be evaluated, as well as different physical therapy techniques and multimodal treatments with traditional objective outcomes that are different (or added) to the overall satisfaction of the patient.

Guide synopsis

1. This panel recommends the use of the clinical and electrophysiological EFNS/PNS diagnostic criteria, classifying the cases as definite,

probable, or possible MMN, according to the level of certainty reached by applying the criteria. (Strong recommendation, high quality of evidence: 1A)

2. In adults with MMN, this panel recommends the use of intravenous human immunoglobulin as the first line of treatment to improve symptoms related to muscle weakness with a possible reduction of disability. (Strong recommendation, moderate quality of evidence, 1B)
3. In adults with MMN, this panel recommends the use of subcutaneous human immunoglobulin as an alternative to intravenous in maintenance therapy to improve symptoms related to muscle weakness. (Strong recommendation, low quality of evidence, 1C)
4. For adults with MMN, this panel does not recommend the use of cyclophosphamide as first-line therapy. Due to the potentially serious effects, treatment should be reserved for patients with severe and progressive symptoms who do not respond to IVIG or with a dependency to it. (Weak recommendation, low quality of evidence: 2C)
5. For adults with MMN, this panel does not recommend the use of eculizumab as first-line therapy. (Strong recommendation, low quality of evidence: 2C) As adjunctive therapy to immunoglobulin, the available information is still insufficient to recommend the use of eculizumab. (Weak recommendation, low quality of evidence: 2C)
6. For adults with MMN, this panel does not recommend the use of rituximab as first-line therapy or as adjunctive therapy to immunoglobulin. (Strong recommendation, low quality of evidence: 2C)
7. For adults with MMN, this panel does not suggest the use of mycophenolate mofetil as monotherapy or adjunctive therapy to intravenous immunoglobulin for the improvement and stabilization of motor disability with reduction of dose and/or frequency of administration of IVIG. (Weak recommendation, moderate quality of evidence: 2B)
8. For adults with MMN, this panel does not recommend the use of immunosuppressants such as azathioprine, cyclosporine, and methotrexate in monotherapy or adjunctive therapy to intravenous immunoglobulin, for the improvement and stabilization of functional status with reduction of dose and/or frequency of administration of IVIG. (Weak recommendation, low quality of evidence: 2C)
9. For adults with MMN, this panel does not recommend the use of steroids for the improvement of disability related to the disease. (Strong recommendation, very low quality of evidence: 1D)
10. For adults with MMN, this panel does not recommend the use of plasma exchange for the improvement of disability related to the disease. (Strong recommendation, very low quality of evidence: 1D)

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Conflicts of interest

There are no potential conflicts of interest for any of the authors in this scientific report.

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