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# Clinical practice guide

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## Recommendations for the diagnosis and treatment of chronic inflammatory demyelinating polyneuropathy

Recomendaciones sobre el diagnóstico y tratamiento de la polineuropatía desmielinizante inflamatoria crónica

## Abstract

**Introduction.** Chronic inflammatory demyelinating polyneuropathy (or *polyradiculoneuropathy*, CIDP) is an uncommon entity of very heterogeneous clinical behavior, but susceptible to treatment. Several proposals on electrophysiological diagnostic criteria exist as well as numerous studies on the response to immunomodulatory treatments. The general consensus about its diagnosis and management, however, has not been reached in Mexico through its major health institutions.

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

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

**Recommendations.** This panel recommends testing and diagnostic criteria proposed by the EFNS/PNS (*European Federation of Neurological Societies / Peripheral Nerve Society*) that are described in the present document. For treatment aspects, this panel recommends intravenous immunoglobulin or steroids as first line treatment for the classical sensorimotor forms of CIDP, immunoglobulin exclusively for pure motor forms and plasma exchange in case of treatment failure

or incomplete response to immunoglobulin or steroids. In case of inappropriate response or required high doses or long periods of first-line drugs, immunomodulatory adjuvant therapy should be considered alone or in combination.

## Keywords

*Clinical practice guideline, chronic inflammatory demyelinating polyradiculoneuropathy, definition, diagnosis, management, treatment.*

# Resumen

**Introducción.** La polineuropatía (o también *polirradiculoneuropatía*) desmielinizante inflamatoria crónica (PDIC) es una entidad infrecuente, de comportamiento clínico muy heterogéneo, pero susceptible de tratamiento. Existen varias propuestas sobre los criterios de diagnóstico electrofisiológico, así como numerosos estudios sobre la respuesta a tratamientos inmunomoduladores. El consenso general sobre su diagnóstico y manejo, sin embargo, no se ha alcanzado en México a través de sus principales instituciones sanitarias.

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

**Métodos.** Un grupo de neurólogos de instituciones mexicanas y pertenecientes al grupo de estudio de Enfermedades Neuromusculares de la Academia Mexicana de Neurología realizó una búsqueda en MEDLINE y revisiones sistemáticas Cochrane, 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 que son sustentados por 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. El panel recomienda la inmunoglobulina humana o esteroides como primera línea de tratamiento para las formas sensitivo-motoras clásicas de la PIDC, exclusivamente inmunoglobulina para la PDIC motora pura y en caso de falla a inmunoglobulina o esteroide debe ser considerado el recambio plasmático. Si la respuesta es inapropiada o se requieren dosis altas o largos periodos con los medicamentos de primera línea, debe ser considerada la terapia coadyuvante sola o combinada con inmunomoduladores.

## Palabras clave

*Definición, diagnóstico, guía de práctica clínica, tratamiento, polineuropatía desmielinizante inflamatoria crónica.*

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## Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP—also known as chronic inflammatory demyelinating polyradiculoneuropathy) is the most common of chronic autoimmune neuropathies.<sup>1</sup> It is a group of acquired disorders of the peripheral nerves and nerve roots that converge in a pathogenesis common to all of them: the immune-mediated demyelination of the peripheral nerve.<sup>1,2</sup> For many decades there have been descriptions of patients with disorders that would today be considered CIDP. The reader should be aware, however, that clinical descriptors are evolving as new scientific evidence accumulates, so the CIDP concept is now considered an “umbrella” descriptor that groups conditions with shared pathogenesis, but whose clinical presentation, subtype of immunopathogenesis, prognosis, and response to treatments is actually very heterogeneous.<sup>1-3</sup>

The estimated prevalence of CIDP in the different populations of the world is as wide as 0.8 to 8.9 per 100,000 inhabitants.<sup>1</sup> These estimates are derived from developed countries and, notably, in Mexico, there are no estimates or direct measurements of the health burden of this entity. CIDP can affect all ages but is more common in men over 40 years old. It is believed that progressive forms are more common in older subjects, while recurrent forms are seen more in younger patients.<sup>3</sup> The classic, pure course with relapses and remissions occurs in a third of patients and the rest is thought to have a single-phase progressive course. However, it is possible that this classification might be reductionist and does not capture the essence of the temporary clinical behavior of CIDP, since perhaps the majority of patients considered with “pure” progressive forms have a superimposed course of relapses over a behavior of progression (mixed or recurrent-progressive forms).<sup>2,3</sup>

No specific predisposing factors for CIDP have been identified, although about 50% of patients have diabetes mellitus or carbohydrate intolerance (prediabetes states), but this, of course, is not specific to CIDP and the diagnosis of this entity

in subjects with diabetes mellitus can often go unnoticed because it is thought to be a diabetic neuropathy, whose pathogenic base is essentially toxic-metabolic.<sup>4</sup> It is possible that in certain populations, like in Mexico, many patients with CIDP are misdiagnosed with diabetic neuropathy. However, this has not been adequately addressed in quality observational studies.

Whether CIDP is a disease or a syndrome continues to be controversial. Independently of this, currently we recognize clinical variants of CIDP that have chronicity, demyelination, inflammation, or immune mediation in common:<sup>1-4</sup> Lewis-Sumner syndrome or multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), pure motor CIDP, sensory-predominant CIDP, focal CIDP, acute-onset CIDP, chronic autoimmune sensory polyneuropathy, distal acquired demyelinating symmetric neuropathy (DADS), and demyelinating neuropathy associated with demyelination of the central nervous system. In contrast, most authors currently consider the following as separate syndromes (non-variants of CIDP) of chronic demyelination of the peripheral nervous system (PNS): multifocal motor neuropathy, distal demyelinating neuropathy with paraprotein IgM with or without anti-MAG (myelin-associated glycoprotein), demyelinating neuropathy with paraprotein IgG or IgA (monoclonal gammopathy of undetermined significance or MGUS), POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) and demyelinating neuropathies associated with systemic diseases (e.g. hepatitis B or C, HIV, lymphoma, diabetes mellitus, systemic lupus erythematosus and other collagenopathies, dysthyroidism, bone marrow transplant, nephrotic syndrome, and inflammatory bowel disease). The classification of inflammatory demyelinating neuropathies will continue to evolve as specific immune mechanisms are clarified.

This document aims to describe the results of a systematic review of diagnosis and management of CIDP, to serve as the scientific basis for the shaping of recommendations on these topics.

## 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 CIDP were posited and an agreement was reached. This produced an agenda for a 12-hour face-to-face session distributed over a day and a half. Prior to the meeting, the topics and clinical questions were distributed among the participating clinicians for response and development in two groups of panelists. The members of the working group systematically formulated the pertinent answers to the questions posed according to the recommendations of the GRADE system (Grading of Recommendations Assessment, Development and Evaluation)(Table 1).<sup>5,6</sup> Briefly, this system is mainly a series of steps to organize the systematized answer of clinical questions of interest, particularly with respect to diagnosis and treatment. It focuses mainly (but not exclusively) on qualifying the quality of the evidence and thus formulating a recommendation structured in a concise statement, which is properly the answer to the clinical question posed.

The workgroup agreed to use the GRADE system in order to systematize the development of the document and to evaluate the evidence, in order to offer the user of the guide certainty about the knowledge that supports each recommendation. The workgroup, however, is aware that there is no system for classifying the evidence that is perfect and that none of them have been scientifically proven in a proper way to support its use over the other systems. That is to say, so far we cannot know which system is the best; nevertheless, this method was chosen because it is widely used today and because it has the strength to provide 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 and PubMed were searched for articles on CIDP with specific keywords and MeSH terms in English related to the design of the study, treatment, and disease, as follows:

- #1. Chronic inflammatory demyelinating polyneuropathy
- #2. CIDP
- #3. Long-term
- #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).<sup>5</sup> When only very low quality evidence was found (opinions of other expert panels, clinical anecdotes, or the working group's own experience), the team made an attempt to reach a consensus and the recommendations were classified as "good practice points."

The statements were reviewed one by one by all the members of the working group and were

**Table 1.** Description of the GRADE system (Grading of Recommendations Assessment, Development and Evaluation).

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	Implications
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.

compiled into a single document that was then reviewed iteratively until a general agreement was reached. Once consensus was reached on a final version of the document, it was formatted according to the journal's author guidelines and distributed via email for the review and approval of all members of the group.

The references and the complete texts were uploaded to an online repository created ex professo, which can be consulted by the readers freely: [http://editor.manuscript-manager.com.mx/GPC\\_PDIC](http://editor.manuscript-manager.com.mx/GPC_PDIC)

## Results

### Definitions

CIDP is characterized by progressive, symmetrical, proximal and distal weakness of the extremities accompanied by paresthesias, with gait instability that evolves for a period greater than eight weeks.<sup>1,2</sup> The physical examination additionally shows generalized hypo- or areflexia. The involvement of cranial nerves is infrequent and, if present, it is generally of lesser magnitude within the picture. Ataxia and distal tremor have been described in a specific subgroup, particularly in cases of CIDP associated with anti-neurofascin-155 antibodies (NF155).<sup>3</sup> The clinical evolution is variable, usually in outbreak-remission (or simply recurrent); however, there are clear descriptions of monophasic forms with escalating outbreaks, primarily progressive forms, and acute



onset forms. The latter ones are challenging to distinguish from Guillain-Barré syndrome (GBS).<sup>1</sup>

The mechanism of injury is undoubtedly immune-mediated. The experimental models of allergic neuritis and the histopathological similarities with GBS support this premise; however, the immunopathogenesis remains imprecise. To date, no triggering event has been identified, the exposure of individuals genetically susceptible to various environmental or infectious agents has been proposed on multiple occasions without being able to firmly establish the association.<sup>1</sup> Recently, autoantibodies against the paranodal proteins contactin-1 (CNTN1) and NF155 have been described in a small subgroup of patients with CIDP with a homogeneous clinical pattern. Outside of these associations, pathogenic autoantibodies or specific antigens are unknown in the PNS.<sup>4</sup> Isolated reports of CIDP associated with tumors (melanoma) or post-vaccination suggest that molecular mimicry could be involved in the pathogenesis.<sup>1-3</sup>

The diagnostic suspicion is established based on suggestive clinical manifestations. The typical CIDP (which is not precisely the most common) presents with at least eight weeks of evolution of distal paresthesias with stocking/glove distribution, symmetric, with progressive distal paresis and eventual involvement of shoulder girdle and pelvic girdle, which can progress to loss of autonomic ambulation and the appearance of atrophy. Still, this is not the only clinical presentation of CIDP, which has led to the recognition of clinical variants (Table 2).

### Diagnostic criteria

Given the wide phenotypic variability (50% of cases), the protocol of diagnostic auxiliaries becomes relevant to confirm the diagnostic certainty and reasonably exclude differential diagnoses. In this vein, the pertinence of lumbar punctures, electrophysiology studies, magnetic resonances, and peripheral nerve biopsies will be weighted according to the best evidence available in the body of this document.

### Electrophysiological criteria

#### Usefulness of neurophysiological evaluation of

#### motor nerves in suspicion of CIDP

*This panel recommends performing neuroconduction tests to explore at least four motor nerves, using the demyelination diagnostic criteria proposed by the EFNS/PNS. (Strong recommendation, high quality of evidence: 1A)*

The criteria of the European Federation of Neurological Societies and Peripheral Nerve Society (EFNS/PNS)<sup>3</sup> have a sensitivity of 81% and specificity of 96% to establish the diagnosis of CIDP, compared to the original criteria proposed by the American Academy of Neurology (AAN) (100% specificity and 45% sensitivity).<sup>7-12</sup> According to the criteria met, the diagnosis of definitive, probable, or possible CIDP can be established (Table 3). The sensitivity of electrodiagnostic criteria for motor nerves can be improved by examining more than four nerves, including proximal stimulation in the upper limb<sup>13,14</sup> and examining sensory nerves.<sup>15,16</sup>

To apply these criteria, evaluate the nerves median, ulnar (stimulus below the elbow), peroneal (stimulus under the fibular head), and tibial on just one side. If the criteria are not met, the same nerves are evaluated contralaterally and/or the median and ulnar nerves are stimulated bilaterally in the armpit and Erb's point. The blockage of the motor conduction is not considered in the ulnar nerve in its passage through the elbow and there must be at least 50% reduction in the amplitude between Erb's point and the wrist to consider a probable conduction block. The temperature should be maintained at least 33°C in the palm and 30°C in the external malleolus.<sup>3</sup>

#### Usefulness of neurophysiological evaluation of sensory nerves in suspicion of CIDP

*This panel recommends conducting sensory neuroconduction to patients with clinical suspicion of typical or atypical CIDP. (Weak recommendation, low quality of evidence: 2C)*

The sensitivity of the electrodiagnostic criteria for motor nerves can be improved by examining more than four nerves, including proximal stimulation in the upper limb,<sup>13,14</sup> and there are reports of cases where atypical CIDP was suspected where the examination of sensory nerves increased the diagnostic certainty.<sup>15,16</sup>

**Table 2.** Currently recognized clinical variants of chronic inflammatory demyelinating polyradiculopathy (CIDP).

Clinical variant	Frecuency (%)	Clinical phenotype
Typical CIDP	40–01	Sensorimotor, distal and proximal, symmetric, evolution >8 weeks.
Sensory CIDP	4–35	Sensory predominant, it can develop minor motor symptoms, distal and proximal, symmetrical, evolution >8 weeks.
DADS	2–17	Sensory predominant, it can develop minor motor symptoms, distal, symmetrical, evolution >8 weeks.
Acute-onset CIDP	2–16	Sensorimotor, distal and proximal, symmetrical, evolution <8 weeks.
Lewis-Sumner syndrome (MADSAM)	6–15	Sensorimotor, frequent onset in upper extremities, asymmetrical, evolution >8 weeks.
Chronic autoimmune sensitive polyneuropathy	5–12	Sensory ataxia, distal and proximal, symmetrical, evolution >8 weeks.
Motor CIDP	4–10	Predominantly motor, distal and proximal, symmetrical, evolution >8 weeks.
Focal CIDP	0–5–1	Sensorimotor, focal, can progress to diffuse form with time, asymmetrical, evolution >8 weeks.

*The percentages do not necessarily add up to 100% due to the variability of the distribution of the variants among the different populations.*

**DADS:** distal acquired demyelinating symmetric neuropathy.

**MADSAM:** multifocal acquired demyelinating sensory and motor neuropathy.

### Are there other useful neurophysiological tests to establish the diagnosis of CIDP?

*This panel suggests performing somatosensory evoked potentials (SEPs) especially in patients with the variant of sensory CIDP or atypical clinical presentations. (Good practice point)*

Somatosensory evoked potentials may be useful to demonstrate alteration of proximal sensory conduction, particularly in sensory CIDP<sup>18,19</sup> and may contribute to the diagnosis of CIDP when neuroconduction studies result insufficient to detect peripheral demyelination.<sup>20</sup>

### Is the repetition of the neurophysiological protocol valid when there is a high clinical suspicion which did not meet the criteria proposed by the EFNS/PNS for CIDP in the initial evaluation?

*This panel suggests repeating the neurophysiological evaluation proposed by the EFNS/EPN, in case of not meeting the criteria for definitive CIDP in the initial evaluation. (Weak recommendation, low quality of evidence: 2C)*

If the electrodiagnostic criteria are not initially met for definitive CIDP, repetition of the study at a later date should be considered. This can avoid false negatives and could narrow the differential diagnosis.<sup>10</sup>



**Table 3.** Electrodiagnostic criteria for chronic inflammatory demyelinating polyradiculopathy (CIDP).

<b>1. Definitive CIDP: at least one of the following</b>
A. Prolonged distal motor latency $\geq 50\%$ above the ULN in two nerves (excluding carpal tunnel syndrome), or
B. Reduction of the CV $\geq 30\%$ under the LLN in two nerves, or
C. F waves with prolonged latency $\geq 30\%$ of the ULN in two nerves ( $\geq 50\%$ if the amplitude of the negative peak CMAP is $< 80\%$ of the LLN), or
D. Absence of F waves in two nerves, if those nerves have amplitudes of distal negative peak CMAP $\geq 20\%$ of the LLN + at least some other demyelination parameter in at least some other nerve <sup>(a)</sup> , or
E. Partial blockage of motor conduction: reduction $\geq 50\%$ of amplitude of proximal negative peak CMAP in relation to distal, if distal negative peak CMAP is $\geq 20\%$ of the LLN in two nerves; or in one nerve + at least some other demyelination parameter in at least some other nerve <sup>(a)</sup> , or
F. Abnormal temporal dispersion ( $> 30\%$ increase in duration between proximal and distal negative peak CMAP) in at least two nerves, or
G. Duration of distal CMAP (interval between the beginning of the first negative peak and the return to baseline of the last negative peak) increased in at least one nerve (median 6.6 ms, ulnar 6.7 ms, peroneal 7.6 ms, tibial 8.8 ms) <sup>(b)</sup> + at least some other demyelination parameter in at least some other nerve <sup>(a)</sup>
<b>2. Probable CIDP</b>
$\geq 30\%$ reduction of the amplitude of the proximal negative peak CMAP in relation to the distal, excluding the posterior tibial nerve, if the distal negative peak is $\geq 20\%$ of the LLN in two nerves, or in one nerve + at least some other parameter of demyelination in at least some other nerve.

### 3. Possible CIDP

Like "1" but in just one nerve

**CV:** Conduction Velocity

**CMAP:** Compound Muscle Action Potential

**ULN:** Upper Limits Normal

**LLN:** Lower Limits Normal

<sup>(a)</sup> Any other nerve that meets any of the A-G criteria

<sup>(b)</sup> Iose S. et al.<sup>15</sup>

#### Lumbar puncture practice for patients with clinical suspicion of CIDP

*This panel recommends that in the event of clinical suspicion of CIDP, a lumbar puncture be performed for routine cytological and cytochemical analysis. (Strong recommendation, high quality of evidence: 1A)*

The presence of hyperproteinorrachia in patients with CIDP occurs between 76 and 90% of patients, where a protein level is demonstrated  $> 45$  mg/dL.<sup>9, 21-22</sup> Normally no pleocytosis should be observed in the CSF; if observed, it usually suggests coexisting infection, for example by HIV.<sup>23</sup> Cyto-protein dissociation is the most

important piece of information in the CSF analysis. Although its usefulness is reported in some studies, the determination of oligoclonal bands for cases without demyelination of the CNS is, in fact, debatable and of limited utility.<sup>23</sup>

#### Nerve biopsy practice in patients with suspicion of CIDP

*This panel suggests performing a sural nerve biopsy when the clinical, neurophysiological, and CSF elements are insufficient to support the diagnosis of CIDP or in selected cases of atypical clinical presentations. (Weak recommendation, low quality of evidence: 2C)*

The nerve biopsy can provide evidence to support the diagnosis of CIDP when the results of other diagnostic tests are inconclusive.<sup>22</sup> However, the histopathological findings are not specific and their absence does not exclude the diagnosis. The biopsy of the sural nerve is preferred because of its easy access and fewer adverse events. The one that is clinically and/or electrophysiologically most affected should be chosen. Other options are the superficial peroneal or superficial radial nerves. Histopathological findings of CIDP include the inflammatory reaction associated with macrophages, onion bulb formations (demyelination-remyelination), endoneurial edema, mononuclear infiltration in endoneurium and variations between the fascicles.<sup>12,25</sup>

#### Nuclear magnetic resonance (NMR) study of plexuses and spinal roots in the diagnosis of CIDP and its variants

*This group suggests conducting NMR imaging of roots and spinal plexuses as a diagnostic aid for CIDP of initial atypical presentation and in which the neurophysiological and CSF evaluation has not allowed to establish a definitive diagnosis. (Good practice point)* In some patients with atypical CIDP, alterations in NMR have been demonstrated, such as hypertrophy of the brachial or lumbar plexus and/or extraforaminal roots with gadolinium uptake, which denotes inflammation with vascular leakage. These alterations are mostly asymmetrical and are more frequently observed in the brachial plexus than in the lumbar.<sup>12,24</sup>

#### NMR of the spinal cord and/or brain in the diagnosis of CIDP and its variants

*This panel does not suggest carrying out routine NMR imaging studies of the spinal cord and/or brain in patients with suspected CIDP, except in cases in which the physical examination indicates involvement of the CNS. (Weak recommendation, low quality of evidence: 2C)*

Some studies have looked for the presence of concomitant alterations in the CNS in patients with CIDP. There are only small series of patients subjected to this type of research and the number of patients in whom this type of alterations have been corroborated has been a minority.<sup>26</sup> White matter hyperintensities in T2 sequences and atrophy of

cervical cord have been described in isolation, but the clinical and prognostic significance of these findings is still controversial.<sup>27-31</sup>

#### Chemical and/or immunological analysis in the patient diagnosed with CIDP

*This panel suggests carrying out the necessary investigations to search for other concomitant diseases in the patient diagnosed with possible, probable, or definite CIDP, based on a detailed clinical history. (Good practice point)*

Mainly based on case reports, numerous diseases have been associated with CIDP.<sup>12</sup> These include diabetes mellitus, monoclonal gammopathies IgG or IgA, monoclonal gammopathy by IgM without antibodies against myelin-associated glycoprotein, HIV infection, chronic active hepatitis, systemic lupus erythematosus or other connective tissue diseases, sarcoidosis, thyroid disease, inflammatory bowel disease,<sup>32</sup> membranous glomerulonephritis,<sup>33</sup> and transplantation of bone marrow or solid organs.<sup>34</sup> There is insufficient evidence to consider a direct association between CIDP and these diseases, however, consider the necessary investigations to rule out concomitant diseases. Perhaps, over time, some of these systemic diseases causing demyelinating neuropathies may be considered forms of CIDP of determinate cause.

#### Treatment

##### Oral steroids for the treatment of CIDP

*This panel recommends prednisone as a first-line treatment for patients with sensory-motor CIDP. (Strong recommendation, high quality of evidence: 1A)* There is only one multicenter, randomized, and controlled study with prednisone at a dose of 60 mg daily that proved superior against not receiving treatment.<sup>33</sup> However, there are many observational studies that indicate the efficacy of prednisone in CIDP, except for pure motor CIDP, whose use could even lead to clinical deterioration.<sup>12</sup> There is no consensus on which is the best prednisone administration scheme considering daily regimens, on alternate days, or intermittent monthly.<sup>12</sup> This panel suggests prednisone 60 mg daily or on alternate days for at least a month or until reaching a symptoms

stabilization phase, then start a gradual reduction scheme of 10 mg per month until reaching 5 mg daily or every other day and complete two years of treatment at this dosage, at the end of which, if the patient is asymptomatic or only minor sensory symptoms persist, prednisone may be discontinued and the patient kept under medical observation 1 to 2 times per year for 3 years.<sup>35-38</sup> (Good practice point.)

#### Intravenous steroids for the treatment of CIDP

*This panel recommends methylprednisolone as a first-line treatment for patients with sensory-motor CIDP. (Strong recommendation, low quality of evidence: 1C)* In some observational studies and clinical trials, intravenous methylprednisolone 1 g has been evaluated for 3 to 5 days, followed by 1 g monthly for 6 months, which has been shown to be as effective as oral steroids at 6 months of follow-up, however, it requires more long-term studies.<sup>39,40</sup>

#### Polyvalent human immunoglobulin for the treatment of CIDP

*This panel recommends the use of human immunoglobulin as the first line of treatment for adult patients with CIDP. (Strong recommendation, high quality of evidence: 1A)*

A meta-analysis that included four randomized, double-blind studies, two of them controlled by placebo, demonstrated the efficacy and safety of intravenous immunoglobulin (IVIG) in patients with CIDP and its clinical variants.<sup>41-44</sup> Given the short half-life of IVIG, it should be administered at regular intervals and at individualized frequency. Crossover studies have shown no difference in efficacy when comparing IVIG against plasma exchange, nor IVIG against prednisolone. A total induction dose of 2 g/kg fractionated in 2 to 5 days is recommended, followed by a maintenance dose of 1 to 2 g/kg fractionated in 2 to 5 days every 2 to 6 weeks.<sup>41-44</sup>

The scheme should be sustained until a symptom stabilization phase is observed, then it is recommended to reduce the dose of IVIG (10 to 15%) before extending the administration intervals. (Good practice point)

In the case that the patient requires sustained full doses of IVIG to maintain stability, it is suggested to add oral steroids or immunomodulatory drugs. (Good practice point)

#### Plasmatic exchange for the treatment of CIDP

*This panel recommends the use of plasma exchange in patients with CIDP refractory to steroids and IVIG in the induction phase. (Strong recommendation, high quality of evidence: 1A)*

In randomized, controlled, and double-blind studies, the manifestations of CIDP have shown short-term benefits with plasma exchange. It is suggested to be administered 2 to 3 times a week. However, a rapid deterioration after the procedure is reported, so the use of other treatment measures is recommended for stabilization in the medium and long term.<sup>45,46</sup>

### General therapeutic recommendations

#### Induction treatment

1. IVIG and steroids are considered first-line treatments in patients with CIDP, except for pure motor CIDP, where steroids could cause clinical deterioration and IVIG should be considered as the first-choice treatment. (Good practice point)

2. The presence of relative contraindications for each of the drugs can influence the therapy decision-making. In either case, the advantages and disadvantages of both options should be discussed with the patients to involve them in making the decision. (Good practice point)

3. For refractory forms of CIDP that do not respond to steroids or IVIG, plasma exchange should be considered as the second line of treatment. (Good practice point)

#### Maintenance treatment

1. In case of effectiveness during the induction phase, the treatment must be maintained until clinical stability is reached and then gradually reduce the dose. (Good practice point)

2. For patients under treatment with IVIG at high doses and short intervals, steroids or



immunosuppressive drugs should be considered as adjuvant therapy. (Good clinical practice point)

## Immunomodulatory drugs

No randomized, controlled study has been conducted to demonstrate the efficacy and tolerance of any immunomodulatory drug in the treatment of CIDP other than azathioprine. Its use is reserved only during the maintenance phase or in cases refractory to conventional treatment.

### Azathioprine

*This panel suggests the use of azathioprine at doses of 100 to 200 mg/day as treatment for sensorimotor CIDP. The use of this immunomodulator is as a steroid-sparing agent and usually in concomitance with prednisone. (Weak recommendation, low quality of evidence: 2C)*

There is only one randomized study with azathioprine in patients with CIDP that did not demonstrate efficacy when used concomitantly with prednisone; however, the study included a small number of patients, the follow-up was short, and the dose used was suboptimal.<sup>47</sup>

### Methotrexate

*This panel suggests the use of methotrexate at a dose of 15 mg/week for the treatment of CIDP. The use of this immunomodulator is as a steroid-sparing agent and usually in concomitance with prednisone. (Weak recommendation, low quality of evidence: 2C)*

There is only one randomized, double-blind, placebo-controlled study that used methotrexate at a dose of 15 mg/week in patients with CIDP but showed no benefit over placebo. However, the study suffered from severe limitations in its design, so its benefit for patients with CIDP remains uncertain.<sup>48</sup>

### Cyclophosphamide

*This panel suggests the use of intravenous cyclophosphamide at a dose of 1 g/m<sup>2</sup> monthly for 6 to 12 months to treat for CIDP. (Weak recommendation, low quality of evidence: 2C)*

An open non-controlled study with cyclophosphamide at a dose of 1 g/m<sup>2</sup> per month

for 6 months was effective in the treatment of CIDP cases that did not respond to steroids, human immunoglobulin, or plasma exchange.<sup>49</sup>

### Mycophenolate mofetil

*This panel suggests the use of mycophenolate mofetil at a dose of 2 g/day for the treatment of sensorimotor CIDP. (Weak recommendation, moderate quality of evidence: 2B)*

One retrospective study evaluated the efficacy of mycophenolate mofetil at a dose of 2 g/day in patients with CIDP, without demonstrating a difference in strength, sensitivity, or modified Rankin scale before and after treatment. A second study, also retrospective, suggested efficacy in the treatment of this condition.<sup>50,51</sup>

### Interferon beta

*This panel does not recommend the use of interferon beta in patients with CIDP. (Strong recommendation, high quality of evidence: 1B)*

A prospective, randomized, double-blind, placebo-controlled study that used interferon beta 1a at a dose of 30 or 60 µg twice a week for 4 months showed no benefit in symptom control or reduced IVIG dosage compared against placebo. In this case, the evidence, although not completely conclusive, is considered of sufficient quality to recommend against the use of interferon beta in cases with CIDP.<sup>52</sup>

## Monoclonal antibodies

### Rituximab

*This panel suggests the use of rituximab at a dose of 375 mg/m<sup>2</sup>, one cycle every week for four weeks in adult patients with CIDP with IgG4 anti-CNTN1/NF155 or hematological diseases antibodies. (Weak recommendation, low quality of evidence: 2C).*

A report of two cases of CIDP associated with IgG4 anti-CNTN1/NF155 antibodies resistant to conventional therapy showed a significant improvement or CIDP associated with hematological pathology or coexisting with another autoimmune disease.<sup>53</sup>

### Alemtuzumab

*This panel suggests the use of alemtuzumab in*

*selected patients with CIDP resistant to conventional treatment. (Weak recommendation, low quality of evidence: 2C)*

A case report that included seven patients with CIDP resistant to conventional therapy treated with alemtuzumab showed prolonged remission in two of them, partial improvement in two, and three had no benefit.<sup>54</sup>

### **Natalizumab**

*This panel suggests the use of natalizumab in selected patients with CIDP resistant to conventional therapy. (Weak recommendation, low quality of evidence: 2C)*

A report of three cases of patients with CIDP resistant to conventional therapy who were treated with natalizumab reported sustained improvement in one, dramatic improvement in another, and stabilization in the third. Other studies have not been consistent in their results.<sup>55</sup>

## **Physical therapy and rehabilitation**

*This panel suggests counseling patients regarding lifestyle changes including a balanced diet, regular physical activity, special dedication to foot care, physical rehabilitation (stretching exercises, strengthening, and occupational therapy) and, depending on the needs of the patients, psychological support. (Good practice point)*

There are no observational or intervention studies that show, with traditional objective outcomes, the effectiveness of different physical therapy schemes. This is an area of opportunity for research. In our experience, almost any regime that provides regular use of facilities and therapist services is associated with greater patient satisfaction, but with minimal effects in the improvement of independence, autonomous ambulation, or reversal of the physical limitations imposed by the disease. Nevertheless, this must be demonstrated with scientific rigor in the future.

## **This guide in perspective**

This is, to the best of our knowledge, the first clinical practice guide on diagnosis and treatment of CIDP using a system of evaluation for the quality of evidence and grading the strength of the recommendations with the participation of members of diverse Mexican institutions. Its text gathers, orders, summarizes, and combines the best available evidence in a clear and simple format in order to reduce the variability of clinical practices in the management of CIDP. Its original design weighs equally the diagnosis and treatment, fostering, on one hand, the encounter between research and clinical practice by reporting the quality of the available evidence in the statements, and, on the other hand, improving the quality of health service management.

## **Research recommendations**

The high variability of treatments, doses, schedules, and routes of administration makes standardization and comparison with different therapeutic maneuvers complex and laborious, partly explained by the heterogeneous nature of the disease discussed. This opens areas of opportunity to design multicenter studies that provide the best level of evidence in terms of diagnosis and treatment as well as explore new diagnostic tools for atypical forms. There should be an evaluation of the role of rescue therapies and second-line therapies, as well as different physical therapy techniques and multimodal treatments with different traditional objective outcomes (or added) to the overall satisfaction of the patient.

# Guide synopsis

## Diagnosis

1. This panel recommends performing neuroconduction tests by exploring at least four motor nerves using the diagnostic demyelination criteria proposed by EFNS/PNS. (Strong recommendation, high quality of evidence: 1A)
2. This panel suggests performing sensory neuroconduction in patients with clinical suspicion of typical or atypical CIDP. (Weak recommendation, low quality of evidence: 2C)
3. This panel suggests performing somatosensory evoked potentials (SEPs) in patients with sensory variant CIDP or atypical clinical presentation. (Good practice point)
4. This panel suggests repeating the neurophysiological evaluation proposed by EFNS/EPN in case of not meeting the criteria for definitive CIDP in the initial evaluation. (Weak recommendation, low quality of evidence: 2C)
5. Recommendation: This panel recommends, in the event of clinical suspicion of CIDP, lumbar puncture. (Strong recommendation, high quality of evidence: 1A)
6. This panel suggests performing a sural nerve biopsy when the clinical, neurophysiological, and CSF elements are insufficient to support the diagnosis of CIDP, or when faced with atypical clinical presentations. (Weak recommendation, low quality of evidence: 2C)
7. This group suggests carrying out NMR imaging of spinal roots and plexuses as a diagnostic aid for CIDP of initial atypical presentation and when the neurophysiological and CSF evaluation have not allowed establishing a definitive diagnosis. (Good practice point)
8. This panel does not suggest performing spinal and/or brain NMR imaging studies in patients with suspected CIDP. (Weak recommendation, low quality of evidence: 2C)
9. This panel suggests conducting the necessary investigations to search for other concomitant diseases in the patient with a diagnosis of

possible, probable, or definite CIDP, based on a detailed clinical history. (Good practice point)

## Treatment

1. This panel recommends prednisone as first-line treatment for patients with sensorimotor CIDP. (Strong recommendation, high quality of evidence: 1A)
2. This panel recommends methylprednisolone as first-line treatment for patients with sensorimotor CIDP. (Strong recommendation, high quality of evidence: 1C)
3. This panel recommends the use of human immunoglobulin as first-line treatment for adult patients with CIDP. (Strong recommendation, high quality of evidence: 1A)
4. This panel recommends the use of plasma exchange in patients with steroid-refractory CIDP and IVIG in the induction phase. (Strong recommendation, high quality of evidence: 1A)
5. This panel suggests the use of azathioprine at doses of 100 to 200 mg/day as treatment for sensorimotor CIDP. (Weak recommendation, low quality of evidence: 2C)
6. This panel suggests the use of methotrexate at a dose of 15 mg/week for the treatment of CIDP. (Weak recommendation, low quality of evidence: 2C)
7. This panel suggests the use of intravenous cyclophosphamide at a dose of 1 g/m<sup>2</sup> monthly for 6 to 12 months for the treatment of CIDP. (Weak recommendation, low quality of evidence: 2C)
8. This panel suggests the use of mycophenolate mofetil at a dose of 2 gr/day for the treatment of sensorimotor CIDP. (Weak recommendation, low quality of evidence: 2B)
9. This panel does not recommend the use of interferon B1 in patients with CIDP. (Strong recommendation, high quality of evidence: 1B)
10. This panel suggests the use of rituximab at a dose of 375 mg/m<sup>2</sup>, one cycle every week for four weeks in adult patients with CIDP associated with IgG4 anti-CNTN1/NF155 or hematological diseases antibodies. (Weak recommendation, low quality of evidence: 2C)



11. This panel suggests the use of alemtuzumab in patients with CIDP resistant to conventional treatment. (Weak recommendation, low quality of evidence: 2C)
12. Recommendation: This panel suggests the use of natalizumab in patients with CIDP resistant to conventional therapy. (Weak recommendation, low quality of evidence: 2C)
13. This panel suggests advising patients on lifestyle changes that include a balanced diet, regular physical activity, extreme foot care, physical rehabilitation (stretching exercises, strengthening, and occupational occupational therapy), and, depending on the patient's need, psychological support. (Good practice point)

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