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REVIEW ARTICLE

Inflammatory neuropathies: How far we've come

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ABSTRACT

Inflammatory polyneuropathies encompass a range of common and treatable conditions arising from an immune response—either humoral or cellular—targeting specific elements of the peripheral nervous system. These conditions may be acute, as in Guillain-Barré syndrome and its variants, or chronic, as observed in chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, POEMS, vasculitis neuropathies, or nodal-paranodal disorders. Diagnosis predominantly hinges on clinical symptoms and electromyographic examinations, facilitating the prompt commencement of treatment. Addressing less common pathologies is crucial when conventional treatments prove ineffective, emphasizing the need for ongoing research in this dynamic field.

Introduction

It's been more than a 100 years since Guillain, Barre and Strohl reported the first two cases of acute ascending flaccid paralysis and 40 years later, Miller Fisher reported a variant of the classical syndrome that now carries his name[1,2]. With this findings, a broad spectrum of peripheral neuropathies responding to immunotherapy opened.

In the past decade, significant progress has been made related to diagnosis and treatment, and although there is still much ground to cover, the discovery of new immune mechanisms affecting peripheral nerves increasingly guides us towards new and better therapeutic approaches. (Figure 1).

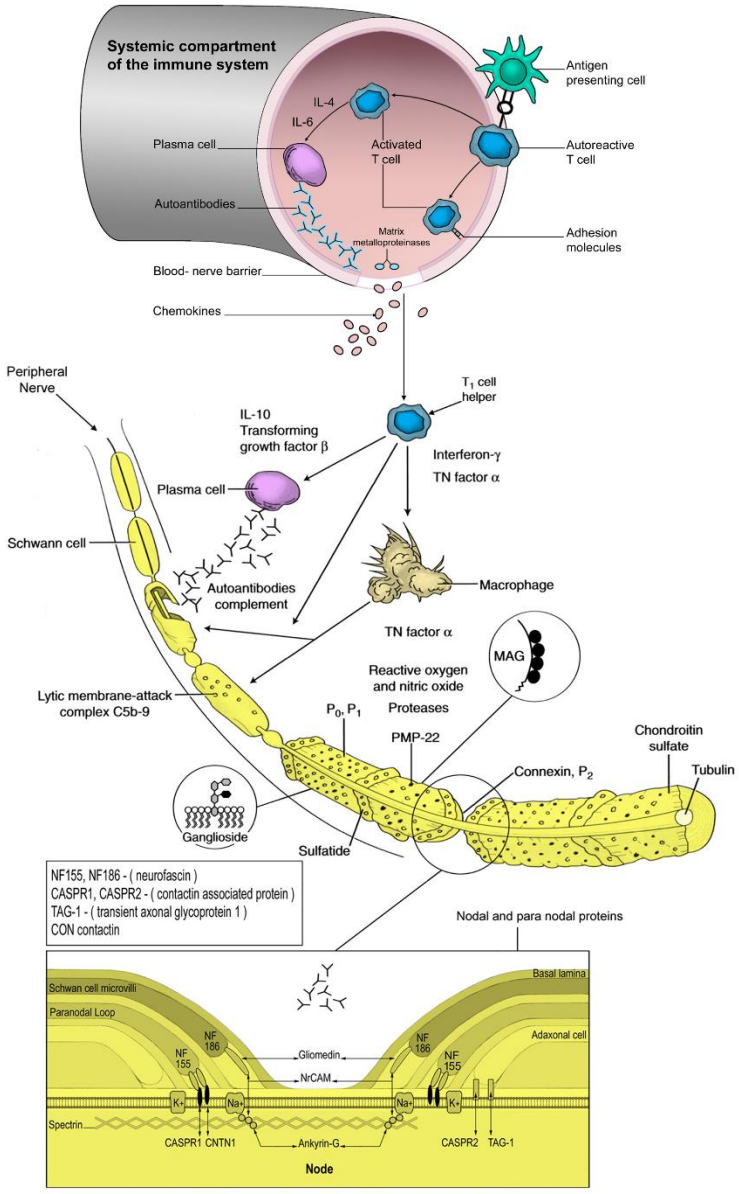

Figure 1. Inflammatory neuropathies pathophysiology. In the systemic compartment the antigen presenting cell activate T lymphocytes which penetrate the blood brain barrier with the help of adhesion molecules, and also releases chemokines and matrix metalloproteinase. There is also activation of plasma cells that secrete antibodies that cross the blood nerve barrier.

This article embarks in a detailed review of acute and chronic inflammatory neuropathies, with special attention to diagnostic strategies and treatment. Most review articles address only few pathologies at once and we found the need to approach the whole spectrum to learn differentiate between the syndromes.

Guillain Barre Syndrome

Guillain Barre Syndrome is the most common acute inflammatory poliradiculopathy. It has a monophasic course that reaches its peak within the first four weeks and is usually preceded by an infection. The estimated incidence goes from 0.81 to 1.89 cases per 100000 persons per year[3]. Median age of presentation is 51 years with a male to female ration of 1.5. There is a wide variation in clinical variants and outcome influenced by geography[4]. Patients often present with paresthesias and symmetric weakness that typically begins in the lower limbs, progressing to the upper limbs and cranial nerves. The classic presentation of this disease doesn't pose a diagnostic challenge, but when variants occur, the diagnosis may be delayed.

GUILLAIN BARRE SYNDROME SUBTYPES

- Acute inflammatory demyelinating polyneuropathy (AIDP) is the most common subtype with a prevalence around 85% of all Guillain Barre syndrome cases[5]. Patients usually presents with flaccid ascending paralysis and sensory involvement, decreased or absent deep tendon reflexes, radicular or muscular pain and minimal sensory involvement. It can also develop cranial nerve involvement with facial diplegia, bulbar and oculomotor symptoms[6].

- Acute motor axonal neuropathy (AMAN) and acute motor-sensory axonal neuropathy (AMSAM): characterised by rapid progressive weakness that might present ventilatory failure but has a better prognosis than the other subtypes[5]. The axonal injury is caused by IgG deposit and complement without demyelination or inflammation by T lymphocytes[6].

- Miller Fisher Syndrome presents with the triad of ophthalmoplegia, ataxia and decreased tendon reflexes. The immune response targets epitopes of paranodal myelin, widely expressed in the extraocular muscles, dorsal root ganglia, and molecular layer neurons of the cerebellum, thus giving rise to the aforementioned symptoms.[5] MFS is associated with anti-GQ1b antibodies in 70% to 90% of patients. Incomplete forms also exist where not all the components of the triad manifest[7].

- Bickerstaff brainstem encephalitis: triggered by the antecedent of an infectious episode, it presents with ophthalmoplegia, ataxia, altered consciousness and serologically positive for IgG anti-GQ1b antibodies. This antibodies enter the brainstem and bind to GQ1b in the reticular formation causing the impaired consciousness[7].

- Pharyngeal-cervical-brachial Guillain Barre syndrome: rapid progressive symmetric weakness in the oropharyngeal and cervical area associated with diminished or absent reflexes in upper extremities without lower extremities symptoms. This form manifests with absence of ataxia or altered consciousness. 70% of cases, it is associated with one of the following antibodies: anti-GT1 and anti-GQ1b[8].

- Pure sensory - ataxia Guillain Barre syndrome: Less than 1% of cases. Presents

with sensory symptoms and may be associated with cerebellar ataxia[9].

PHYSIOPATOLOGY

Up to 76% patients with Guillain Barre syndrome reported an infectious antecedent up to four weeks before the beginning of the neurological symptoms, the majority of patients reported mainly upper respiratory tract infection (35%) or gastroenteritis (27%).[4] Several infectious antecedents, both viral and bacterial, have been linked to Guillain Barre syndrome in association with specific regions. AMAN and AMSAM are commonly related with the previous infection by *Campylobacter jejuni*. Some case-control studies have established an association between this syndrome and Haemophilus influenzae, Mycoplasma pneumoniae, Cytomegalovirus, Epstein Barr Virus, Zika virus, among others.[6] Since 2019 SARS-CoV-2 virus has been the focus of many researches, but studies have not found a relationship between this virus and GBS[10,11].

The demyelinating variant is characterized by perivascular and endoneural inflammatory infiltrates in peripheral nerves and nerve roots, with segmental demyelination caused by T lymphocytes and macrophages.[6] Macrophages penetrate the basal membrane of Schwann cells, making direct contact with the outer layer of myelin without causing axonal damage. T cells produce proinflammatory cytokines that activate macrophages and increase local inflammation[12]. In AMAN, there is axonal destruction mediated by antibodies and complement with evidence of molecular mimicry due to cross-reactivity between bacterial lipo-oligosaccharides and specific gangliosides that are abundant in peripheral nerves[5].

DIAGNOSIS

History and physical examination continue to be the basis of diagnosis, supported by electromyography and cerebrospinal fluis analysis. The Brighton criteria and National Institute of Neurological Disorders (NINDS) in 1978 are widely used for epidemiological studies[13,14].

Electrodiagnostic studies help differentiate between demyelinating and axonal presentation and identify a relationship between a preceding infection, antibodies and patient's prognosis[15]. Sensitivity of this studies are suboptimal in early Guillain Barre syndrome, varying between 39.2% to 88.2% between the first and third week. The sensory nerve studies reveal sural sparing, low amplitud medial plantar response and abnormal sensory and ulnar ratio can help secure the diagnosis[16]. During the first 15 days electrodiagnostic studies are usually not reliable, but there are certain finding that can orient the diagnosis: bilateral absent H reflex is the most sensitive parameter, F waves abnormalities and proximal rather than distal compromise is also seen[17].

The cerebrospinal fluid analysis classical finding is albuminocytological dissociation; hyperproteinoraquia with normal cell count, mainly used to exclude other diagnoses in a context of acute flacid paralysis. This finding has a sensitivity lower than 50% during the first week, but up to 84% the second week[4,18]. Low total protein leves in cerebrospinal fluid are linked with a better short term prognosis within the first 2-4 weeks. An elevated cell count should be consider a red flag, but new studies suggest that It can be part of Guillain Barre syndrome after excluding other posible diagnoses. Cell count greater than 50 cells

occurs only in 1% of patients with this syndrome and the diagnosis must be confirmed with a thorough workup[19].

There are other red flags that should be taken into consideration when having a patient with acute placid paralysis: persistent asymmetric presentation, fever on presentation, nadir before 24 hours of presentation, sensory level, hyperreflexia or clonus, abdominal pain, clinical progression more than 4 weeks and impaired consciousness (with the exception of Bickerstaff brainstem encephalitis). (Table 1)

Table 1. Diferential diagnoses GBS

Central nervous system	Medullary compression, poliomyelitis, transverse myelitis, brainstem stroke, vitamin deficit.
Muscular	Metabolic: hypokalemia, hypophosphatemia, hypomagnesemia. Myopathies: infectious, inflammatory, rhabdomyolysis, Mithochondrial disease, drug induced myopathy.
Neuromuscular junction disease	Miastenia gravis, Lambert - Eaton Syndrome, organophosphate poisoning.
Polyneuropathies	CIDP, critical illness polyneuropathy, Infectious disease (Lyme, diphtheria, HIV) Metabolic (diabetes mellitus, porphyria, uremia) Vasculitic neuropathies, Toxicity (botulism, heavy metals, diphtheria)

TREATMENT

Treatment requieres multidisciplinary medical care and immunotherapy. The choice of treatment usually depends on the patient and the hospital resources. In the acute phase, patients require hospital admission and close monitoring. Besides starting immunological treatment, secondary complications related to immobility, respiratory insufficiency, autonomic dysfunction and pain must be prevented.

Plasma exchange of 200 to 250 ml/kg over five sessions and human immunoglobulin at a dose of 2gr/kg divided in 5 doses have proven to be effective[20]. Neither of these treatments has shown superiority over the other, so the availability of treatment and the individual patient's characteristics should be considered when choosing between them. In patients with poor prognosis or those who show no improvement despite treatment, repeating human immunoglobulin treatment or complementing it with plasmapheresis is not recommended, as there is no demonstrated benefit and, conversely, it increases the risk of adverse effects[21,22,23].

Miller-Fisher syndrome usually have a complete or nearly complete recovery after 6 months. Patients who experience weakness in addition to the classic symptoms, the use of immunomodulatory treatments should be considered[20]. Patients particularly during the acute stage of Bickerstaf brainstem

encephalitis treatment is justified due to the severity of the clinical presentation[5].

Around 40% of patients do not improve in the first 4 weeks and 8-16% of patients may experience clinical worsening in the first 8 weeks after completing treatment with intravenous immunoglobulin (IVIG) or plasmapheresis[9]. Regarding the treatment of moderate GBS, defined as cases where the patient is able to walk without assistance in the first 4 weeks of presentation, there is no consensus on the benefits of treatment. A trial with IVIg showed that 41% of treated and untreated patients had symptom at 1 year[24].

Multiple studies on the use of corticosteroids have shown no beneficial effect and may even delay recovery[25]. A study on the use of eculizumab in 2018 did not demonstrate benefits[26,27]. So far, none of the alternative therapies to the use of human immunoglobulin or plasmapheresis have shown promising results, which is why new studies are needed[27].

PROGNOSIS

Guillain Barre syndrome presents spontaneous recovery after a plateau is reached. Immunotherapy aims for a quicker and more complete recovery. The mortality rate ranges from 3-10%, usually due to cardiovascular and respiratory complications that can present during acute onset or recovery phase.[9] Around 20% of patients are unable to walk after a year, and many are left with residual symptoms, underscoring the critical importance of prompt diagnosis and treatment[20]. Advanced age, antecedent of C. jejuni infection, mechanical ventilation and axonal subtype are poor outcome predictors[6].

Modified Erasmus GBS Outcome Score (mEGOS) predicts the risk of being unable to walk independently within the first 6 months evaluating age, Medical Research Council (MRC) sum score and the antecedent of diarrhea. In 2022, this score was validated to be used in any patient with GBS or variants to predict the risk of poor outcome and also developed a modified mEGOS score for European countries and North America[28]. Erasmus Guillain-Barre Syndrome Respiratory Insufficiency Score (EGRIS) evaluates time from onset of weakness to hospital admission, facial or bulbar weakness and MRC sum score at admission and estimates the risk of respiratory failure during the first week. This score was able to differentiate between high and low risk for mechanical ventilation and ICU admission[29]. In the search for new markers, low-density neutrophils count and ratio have shown to be an accessible prognostic indicator for acute onset and recurrent phases of GBS and also correlate with disease progression and severity[30].

Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy is rare disorder characterised by motor and sensory symmetric symptoms with a progressive or relapsing course during at least 8 weeks. The reported incidence and prevalence varies between studies, a new retrospective, population-based cohort study determined an incidence 0.68 per 100000 person-year and prevalence of 7 per 100000, with higher rates in males and persons of 50 years or older[31].

PHYSIOPATHOLOGY

The pathophysiology involves a complex interplay of immune responses, inflammation,

and damage to peripheral nerves. Ongoing research aims to elucidate the precise molecular and cellular mechanisms underlying the disorder, which could potentially lead to more targeted and effective therapeutic interventions[32].

The microvessel endothelium at the spinal roots and dorsal root ganglion in the peripheral nervous system is fenestrated, possibly explaining why the damage to the nerves occurs in that location. Loose connections allow cell leakage developing an immune mediated response. Macrophages are the most common infiltrating cell and cause demyelination by phagocytosis[33].

SUBTYPES

The 2021 EAN/PNS task force redefined the criteria for chronic inflammatory demyelinating polyneuropathy changing the denomination for typical CIDP and variants that correlate with specific clinical and electrodiagnostic criteria[34]. Typical CIDP presents with progressive and relapsing weakness, more commonly in the legs.

The variants present common features and respond to immune therapy.

- Distal CIDP or distal acquired demyelinating symmetric neuropathy (DADS): distal sensory involvement in upper and predominantly lower limbs associated with gait instability. It is usually associated with IgM paraproteinaemic neuropathy and antibodies against myelin-associated glycoprotein (MAG).

- Multifocal CIDP (MADSAM): asymmetric sensory and motor involvement that predominates in upper extremities and can affect cranial nerves.

- Focal CIDP: might affect brachial or lumbosacral plexus and also peripheral nerves.

- Motor CIDP: proximal and distal symmetric weakness with no sensory involvement.

- Sensory CIDP: presents with gait ataxia and sensory symptoms like impaired sensation and vibration sense.

DIAGNOSIS

Diagnosis is based on clinical and electrophysiological criteria supported by neuroimages and albuminocytologic dissociation in cerebrospinal fluid analysis. Misdiagnosis is common mainly due to wrong interpretation of nerve conduction studies as demyelinating, slight elevation of proteins and non-objective response to immunotherapy, leading to unnecessary administration of immunotherapy.[35] In an attempt to have a more accurate diagnosis de EAN/PNS task force published new electrodiagnostic criteria trying to unify all the information[34].

After a thorough assessment of the past medical history, present illness and physical exam, electrodiagnostic studies with supporting evidence of demyelination are fundamental for diagnosis. Because there is no gold standard, the new classification classifying it between CIDP and possible CIDP[34]. (Table 2).

Table 2. EAN/PNS 2021 CIDP diagnostic criteria

Clinical Criteria	
Pattern of clinical involvement	Progressive or relapsing, symmetric, proximal and distal muscle weakness of upper and lower limbs, and sensory involvement of at least two limbs
Reflexes	Absent or reduced tendon reflexes in all limbs
Time of course	Developing over at least 8 weeks
Electrodiagnostic studies	One of the following: - Motor distal latency prolongation >50% above ULN in two nerves - Reduction of motor conduction velocity >30% below LLN in two nerves - Prolongation of F-wave latency ≥ 20% above ULN in two nerves - Absence of F-waves in two nerves - Motor conduction block - Abnormal temporal dispersion - Distal CMAP duration prolongation - Sensory conduction abnormalities (prolonged distal latency, or reduced SNAP amplitude, or slowed conduction velocity outside of normal limits) in two nerves
CSF studies	Not recommended if diagnostic criteria are already met.
Nerve biopsy	Not recommended
Level of diagnostic certainty	
Definite	Clinical criteria + motor conduction criteria in two nerves + sensory conduction abnormalities in two nerves
Possible	Clinical criteria + motor conduction criteria in one nerve + sensory conduction abnormalities in two nerves

Neuroimaging is a repeatable and non invasive approach when there is no certainty with clinical and Electrodiagnostic criteria, gaining a role as a supporting method for diagnosis. Nerve ultrasound evaluates cross sectional area, vascularity, echogenicity, fascicle size and epineurium thickness. In a study of 100 patients with clinical suspicion of CIDP, nerve ultrasound and nerve conduction studies were compared finding superior sensitivity of 97.4% in the former and specificity of 93.5% in the latter[36]. High scores

in US have the potential to predict progression and serve as markers to differentiate CIDP and AIDP with a sensibility and specificity around 90%[37]. MRI of the brachial and lumbosacral plexus shows hypertrophy with increased signal intensity and enhancement[38]. (Figure 2)

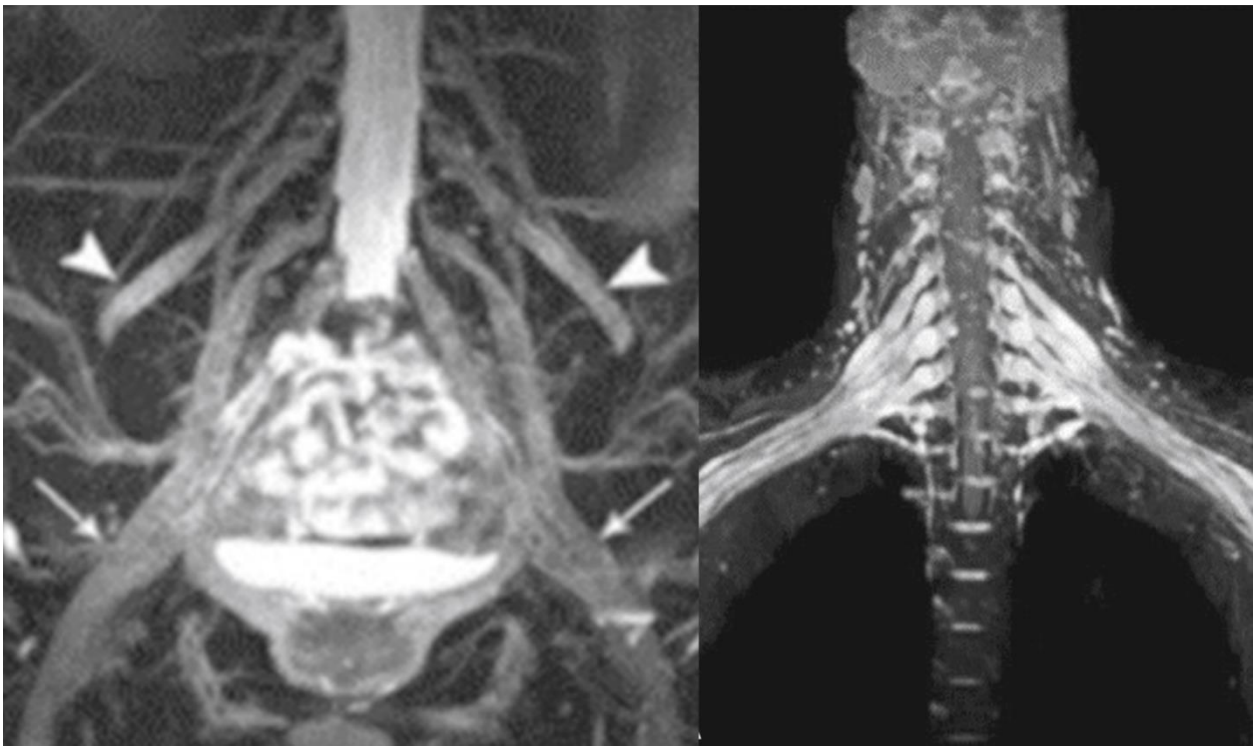

Figure 2. In patients with antibodies against NF-155, magnetic resonance with neurography shows bilateral hypertrophy of the brachial and lumbosacral plexuses. In the left image, a coronal section of the lumbosacral plexus displays bilateral hypertrophy affecting the terminal branches, femoral intrapelvic nerves, and sciatic nerves. In the right image, a coronal section of the brachial plexus depicts hypertrophy primarily in the nerve roots, gradually normalizing distally the distal part.

As secondary diagnostic tests, CSF findings show albuminocytologic dissociation with an increased celular number suggesting infection or malignancy[39]. Nerve biopsy is not recommended as a routine exam but only for cases that can't be confirmed[34].

Nodopathies - paranodopaties

The node of Ranvier ensures a rapid and long distance transmission of impulses making it a crucial structure for nerve conduction. In 2013, Uncini proposed the new term nodo - paranodopaties focusing on the disruption or disfunction of the nodal region associated with antibody mediated neuropathies[40]. This type of neuropathies are characterised by a continuum between conduction block and axonal degeneration (table 3).

Table 3. Nodopathies - paranodopathies

	Proteins and function	Presentation	Response to treatment
Antibodies agains contactin-1[43]	Adhesion protein. Paranodal juntions.	Late onset. Acute or subacute, rapidly progressive severe weakness and sensory symptoms.	Good response to steroids and rituximab. Poor response to IVIg.
Antibodies against neurofascin 186[44]	Cell adhesion molecule. Clustering of voltage gated Na channels.	Acute-subacute onset. Distal aquired demyelinating syndrome, sensory ataxia, craneal nerves impairment.	Good response to IVIg and steroids.
Antibodies against CASPR1[45]	Adhesion proteins.	Painful polineuropathy, ataxia and affects also craneal nerve.	Good response to rituximab, intermediate response to IVIg.
Antibodies against neurofascin 155[46]	Axoglial junction	Progressive and chronic course. Symmetric weakness with distal predominance, sensory deficit more frequent en lower limbs, tremor, ataxia and cranial nerve involvement.	Good response to Rituximab (77.3%), poor response to IVIg (13.1%), steroids (27.8%) and PLEX (38.9%).

Antibodies can be directed against different proteins at the node, including neurofascin-155, CASPR1, contactin, among others[41]. The presence of specific antibodies against node proteins has a diagnostic specificity close to 100%[42].

Multifocal motor neuropathy

Multifocal motor neuropathy is an uncommon, immune-mediated inflammatory mononeuropathy characterised by slowly progressive asymmetric distal weakness with preservation of proximal muscles[47]. Up to 40% of patients present with anti-GM1 IgM antibodies, with a specificity of up to 90% when titres are elevated. Anti-GM1 antibodies cause direct and complement-mediated injury to axons and the Ranvier node, making it a part of nodo-paranodopathies[48].

Classical clinical presentation involves multiple pure motor mononeuropathies in the upper limbs associated with prominent atrophy, fasciculations and cramps can be seen in 40% of cases. Exacerbation of weakness by cold temperatures is seen in 83% of cases. (48) in 2010, the European Federation of Neurological Societies created a set of clinical and electrophysiological criteria for diagnosis of multifocal motor neuropathy with three diagnostic categories: definite, probable and possible[49]. (table 4) (Figure 3).

Table 4. Diagnostic criteria for MMN 2010

Core criteria (must be present) - Slowly progressive or stepwise progressive, focal, asymmetric limb weakness, with motor involvement in the motor nerve distribution of at least two nerves for more than 1 month. - No objective sensory abnormalities except for minor decrease vibratory sensation in the lower limbs.	Electrophysiological criteria 1. Definite motor CB: Negative peak CMAP area reduction of at least 50% on proximal vs. distal stimulation. Negative peak CMAP amplitude on stimulation of the distal part of the segment with motor CB must be >20% of the lower limit of normal and >1mV and increase of proximal to distal negative peak CMAP duration must be ≤30% 2. Probable motor CB: negative peak CMAP area reduction of at least 30% over a long segment of upper limb nerve with increase of proximal to distal negative peak CMAP duration ≤30% or negative peak CMAP area reduction of at least 50% with an increase of proximal to distal negative CMAP duration >30% 3. Normal sensory nerve conduction in upper limb segments with CB
Supportive clinical criteria - Predominant upper limb involvement - Decreased or absent tendon reflexes in the affected limb - Absence of cranial nerve involvement - Cramps and fasciculations in the affected limb - Response in terms of disability or muscle strength to immunomodulatory treatment	
Exclusion criteria - Upper motor neuron signs - Marked bulbar involvement - Sensory impairment more marked than minor vibration sense loss in lower limbs - Diffuse symmetric weakness during the initial weeks	

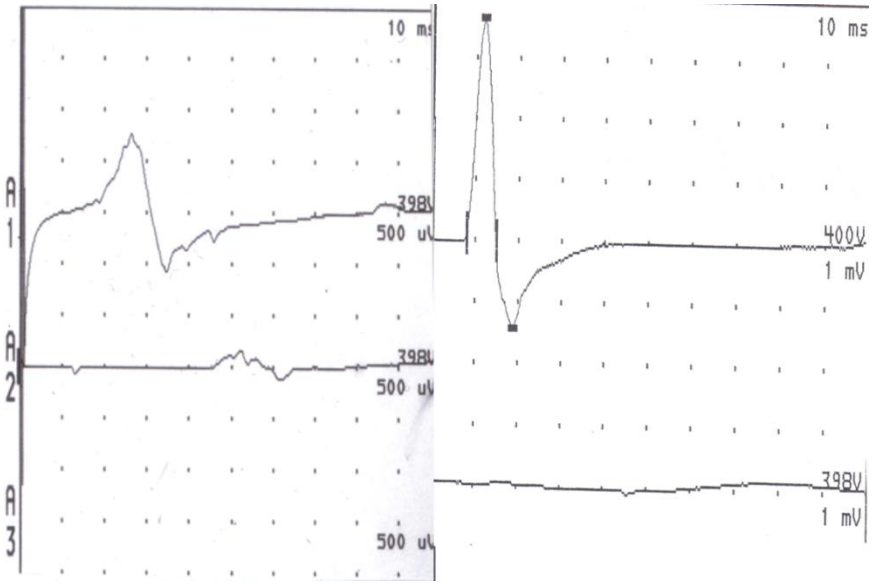

Figure 3 **A.** Partial conduction block and dispersion of the CMAP **B.** Normal CMAP of APB muscle with median nerve stimulation at the wrist and lack of response upon stimulation at the elbow showing complete conduction block.

IgM anti-MAG neuropathy

Myelin-Associated Glycoprotein (MAG) is located in the paranodal region, making it a susceptible target for autoantibodies. Anti-MAG neuropathy is the most common IgM paraproteinemic neuropathy, being found in up to 1% of individuals over the age of 50, with an incidence that increases proportionally with age[50]. It is associated with dysfunction or loss of large myelinated fibers, presenting as slowly progressive distal paresthesias primarily in the lower limbs. This condition progresses to proprioceptive impairment, sensory ataxia, gait instability, distal weakness, and tremor[51]. Clinical presentation corresponds to the distal variant in 83% of cases. The detection of anti-MAG antibodies forms the basis of diagnosis, which can be found in serum through ELISA or Western blot analysis[50]. (Figure 4).

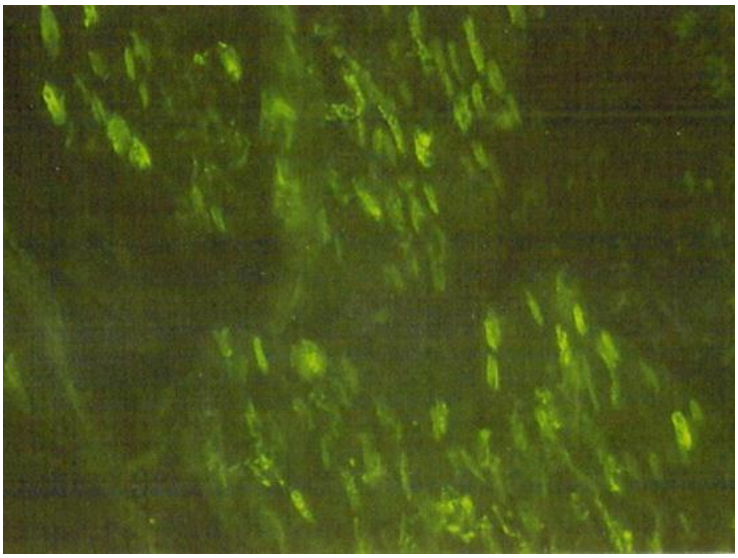

Figure 4. IgM immunoflourescence in anti-MAG neuropathy. 400X

POEMS syndrome (polineuropathy, organomegaly, endocrinopathy, M protein and skin changes)

Characterised by its acronym, POEMS is a rare paraneoplasic syndrome caused by a plasma cell disorder[53]. The peripheral neuropathy shares multiple features with CIDP, having a progressive course, primarily motor and albuminocytological dissociation. Vascular endothelial growth factor (VEGF) is an important marker for diagnosis and follow-up as it shows association with disease activity, being useful to rule out differential diagnoses like CIDP and multiple myeloma[53,54]. False positive results can occur in the setting of hypoxia, anemia and low iron, but values in POEMS tend to be as high as two or three times the upper limit[55]. New studies are researching on different markers, IL-6 has shown some concordance with VEGF but still needs more investigation[56].

Vasculitic neuropathies and crioglobulinemia

Vasculitis neuropathies are caused by inflammation of the vessels surrounding the peripheral nerves (vasa nervorum) leading to secondary ischemic injury. The classification of vasculitic neuropathies is a pivotal aspect of comprehending their clinical heterogeneity. Notable schemes include the Peripheral Nerve Society's 2010 classification, which stratifies primary vasculitides based on the caliber of affected vessels[57]. Additionally, the International Chapel Hill Consensus Conference classification of vasculitides in 2012 introduced a subdivision of small-vessel vasculitides with or without associated immunoglobulin deposition[58]. These classification systems provide a framework for characterising the diverse spectrum of vasculitic neuropathies. (Figure 5).

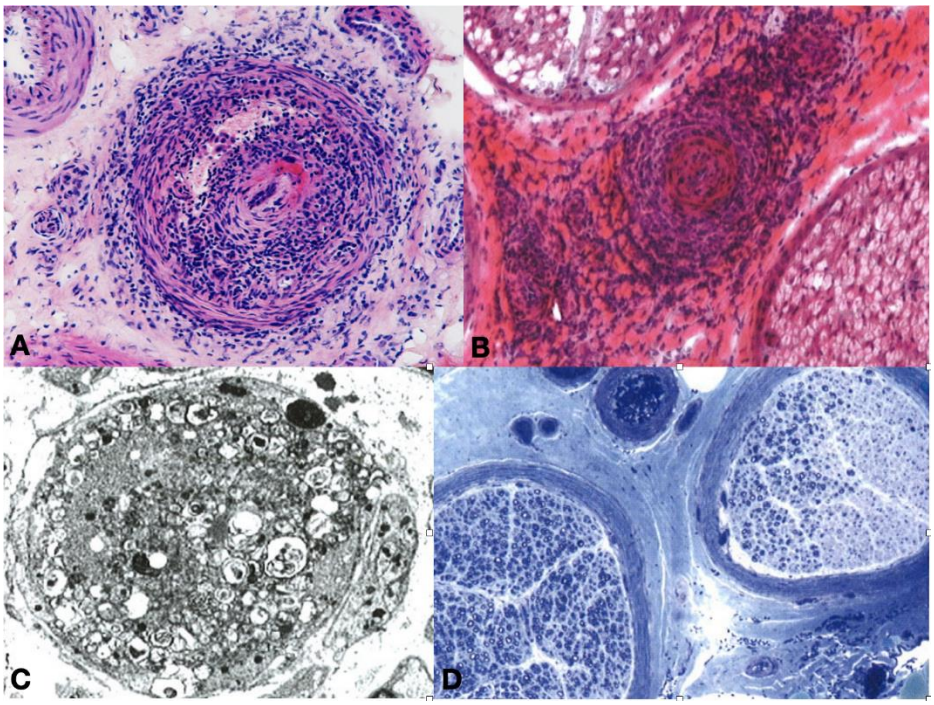

Figure 5. **A**. Inflammatory cells invading a vessel wall with recanalization and fibrinoid necrosis. H-E X 400 **B**. Interstitial and perivascular inflammatory infiltrate. **C**. axonal degeneration from vasculitus. Electron Microscopy X 4000 **D**. Focal loss of myelinated axons on a vasculitis case. Toluidine blue stain X 100

This neuropathies manifest in acute or subacute presentations, often characterised by multiple painful mononeuropathies with sensory or sensorimotor deficits. The clinical course typically evolves, progressively resembling a distal polyneuropathy due to cumulative nerve involvement. Ischemic lesions frequently impact proximal nerves, contributing to the intricate clinical presentation. Disease progression displays both stepwise exacerbations in two-thirds of cases and gradual progression in the remaining subset with 5-10% of patients have an acute presentation[59]. Non-systemic vasculitic neuropathies selectively target peripheral nerves, often presenting three classical patterns: multifocal neuropathy (13%), asymmetric polyneuropathy (85%) and distal symmetric polyneuropathy (2%). Examples include Wartenberg migratory sensory neuropathy, post-surgical inflammatory neuropathy, neuralgic amyotrophy, and painful diabetic radicular neuropathy[61].

Diagnosis is difficult and usually delayed approximately for 2 year and up to 8 to 13 years[61]. Definite diagnosis of vasculitis requires evidence of vascular inflammation and signs of vascular destruction like fibrinoid necrosis, hemorrhage or thrombosis. When biopsies lack complete evidence of vasculitis, probable or healed vasculitis should be considered[60]. The realm of vasculitic neuropathies extends beyond primary forms, encompassing secondary associations with connective tissue diseases, neoplasms, pharmaceutical agents, and other systemic inflammatory conditions. Consequently, a comprehensive diagnostic approach is crucial to exclude these underlying pathologies[5].

TREATMENT

According to the most recent update of EAN/PNS CIDP task Force treatment protocols in CIDP include corticosteroids or intravenous immunoglobulin for the treatment of typical CIDP and variants. Corticosteroids are widely available, but there is no agreement on which is the best regime. There is no difference between dexamethasone or metylprednisolone for induction and prednisone or prednisolone for maintenance[34]. In 2010, the PREDICT study showed no difference with high-dose pulsed dexamethasone or continuous prednisolone treatment in 6 months, but dexamethasone patients improved twice as fast[62]. Some patients may deteriorate with corticosteroids, specially the motor variant. In this patients IVIG should be considered the first-line treatment and only using corticosteroids if resistant to IVIG[63,64].

In 2008, ICE study proved the efficacy of IVIG for CIDP with a response of 94% of patients to an induction dose of 2gr/kg and 1gr/kg for maintenance every three weeks[65,66]. In 2018, the PATH study showed that SCIg is a less invasive alternative to IVIg for maintenance and more adequate for patients with difficult access, severe adverse effects to IVIg and wear-off phenomenon. IVIg has shown faster clinical improvement, less adverse effects and less drop out than methylprednisolone in a 6 month study[67].

There is no correct answer when choosing IVIg or corticosteroids, the proportion of relapse is similar with both treatments with a longer median time to relapse in with methylprednisolone[68]. IVIg has shown faster clinical improvement, less adverse effects and less drop out than methylprednisolone in a 6

month study. In the OPTIC protocol, the use of combined IVIg and methylprednisolone induced remission in 60% of treated patients in 20 patients, still needs to have a larger study[69].

Plasma exchange is recommended for the treatment of CIDP with initial course of five exchanges in two weeks. Between 22% and 66% of patients with CIDP have shown short term improvements with plasma exchange[70]. In 2018, the FORCIDP trial did not show beneficial effect between fingolimod and placebo[71]. Immunosuppressants such as cyclophosphamide, mycophenolate mofetil, azathioprine and methotrexate can be used in refractory patients, although further studies are needed[5].

Patients with nodopathies are resistant to IVIg and usually follow a treatment selection based on trial/error. Rituximab has been effective in patients resistant to conventional therapies[72]. New studies have shown that the monospecific and bivalent antiNF155 are the pathogenic ones. Transforming IgG4 into monovalent Fab through Fab-arm exchange decreases pathogenicity and paranodal alterations[73].

Anti-MAG neuropathy is often refractory to most of the conventional therapies, requiring specific treatment. Antibodies in this neuropathy have a direct effect in myelin structure and function, monoclonal antibody anti CD-20, Rituximab has shown an improvement in 30% - 50% of pacientes with a dose of 375mg/kg weekly for 4 weeks[50]. Despite the fact that anti-MAG IgM levels do not correlate with disease severity, a reduction of this values has been associated with clinical improvement being a marker of response to therapy. The removal of anti-MAG antibodies can be a target for future research[74].

The only effective therapy for multifocal motor neuropathy demonstrated in a Cochrane meta-analysis is IVIG, which demonstrated improvement in muscle strength in 78% of patients compared with 4% on placebo[75]. In a small study with MMN patients on maintenance IVIg, cyclophosphamide was added to their treatment and all patients showed improvement their muscle strength, but there have been no new studies[76]. Other treatments like corticosteroids, plasma exchange, rituximab and eculizumab haven't shown benefit and may worsen the condition[48].

The main goal in POEMS treatment is suppression of the plasma cell clone. Focal disease, characterised by 1 to 3 plasmacytomas seen in gammagraphy and no bone marrow lesions, radiotherapy in the indicated treatment. The presence of more than three lesions or bone marrow involvement is considered systemic disease and should receive systemic treatment. High dose melphalan followed by bone marrow transplant is the most effective therapy[54]. VEGF has proven to be a good biomarker in POEMS, but anti-VEGF monoclonal antibody, bevacizumab, has been ineffective suggesting that targeting VEGF alone is not enough to battle the disease[77].

Immunosuppression to stop inflammatory damage, followed by long-term maintenance is the treatment of choice for vasculitic polyneuropathies. Corticosteroids and cyclophosphamide for induction and maintenance demonstrate a better survival rate at 5 years. The French Vasculitis Study Group reported in 2015 that 50% of patients with corticosteroids monotherapy ended up requiring combination therapy with other inmmunosuppresive agent due to inadequate response or relapse[61].

Conclusion

Inflammatory neuropathies are a broad spectrum of treatable diseases and because of that reason all the efforts must go into having an adequate diagnosis aiming a good therapeutic response and recovery. When a patient doesn't show recovery with the more conventional treatments, it is important to reassess and think of less frequent pathologies.

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