Explorarea neurofiziologica in CIDP

Tudor Lupescu

- Neuropatie motorie / senzitiva
- Demielinizare, bloc de conducere,
- Uneori suferinta axonala
- Afectare predominant proximala
- Severitate, distributie

Criterii propuse 2000

BC parţial	scădere cu ≥ 20% arie / A
VC	¤ ↓ < 80% LIN dacă **A CMAP** > 80% LIN
	¤ ↓ < 70% LIN dacă **A CMAP** < 80% LIN
LD	- ↑ > 125% LSN dacă **A CMAP** > 80% LIN
	- ↑ > 150% LSN dacă **A CMAP** < 80% LIN
Unda F	# absent sau ↑ > 125% LSN dacă **A CMAP** > 80% LIN
	# ↑ > 150% LSN dacă **A CMAP** < 80% LIN

- Modificari:

Electroneurografie 1

Conducere motorie:

- VCM ↓
- Bloc de conducere (A d/p > 30% mb sup, >50% mb inf)
- Unda F: lat ↑, persistenta ↓
- Latenta distala ↑
- A_{CMAP} distal - initial N; A ↓ & ld N – suferinta axonala
- A CMAP ↓ - prin dispersie temporala & pierdere axoni

Electroneurografie 2

Conducere senzitiva

- VCS ↓ / nu se obtine
- A_{SNAP} ↓

Electromiografie

- Cazuri usoare – suferinta neurogena usoara, subacuta/inactiva, mm distali
- Cazuri severe – implica si muschii proximali

Modificari sistem nervos vegetativ:

- Int R-R anormal
- SSR anormal

Procedura (Stahlberg)

ENG

- Motor: nn tibial, peronier, median, ulnar unilat
- Senzitiv: n radial, n sural unilat

EMG

- 1 m prox & 1 m distal la mb inf & sup

Teste vegetative (optional)

- Int RR, SSR

Prag senzitiv (optional)

Procedura Brown, Bolton, Aminoff

- 1. Studii conducere senzitiva: nn sural & median (*raspunsuri cu A↓, absente – sustin dgn)*
- 2. Studii conducere motorie: nn. peroneal, tibial, ulnar, median – unilat suficient(*VCM ↓, raspunsuri cu A↓, absente – sustin dgn)*
- 3. EMG – 1 m distal + 1 m proximal, mb sup & inf (*a.s.↑ - afectare axonala; recrutare ↓/0 cu PUM N - BC)*

Dar:

- Deseori demielinizarea este predominant proximala
- Nivelul de incetinire a conducerii variaza pe diferite segmente ale nervului, sau intre diferiti nervi
- Tipic pt neuropatia demielinizanta dobandita:

Scadere nonuniforma a VCM + BC.

Sugerez explorare bilaterala cel putin conducerea motorie.

ENG – conducere motorie

- N. tibial – VCM (stimulare retromaleolar, fosa poplitee) + unda F
- N peronier – VCM (stim glezna, col peroneu, fosa poplitee)
- N. median – VCM (stimulare pumn, cot, brat) + unda F
- N ulnar – VCM stimulare pumn, sub cot, deasupra cotului, brat) + unda F
- BILATERAL

ENG – conducere senzitiva

- Nn. peronier superficial, sural
- Nn. median, ulnar

UNILATERAL

EMG

- Mm. tibial anterior, vast medial
- Mm. deltoid, IOD1/ADM/APB

UNILATERAL

Observatii

Clinical Diagnostic Criteria (EFNS/PNS)

1. Inclusion Criteria

a. Typical CIDP

Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and absent or reduced tendon reflexes in all extremities

b. Atypical CIDP

One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs):

- Predominantly distal weakness (distal acquired demyelinating symmetric, DADS)
- Pure motor or sensory presentations, including chronic sensory immune polyradiculoneuropathy affecting the central process of the primary sensory neuron (Sinnreich et al, 2004)
- Asymmetric presentations (multifocal acquired demyelinating sensory and motor, MADSAM, Lewis-Sumner syndrome
- Focal presentations (e.g., involvement of the brachial plexus or of one or more peripheral nerves in one upper limb
- Central nervous system involvement (may occur with otherwise typical or other forms of atypical CIDP)

2. Exclusion Criteria

- Diphtheria, drug or toxin exposure likely to have caused the neuropathy
- Hereditary demyelinating neuropathy, known or likely because of family history, foot deformity, mutilation of hands or feet, retinitis pigmentosa, ichthyosis, liability to pressure palsy
- Presence of sphincter disturbance
- Multifocal motor neuropathy
- Antibodies to myelin-associated glycoprotein

Electrodiagnostic Criteria (EFNS/PNS)

1. Definite

At least one of the following:

a. At least 50% prolongation of motor distal latency above the upper limit of normal values in two nerves, or
b. At least 30% reduction of motor conduction velocity below the lower limit of normal values in two nerves, or
c. At least 20% prolongation of F-wave latency above the upper limit of normal values in two nerves (>50% if amplitude of distal negative peak CMAP, 80% of lower limit of normal values), or v
d. Absence of F-waves in two nerves if these nerves have amplitudes of distal negative peak CMAPs at least 20% of lower limit of normal values + at least one other demyelinating parameter* in at least one other nerve, or
e. Partial motor conduction block: at least 50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter* in at least one other nerve, or
f. Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in at least two nerves, or
g. Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) of at least 9 ms in at least one nerve + at least one other demyelinating parameter* in at least one other nerve

2. Probable

At least 30% amplitude reduction of the proximal negative peak CMAP relative to distal, excluding posterior tibial nerve, if distal negative peak CMAP at least 20% of lower limit of normal values, in two nerves, or in one nerve + at least one other demyelinating parameter* in at least one other nerve

3. Possible

As in (1) but in only one nerve

CMAP, compound muscle action potential. To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. Temperatures should be maintained at least 33° C at the palm and 30° C at the external malleolus (good practice points).

* Any nerve meeting any of the criteria (a-g).

Supportive Criteria (EFNS/PNS)

1. Elevated cerebrospinal fluid protein with leukocyte <10/mm3 (level A recommendation)

2. Magnetic resonance imaging showing gadonlinium enhancement and /or hypertrophy of the cauda equine, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexus (level C recommendation)
3. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination in >5 fibers by electron microscopy or in >6 of 50 teased fibers
4. Clinical improvement following immunomodulatory treatment (level A recommendation)

CIDP with Concomitant Diseases (EFNS/PNS)

One of the following is present:

a. Conditions in which, in some cases, the pathogenesis and pathology are thought to be the same as in CIDP
- Diabetes mellitus
- HIV infection
- Chronic active hepatitis
- IgG or IgA monoclonal gammopathy of undetermined significance
- IgM monoclonal gammopathy without antibodies to myelin-associated glycoprotein
- Systemic lupus erythematosus or other connective tissue disease
- Sarcoidosis
- Thyroid disease

b. Conditions in which the pathogenesis and pathology may be different from CIDP
- Borrelia burgdorferi infection (Lyme disease)
- IgM monoclonal gammopathy of undetermined significance with antibodies to myelin-associated glycoprotein*
- POEMS syndrome
- Osteosclerotic myeloma
- Others (vasculitis, hematological and non-hematological malignancies, including Waldenström's macroglobulinemia and Castleman's disease)

Diagnostic Categories (EFNS/PNS)

Definite CIDP

- Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 1; or
- Probable CIDP + at least one supportive criterion; or
- Possible CIDP + at least two

Probable CIDP

- Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 2; or
- Possible CIDP + at least one supportive criterion

Possible CIDP

- Clinical criteria 1 (a or b) and 2 with electrodiagnostic criterion 3 CIDP (definite, probable, possible) associated with concomitant diseases

Investigations to Be Considered (EFNS/PNS)

To Identify CIDP

- Nerve conduction studies
- Cerebrospinal fluid cells and protein
- MRI spinal roots, brachial plexus, and lumbosacral plexus
- Nerve biopsy

To Detect Concomitant Diseases

- Serum and urine paraproteins detection by immunofixation (repeating this should be considered in patients who are or become unresponsive to treatment)
- Oral glucose tolerance test
- Complete blood count
- Renal function
- Liver function
- HIV antibody
- Hepatitis B and C serology
- Borrelia burgdorferi serology
- C reactive protein
- Antinuclear factor
- Extractable nuclear antigen antibodies
- Thyroid function
- Angiotensin-converting enzyme
- Chest radiograph
- Skeletal survey (repeating this should be considered in patients who are or become unresponsive to treatment)

To Detect Hereditary Neuropathy

- Examination of parents and siblings
- PMP22 gene duplication or deletion (especially if slowing of conduction is uniform and no evidence of partial motor conduction block or abnormal temporal dispersion)
- Gene mutation known to cause CMT1 or heredity neuropathy with liability to pressure palsies

CMT1, Charcot-Marie-Tooth disease type 1

Similar Disorders to CIDP

Several disorders are similar to chronic inflammatory demyelinating polyneuropathy (CIDP), but considered distinct from CIDP.

Multifocal Motor Neuropathy (MMN)

Multifocal Motor Neuropathy (MMN) is a pure motor disorder in which there is a multifocal attack on the motor nerve fibers of individual peripheral nerves. Essentially, it is a pure motor mononeuropathy multiplex. The characteristic feature of MMN is conduction block with or without other electrophysiologic features of segmental demyelination. MMN is considered distinct from CIDP because:

1. In a significant number of MMN patients (35-83%) there are high titers of antibodies directed against GM1 ganglioside.
2. CSF protein is not elevated
3. Reflexes are lost only in a multifocal fashion
4. MMN does not respond to corticosteroids or plasmapheresis

Lewis-Sumner Syndrome (L-SS)

In contrast, **L-SS,** a multifocal sensorimotor mononeuropathy multiplex, which is also characterized by multifocal persistent conduction block and is considered a variant of CIDP. L-SS tends to have higher CSF protein, no anti-GM1 antibodies and responds to treatment in a similar way to patients with symmetric CIDP. As such, except for the multifocal features, no other distinctions between L-SS and CIDP have been found.

Paraproteinemic Neuropathies

IgM is distinct from CIDP but IgA and IgG are not. There are strong reasons why IgM neuropathies are considered distinct from CIDP while patients with neuropathies and IgA and IgG paraproteins are considered to be variants of CIDP. IgG paraproteins can be seen in the normal aging population unrelated to any clinical disorder. Studies have shown that there is no increase in the incidence of neuropathy in people with IgG paraproteins. This also appears to be the case with IgA paraproteins. However, the incidence of neuropathy, particularly demyelinating neuropathies is significantly increased with IgM paraproteins. Thus, a patient with demyelinating neuropathy may have a coincidental IgG or IgA paraprotein but it is much more likely that an IgM paraprotein is related. It should be noted that IgA and IgG paraproteins may be seen in POEMS which should be carefully considered.

Approximately 50% of patients with demyelinating neuropathy and an IgM paraprotein have high titer antibodies directed against Myelin Associated Glycoprotein. These patients have a distinct clinical presentation of distal sensory predominant symptoms, distinct electrophysiologic features of distal accentuated conduction slowing, and a distinct lack of response to most immunosuppressive treatments. It is therefore very clear that anti-MAG neuropathies are distinct from CIDP.

The issue with other IgM neuropathies is less clear. The EFNS/PNS guidelines point to separating anti-MAG neuropathies from CIDP but not separating other IgM neuropathies. However, the literature

tends not to show any differences between patients with distal sensory predominant neuropathy and IgM paraproteins and anti-MAG antibodies and those without the antibodies. Both groups of IgM neuropathies have distal accentuated slowing and poor response to immunosuppression. For that reason, many authors believe that all demyelinating neuropathies with IgM paraproteins should be considered distinct from CIDP.

Other peripheral neuropathies

Other systemic conditions or infectious agents that cause inflammatory peripheral neuropathy include

- Waldenström's macroglobulinemia,
- collagen vascular disease,
- immune complex disease,
- cryoglobulinemia associated with hepatitis,
- Borrelia burdorferi,
- Mycobacterium leprae, and
- Trypanosoma cruzi.

Applying Diagnostic Criteria in Clinical Practice

One of the critical issues facing the practicing neurologist is early recognition and treatment of CIDP patients when they are more likely to respond and, in some cases, go into remission. Unfortunately, there is no definitive diagnostic test for CIDP.

Diagnosis is based on

- the clinical history,
- neurological examination and supported by electrodiagnostic studies,
- cerebrospinal fluid (CSF) findings,
- blood studies to exclude other disorders, and
- nerve biopsy (infrequently performed).

Particularly, patients with early symptoms of the disorder may have predominantly sensory episodes of paresthesia prior to the onset of motor weakness. However, even then nerve conduction studies can display features of peripheral nerve demyelination with partial motor conduction block at other than compression points, temporal dispersion of compound action potentials, prolonged distal and F wave latencies, and reduced conduction velocities that involve at least two and frequently more nerves as the course extends over time. Identification of these changes in even one nerve at a non-compression area would indicate the need for close follow up and, with more widespread clinical progression, the institution of a therapeutic measure.

Increased protein and normal cell counts in the CSF can be used to support the diagnosis and confirm the disorder. Nerve biopsy is usually not required but should be considered in cases were the diagnosis is in question for example with pure sensory syndromes or where other etiologies such as vasculitis are suspected.

Treatment Options

Carol L. Koski, M.D., Principal Author

Initial treatment for CIDP commonly commences when disease progression occurs rapidly or when patient mobility is compromised. However, it is important to provide treatment before axonal loss occurs because recovery is much more difficult once axons are damaged. In general, therapies are initiated to block the immune processes, thereby arresting inflammation and demyelination, and preventing secondary axonal degeneration. (Koller, 2005)

Although the pathophysiology underlying CIDP is not well understood, approximately 50% to 70% of patients with CIDP respond adequately to the initial therapy chosen. Those who do not respond to initial therapy may be helped by trying a different treatment. Eventually, up to 80% of patients with CIDP respond to one or more therapeutic regimens, either as monotherapy or in combination.

Three treatments are commonly used for initial therapy for CIDP and all of them appear to be equally effective in for short term (weeks). (Dyck, 1994; Hughes, 2001) They are:

- high dose intravenous immunoglobulin (referred to by the acronyms: IVIG, IgIV, or IGIV),
- plasma exchange (referred to by the acronym PE; also called plasmapheresis), and
- corticosteroids

Treatment recommendations have recently been proposed by a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. (Joint Task Force, 2005)

The joint task force recommends:

1. Intravenous immunoglobulin (IVIG) or corticosteroids should be considered first line in sensory and motor CIDP;
2. IVIG should be considered as an initial treatment in pure motor CIDP;
3. If IVIG and corticosteroids are ineffective, plasma exchange should be considered;
4. If the response after 3 months is inadequate or the maintenance doses of the initial treatment are high, combination treatments or adding an immunosuppressant or immunomodulating drug should be considered; and
5. Symptomatic treatment and multidisciplinary management should be considered.

The EFNS/PNS Guidelines as noted above suggest that IVIG should be considered as an initial treatment in pure motor CIDP. Pure motor CIDP is clinically distinct from many of the other demyelinating neuropathies.

The guidelines above address the recommendation of prescribing plasma exchange therapy when IVIG or prednisone therapies have not proved to be effective. Most researchers and many practicing neurologists will continue the trial of initial therapy of IVIG or prednisone **for at least one month**, sometimes two months or even longer, depending on the patient and symptoms, before initiating plasma exchange therapy. Still others will prescribe plasma exchange for patients while the patient is still on initial therapy.

Also, the guidelines recommend combination treatment or adding other drugs to the initial regimen. The addition of 30 mg to 40 mg of prednisone daily reduced the frequency of repeated IVIG therapy. (Hahn, 1996); the addition of cyclophosphamide and cyclosporin has been of limited benefit in some patients. (Gorson, 1997)

IVIG exerts multiple actions on the body's immunoregulatory network that operate in conjunction with each other. (Dalakas, 2004) These actions include:

1. modulating pathogenic autoantibodies,
2. suppressing idiotypic antibody,
3. upreguating Inhibitory FcγR on macrophages to inhibit phagocytosis and decrease TNF-alpha production (Nimmerjahn, 2007), and
4. suppressing various inflammatory mediators (including cytokines, chemokines, and metalloproteinases).

IVIG Dosing and Tolerability

Carol L. Koski, M.D., Principal Author

IVIG is usually administered at a dose of 2.0g/kg body weight which may be divided into 5 daily doses of 0.4 g/kg, or can be given slowly as 2 daily doses of 1 g/day, depending on patient tolerance (Koski, 2005).

The following recommendations are based on faculty experience and some of this is supported by current literature.

1. Children can tolerate a 2 g/kg without side effects as a single infusion.
2. Young adults without co-existing disorders can well tolerate 1g/kg as a single infusion.
3. In older patients or those with concurrent renal or cardiovascular disorders, a slow rate of infusion totaling 400mg /kg per day is advisable.

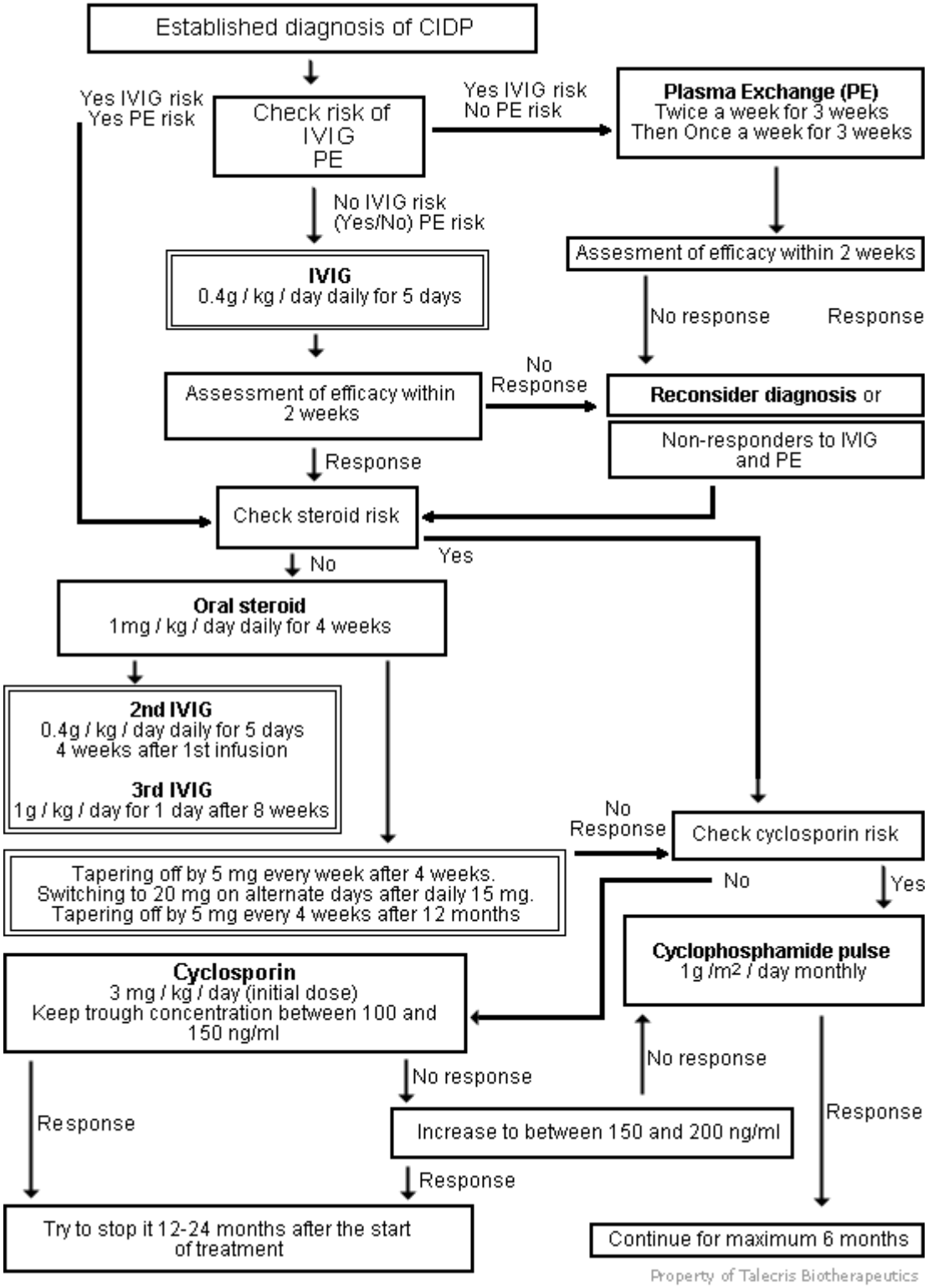
Overall, IVIG is usually well tolerated, particularly in initial courses of IVIG, and preparations available today are safe. Generally, the differences in IVIG preparations are in the amount of IgA and sugar content present. Some of the IVIG preparations contain sucrose, glucose or some other sugar as a stabilizer. Some IVIGs do not contain preservatives.

Rarely, IVIG may be associated with renal dysfunction, acute renal failure, osmotic nephrosis, and death. Thrombotic events have been reported in association with IVIG. There have also been reports of noncardiogenic pulmonary edema and very rare reports of aseptic meningitis.

IVIG: Administration

A needle attached to tubing is inserted into a vein and a solution of IVIG is infused. Depending on the institution, the product, and the size of the patients, protocol for rate of infusion can take several hours.

CIDP flow-chart treatment pharmacological protocol



Many institutions require hospitalization for at least the first round of IVIG therapy. Depending on the practice, most patients are able to receive subsequent treatments at home using the services of a home health care agency. Others are able to receive IVIG infusion on an outpatient basis.

IVIG therapy can be given in combination with steroids, methotrexate, and other immunosuppressants. In addition, IVIG therapy can be used in conjunction with antibiotics. However, IVIG should always be infused alone and never mixed in the same bag with other medications.

Not All IVIGs Are The Same

Carol L. Koski, M.D., Principal Author

Different IVIG products have the potential to match different patients. Clinicians need to be aware of the differences among the various products when administering IVIG to high-risk patients. Some examples include:

- Patients with congestive heart failure or compromised renal function may fare better if they receive a product with a low osmolality and low volume;
- Patients who are diabetic should receive a product containing no sugars; patients receiving products with sucrose may be at a higher risk for renal failure;
- Patients with immunoglobulin A (IgA) deficiencies who also have anti-IgA antibodies should only receive products with the lowest amount of IgA to avoid possible anaphylactic reactions. THIS APPLIES TO ALL OF THE PRODUCTS.
- Patients with small peripheral vascular access or a tendency toward phlebitis may want to avoid preparations with a low pH.

Because of the ease of IVIG administration through a peripheral line and the ability to give the drug in the outpatient setting, IVIG therapy is usually an initial treatment of choice. **In many patients, a beginning response to IVIG therapy can be documented with improved motor function within 3 to 5 days of the infusion.** (Koski, 2005)

Knowing Your Patient's Risk Prior to Infusion of IVIG

Despite the overall safety record of IVIG, as more patients are receiving higher doses, reports of significant adverse events have increased. Strikingly, the development of a severe adverse event may occur with the first infusion and is not predictable (Hamrock, 2006). As a result, it is important as much as possible to define potential risk factors in the patient prior to choosing an IVIG product. Careful risk assessment coupled to understanding of the composition of different IVIG preparations may help prevent short- and long-term complications. The table outlines a scheme for matching patient risk factors and potential risk factors intrinsic to the composition of the IVIG preparations. Selection of a product that minimizes fluid load, and is at physiologic osmolality with low sugar and sodium content may be the safest option. In the presence of obvious risk factors, screening for Factor V Leiden, renal function, or other coagulopathies may be indicated, as well as careful attention to the total dose in a single infusion and the rate of infusion.

Because all IVIG products are not the same, the likelihood of a safe and successful outcome will be increased by the careful selection of the appropriate IVIG.

Matching Risk Factors

	IVIG Risk Factors					
Patient Risk Factors	**Volume Load**	**Sugar Content**	**Sodium Content**	**Osmolality**	**pH**	**IgA**
Cardiac Impairment	x		x	x		
Renal Dysfunction Anti-IgA Antibodies	x	x	x	x		x
Thromboembolic Risk	x		x	x		
(Pre) Diabetic		x				
Elderly Patients	x	x	x	x		
Neonates/Pediatrics	x		x	x	x	

Corticosteroids

Oral glucocorticoids are another initial treatment option. **A six-week course of oral prednisone, starting at 60 mg daily, produced a benefit that was not significantly different than that seen by a single course of IVIG 2.0 g/kg.** (Hughes, 2001)

Oral prednisone may be administered at 50 mg to 100 mg/day (usually 1mg/kg/day) for at least one month or until clinical improvement begins, followed by a gradual dose reduction of 5 mg every 2-4 weeks, to every other day therapy without disease breakthrough. The risk of recurrent symptoms when tapering the dose varies with disease types. However, with CIDP, relapse is more common in patients who have had their disease for greater than one year, and the relapse is greater in adults, more so than children. As noted in several studies (Lindenbau, 2001, Mehndiratta, 2001, and Van der Meche', 1995), **up to 70% of patients relapse when the dose of prednisone is reduced**.

In the Cochrane review (Van Schaik, 2002) mild and transient side effects were reported in 38 out of 99 (38%) IVIG patients, 9 out of 46 (20%) placebo-treated patients, and in 11 out of 27 (41%) prednisone-treated patients. Serious side-effects like, aseptic meningitis (1), transient hypertension (3), and heart failure (1) were encountered in 5 out of 99 (5%) IVIG patients, in 2 out of 46 (4%) placebo-treated patients, in 2 out of 27 (7%) prednisone-treated patients, and in 2 out of 17 (12%) plasmapheresis patients. These differences were not statistically significant. However, it should be noted that serious side-effects known to occur after prolonged treatment with steroids were not seen due to very short prednisone regimes given in this particular trial.

Immunosuppressant Issues

Carol L. Koski, M.D., Principal Author

Various immunosuppressive agents are used to treat CIDP. Listed below are the various agents and the side effects noted for each agent. Note also that several of the agents have a Warning Box included in their package insert, as well.

- Azathioprine Side Effects
- Cyclophosphamide Side Effects
- Mycophenolate mofetil Side Effects
- Rituximab Side Effects
- Etanercept Side Effects
- Interferon-a Side Effects

Pathogenesis (Immunopathogenesis)

Marinos C. Dalakas, M.D., Principal Author

CIDP is a multifocal disorder that primarily affects spinal nerve roots, spinal nerves, major plexus, proximal nerve trunks and peripheral nerves. (Kieseier, 2002) CIDP lesions extend throughout the peripheral nervous system (PNS). In some cases, these lesions also extend to the intramuscular nerves, the sympathetic trunks, and the terminal autonomic nerves. (Dyck, 1993) Both cellular and humoral immune factors are involved in CIDP. (Rezania, 2004)

Cellular Immune Response

Marinos C. Dalakas, M.D., Principal Author

In autoimmune diseases, such as CIDP, autoreactive T and B cells are unleashed, become activated, and cause organ-specific damage. (Kieseier, 2002; Quattrini, 2003) Evidence of T-cell activation in the systemic immune compartment in patients with CIDP exists, although antigen specificity remains largely unknown. (Hartung, 1991; Dalakas, 1999; Van den Berg, 1995) Activated T cells cross the blood-nerve barrier (BNB) of patients with CIDP. As a result, these patients have increased levels of soluble adhesion molecules, chemokines, and matrix metalloproteinases in serum, in cerebral spinal fluid (CSF), or in both. (Keiseier, 2002; Previtali, 1998; Previtali, 2001; Kastenbauer, 2003; Leppert, 1999; Keiseier, 1998)

The activated T cells, once they have entered the PNS, may undergo clonal expansion following an encounter with an antigen presented in the context of appropriate major-histocompatability-complex molecules and co-stimulatory signals expressed on the macrophages and the Schwann cells. (Köller, 2005; Murata, 2000)

Humoral Immune Response

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For more than 20 years, it has been acknowledged that autoantibodies contribute to the pathogenesis of CIDP, due to the discovery of immunoglobulin and complement deposition on myelinated nerve fibers and the presence of IgG bands in cerebrospinal fluid. (Dalakas, 1980)

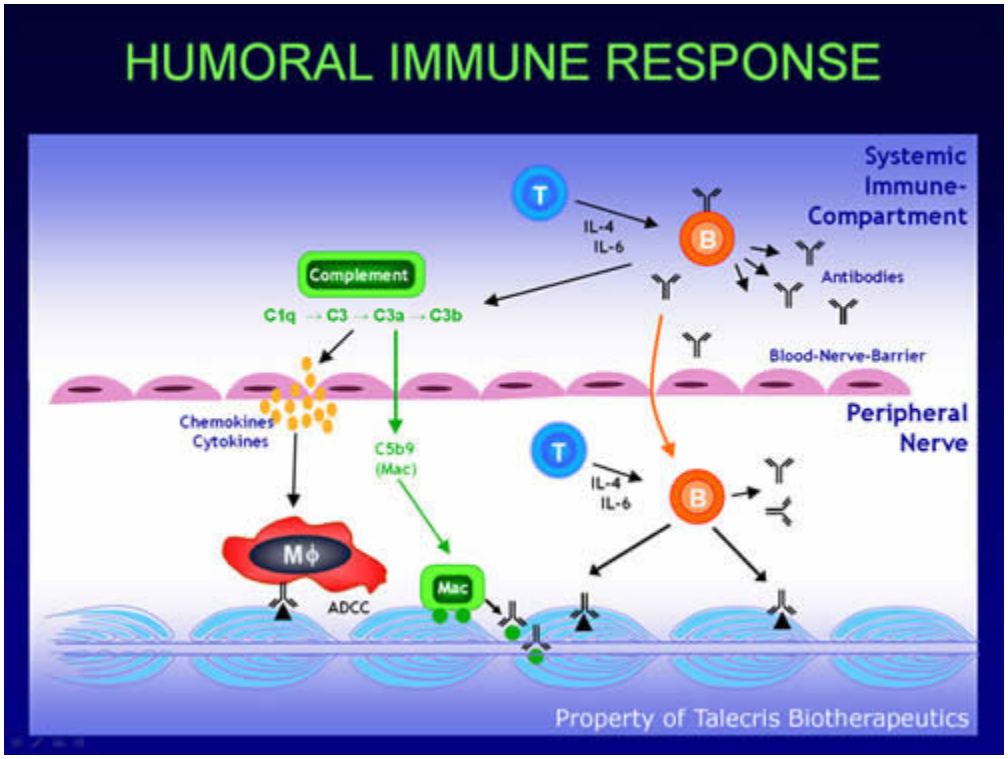
Passive transfer experiments have demonstrated that serum or purified IgG from a small number of patients with CIDP induces conduction block and demyelination in rat nerves with the 28-kD myelin protein zero being identified as one of the putative target antigens. (Yan, 2000). Passive transfer of CIDP IgG prolongs NCV in marmoset monkeys (Heininger, 1984).

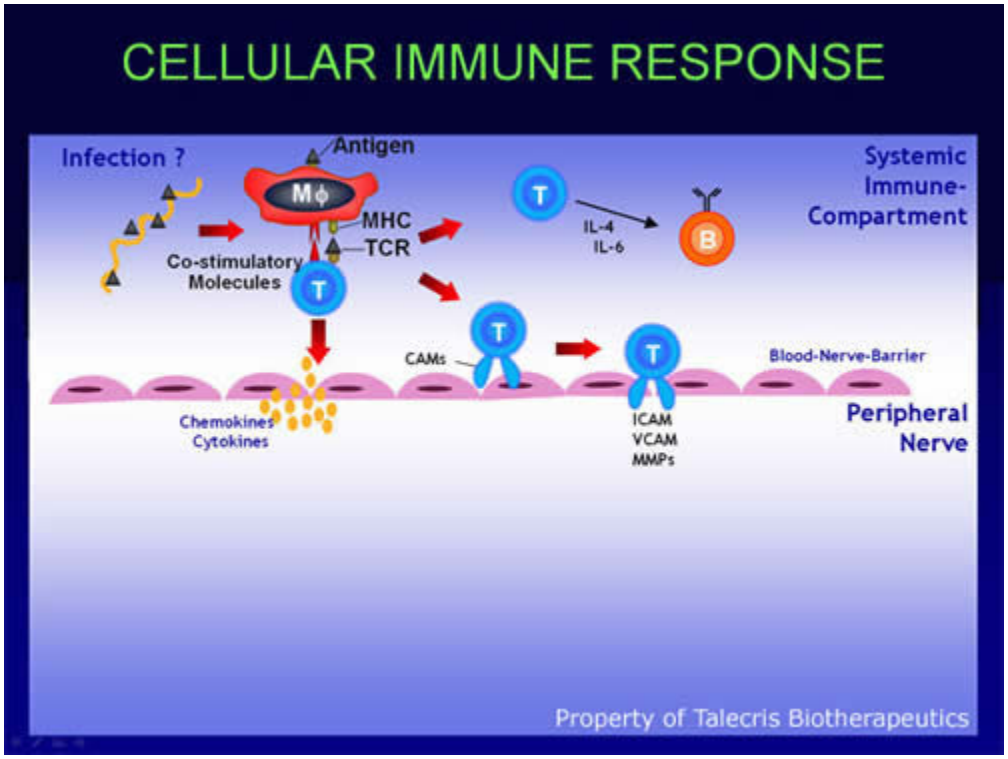
Other target antigens may be gangliosides and/or related glycolipids. In a few patients with CIDP, serologic evidence shows recent infection with Campylobacter jejuni. Given the shared expression of carbohydrate epitopes in nerve glycolipids and microbial lipopolysaccharides, this finding may hint at molecular mimicry as the underlying cause of CIDP in rare cases. (Melendez-Vasquez, 1997) The best example of molecular mimicry in CIDP is when the disease is rarely associated with melanoma because several carbohydrate epitopes are shared by the myelin sheath and the melanoma. (Weiss,1998)

In a small study of 46 patients with CIDP, 12 patients had serum reactivity against presumably nonmyelin antigens on Schwann cells. (Kwa, 2003)

A role for complement, autoantibodies or and immune complexes in CIDP is also supported by the presence of complement activation products in peripheral nerve or plasma and deposition of IgM, IgG and C3 of some patients (Dalakas 1980, 1982; Nyland, 1981; Koski,1985, 1990)

Demyelination and conduction block may also result from serum constituents such as cytokines, complement, or other inflammatory mediators (e.g., nitric oxide). The low frequency of specific antibodies seen in patients with CIDP may imply that various antibodies and separate mechanisms are involved in individual patients.



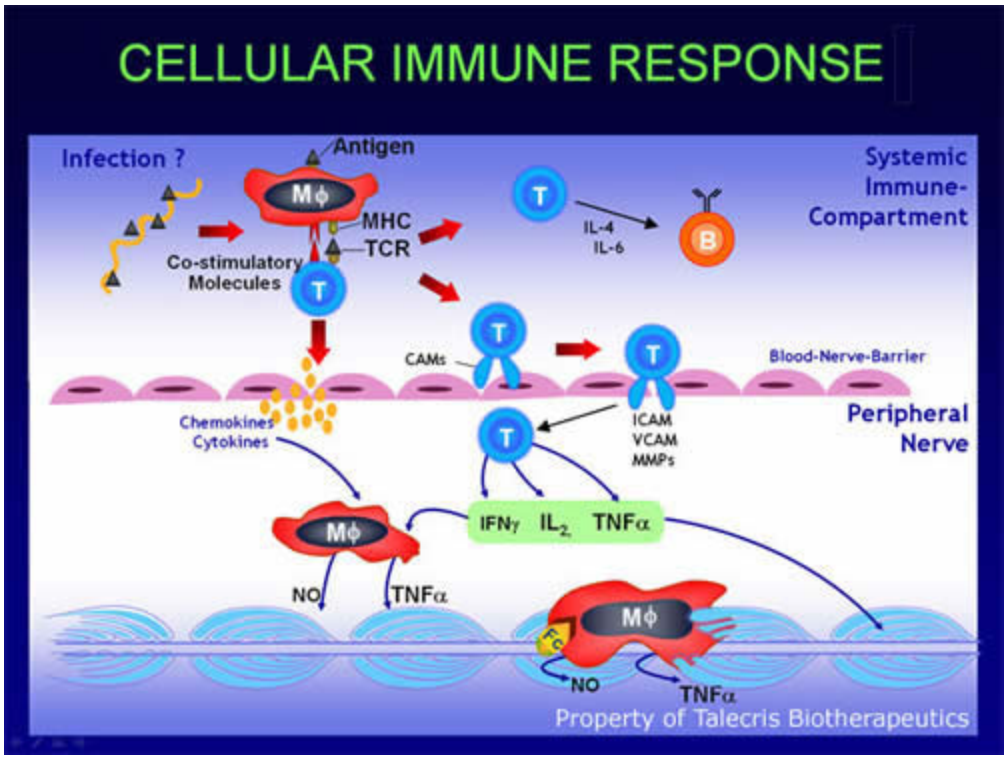


Activated T cells express and secrete cytokines, including tumor necrosis factor (TNF), alpha and interferon-γ, and interleukin-2. (Gold, 1999; Mathey, 1999). T cells then activate resident endoneurial macrophages, which secrete several neurotoxic and immunopotentiating molecules, such as oxygen radicals, nitric oxide metabolites, proteases, and complement components. (Keifer, 2001; Hu, 2003). T cells also engage in increased phagocytic and cytotoxic activity against myelin or Schwann cells.

Specialized subpopulations of T cells may terminate the acute immunoinflammatory process by secreting down-regulatory cytokines (e.g., transforming growth factor β;) or other molecules. (Köller, 2005) Macrophages may also serve as antigen-presenting cells in CIDP, a finding that is made evident by the observed expression of the major-histocompatability-complex class II molecule CD1a in nerve-biopsy specimens. (Van Rhijn, 2000)

Co-stimulatory. molecules B7-1 and B7-2, which are essential for effective antigen presentation, may determine the differentiation of T lymphocytes into a phenotype of type 1 or type 2 helper cells. (Köller, 2005) These molecules are expressed on endoneurial macrophages and Schwann cells, both of which may serve as antigen presenting cells in CIDP.

The cellular immune response within the PNS is tightly regulated at the transcriptional level. One of its key regulators is the transcription factor nuclear factor-κβ which is up-regulated predominantly within the endoneurial macrophages in CIDP. (Köller????
??)



Axonal Loss

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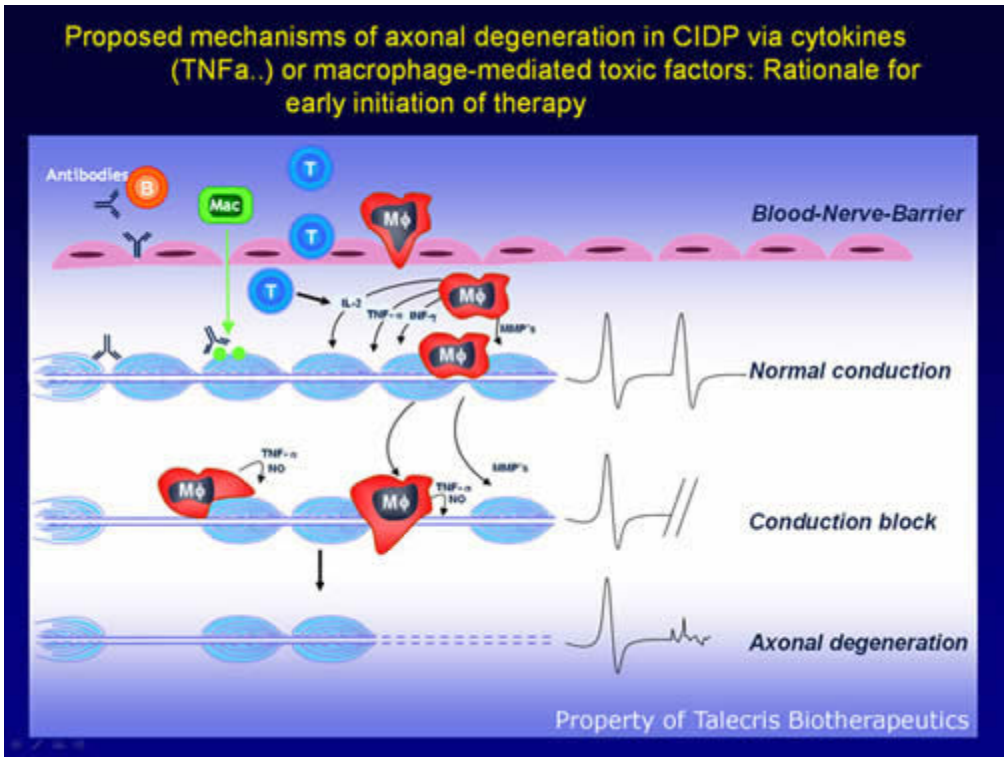
A concomitant axonal loss has been attributed to the primary demyelinating process in patients with CIDP. It is not fully known whether or not the release of neurotoxic cytokines (e.g., TNFα) and noxious mediators, such as nitric oxide and metalloproteinases, enhance axonal loss. (Bouchard, 1999; Dalakas, 1999) However, since the long-term prognosis of CIDP depends on the magnitude of axonal loss rather than on the degree of demyelination, this finding is very important. (Köller, 2005)

Axonal degeneration and loss has a greater long-term prognostic impact of CIDP than active demyelination, inflammatory infiltrates, or onion-bulb formations. (Rezania, 2004)



What is CIDP?

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Chronic inflammatory demyelinating polyneuropathy (or polyradiculoneuropathy), abbreviated as CIDP, is the **most commonly acquired demyelinating neuropathy**. Since the etiology remains unknown, CIDP remains a syndrome with several variants, primarily defined by differences in clinical presentation. The classification is still debated but virtually all neurologists define the disorder as being **chronic (> 8 weeks progression), demyelinating, and inflammatory or immune-mediated**.

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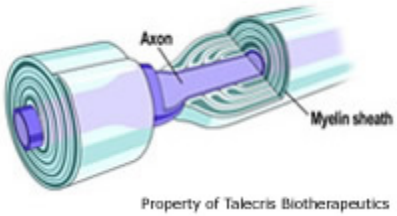


CIDP is considered to be an **autoimmune disorder whereby autoantibodies attack and destroy the myelin sheath** of the peripheral nerves. (Latov, 2002) It can commonly present either as a continuously progressive affliction or, less often, as a recurrent disorder in which episodes (relapsing and remittent) in individual patients may be separated by months or years.

Classic CIDP, Variant s , and GBS Similarities

The **"classic" form of chronic inflammatory demyelinating polyneuropathy** is characterized by symmetric proximal and distal weakness, some sensory involvement, and loss of deep tendon reflexes. However, some patients who are considered to have "variants" of CIDP present with a pure sensory disorder, some with a multifocal, asymmetric disorder, or in association with other systemic or neurologic disorders.

While the disorder is distinguished from Guillain-Barre syndrome (GBS) because of its **chronic** course, CIDP and GBS share many features, including:

- elevated cerebrospinal fluid (CSF) protein levels
- symmetric proximal and distal weakness
- areflexia
- demyelination
- immunopathologic features

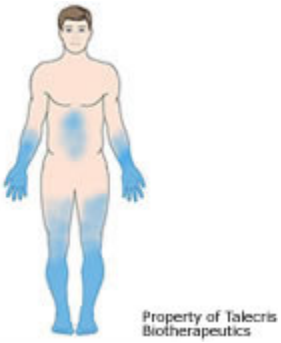
Causes of CIDP

The cause of CIDP is not known. As a syndrome, different causes and triggers are likely. However, it is generally accepted that most, if not all, CIDP manifestations are autoimmune, triggered by infections or

toxins in genetically susceptible individuals. The autoimmune nature of CIDP is suspected because of its occasional association with other immune-mediated diseases, such as systemic lupus, hepatitis B and C, HIV, and multiple sclerosis (MS), its response to immunosuppressive and immunomodulatory treatments, and pathologic findings on nerve biopsy. Other causes of neuropathy that may be difficult to distinguish from CIDP include:

- inherited neuropathy
- systemic inflammatory-autoimmune disorders
- dysproteinemias
- diabetes mellitus
- vasculitis
- other metabolic and toxic neuropathies

Clinical Manifestations



In the "classic" form, the onset of chronic inflammatory demyelinating polyneuropathy (CIDP) is usually gradual. The disorder is characterized primarily by progressive, usually symmetrical, weakness in the legs and arms that increases for more than 2 months (thereby distinguishing itself from Guillain Barre syndrome (GBS), which reaches its zenith within 2 to 3 weeks, followed by a plateau period and subsequently a gradual, but complete, recovery).

Hyporeflexia, impaired ambulation, sensory loss, often with distal loss of proprioception, and prominent electrophysiological signs of demyelination are evident in CIDP patients.

Limb weakness involving both proximal and distal muscles (Dyck, 1975) is usually symmetrical but in some CIDP patients can begin asymmetrically.

Most CIDP patients experience a chronic progressive course but some, usually younger patients, may have a relapsing and remitting course. Although occasionally patients achieve a sustained remission without the requirement of therapy, and some patients do go into remission after treatment, in most patients, CIDP remains a chronic disorder requiring maintenance therapy indefinitely.

Most CIDP patients who present with motor symptoms only have some sensory abnormality on clinical examination and/or sensory abnormalities on electrodiagnostic testing. More sensory symptoms and signs may develop as the disorder progresses, but the motor features usually remain predominant. On

the other hand, as many as 15% of CIDP patients may present with only sensory symptoms including tingling, "pins and needles" sensations, and lack of coordination. They may have no clinical weakness, but motor conduction studies reveal conduction slowing in motor nerves as well as in sensory nerves. While many of the CIDP patients who start with only sensory symptoms develop motor signs within two to three years, many persist with a pure clinical sensory disorder. (van Dijk, 1999)

Tremor may occur in about 10% of patients and become more prominent during subacute worsening of the disorder. (Dalakas 1991; Dalakas 1984) Cranial nerves may be affected in at least 10% of patients, (Dyck et al 1975) but not as often as in GBS. Optic neuritis also may be seen, implying coexisting central demyelination.

CIDP, originally described as a steroid-responsive disorder by Austin (1948), responds to immunotherapies. After a year of successful therapy, nearly 75% of CIDP patients regain a reasonable functional status. Early diagnosis and treatment can play an important role in increasing the prospects for a good recovery. Death from CIDP is uncommon.