Life After CIDP

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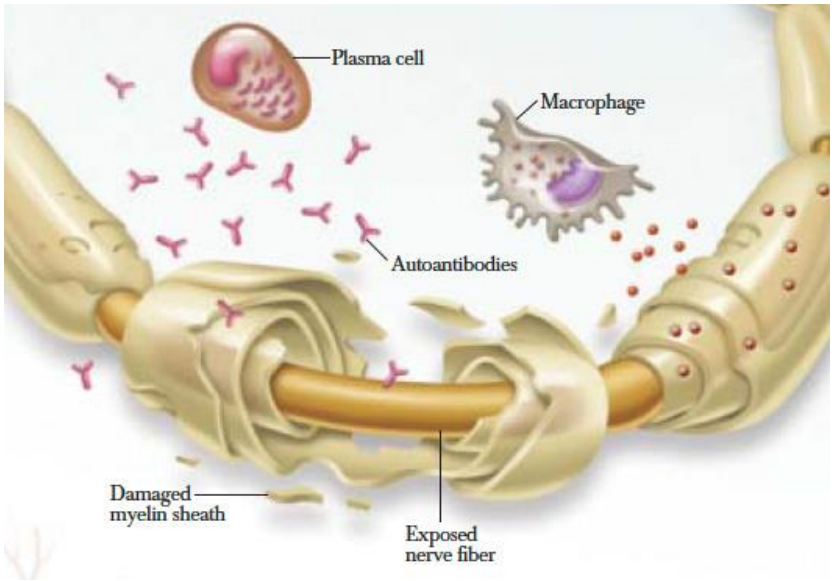
Patients' reactions after dx of CIDP

Is there any treatment for this condition?

What is CIDP?

* Chronic inflammatory demyelinating polyneuropathy (CIDP) is an autoimmune disorder characterized by inflammation of peripheral nerves and nerve roots resulting in destruction of myelin sheath (fatty protective covering).



Medgadget

CIDP- cont'd

* Incidence (new cases): 0.7 -1.6/100,000 per yr; prevalence: 0.8-8.9/100,000
* Men > women (2:1)
* Can affect all ages; average age of onset ~50 y/o
* It can be progressive (14.5%), relapsing-remitting (71%), or monophasic (one bout lasting 1-3 yrs) (14.5%) (Mahdi-Rogers, 2010).
* Other studies: relapsing form (20-35%)(Vallat 2010); monophasic in 53%, relapsing in 47% (Barohn 1989)

Historical Perspectives

* 1874: The first case report of “recurrent neuritis” (Eichhorst H. Virchows Archiv 1874).
* 1921: Association of recurrent neuritis with nerve hypertrophy was reported (Nattrass FJ . J Neurol Psychopathol. 1921)
* 1958: “Recurrent, steroid responsive neuropathy” was described in 2 patients and clinical features reviewed in additional 9 patients (Austin JH. Brain 1958)
* 1975: The term “chronic inflammatory demyelinating polyradiculoneuropathy” was coined, analyzed clinical/ pathological data from 53 patients (Dyck PJ, et al. Mayo Clin Proc 1975).
* 1982: first report of plasmapheresis in CIDP (Tindall RS. Prog. Clin. Biol. Res 1882)
* 1985: The first use of IV immunoglobulin (IVIG) in CIDP (Vermulen M, et al, J Neurol. Sci 1985)

Clinical Features of CIDP

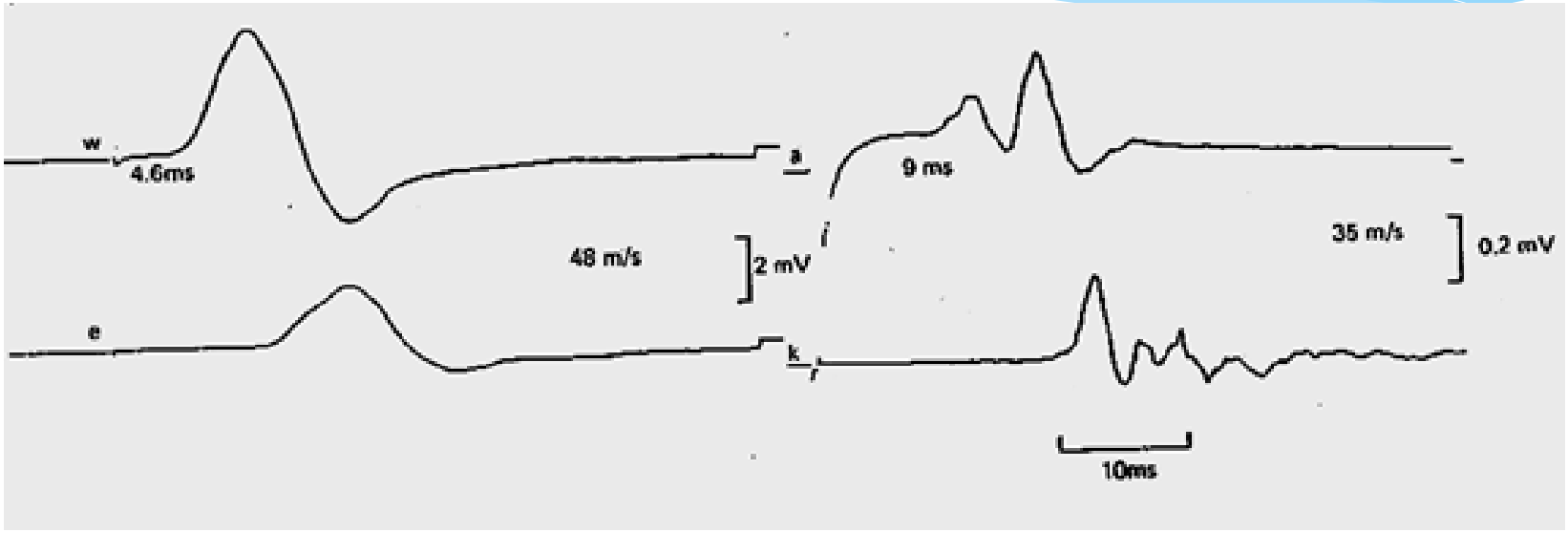
* Clinical features:
  * Symmetric weakness of proximal and distal muscles progressing over 2 months
  * Varying degrees of tingling and numbness
  * Reflexes reduced or absent
  * Cranial nerves may be involved (e.g. facial weakness).

* Other symptoms (+/-): fatigue, neuropathic pain, tremors, restless leg syndrome, mild autonomic dysfunction (GI & GU)

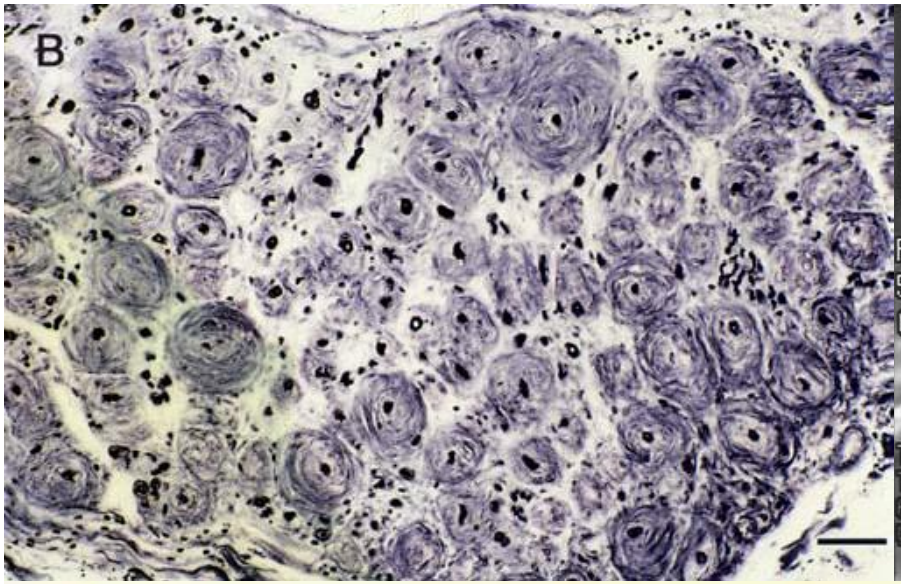
W/u for CIDP

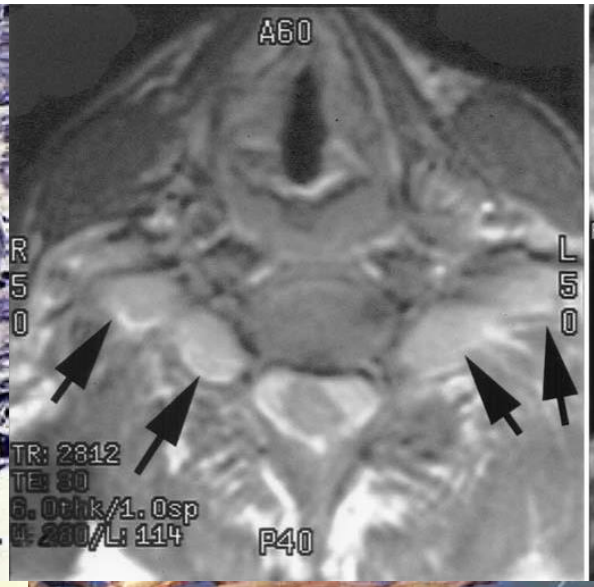
* Laboratory tests
  * Looking for mimics
  * Antibodies against PNS (ganglioside Ab, anti-MAG etc)
* Nerve conduction testing: very slow conduction velocities
* Spinal tap: high protein
* Sometimes nerve biopsy is done to exclude other inflammatory neuropathy (sarcoidosis, vasculitis)
* Lumbar spine MRI: may show enlarged nerve roots

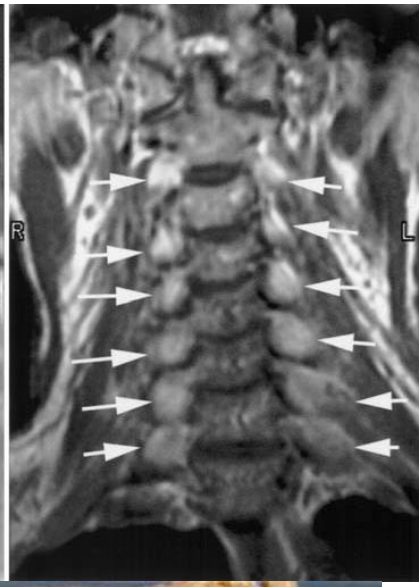
NCS/EMG



Demyelinating features on NC studies







Pytel P, et al. Acta Neuropathol. 2003

What causes CIDP?

* It is an autoimmune disorder whereby the immune system attacks the myelin sheath, but **the triggering factor is unclear.**
* The autoantigen is unknown in the majority of cases.
* Antibodies to nerve components such as gangliosides, P0 and paranodal proteins reported in a small percentage of patients
* Different antigens and immunopathogenesis could be involved in different CIDP subtypes.

Animal models of CIDP

* Chronic EAN
  * Immunization with PNS myelin + low dose CsA caused a relapsing from of EAN in Lewis rats, whereas high dose CsA attenuated the disease (McCombe PA, et al. J. Neuroimmunol. 1990).

* Spontaneous autoimmune polyneuropathy
  * B7-2 knockout nonobese diabetic (NOD) mice (Salomon et al., 2001; Kim et al., 2008)
  * NOD.Aire$^{GW/+}$ (Su et al., 2008)
  * Others

Do I really have CIDP?

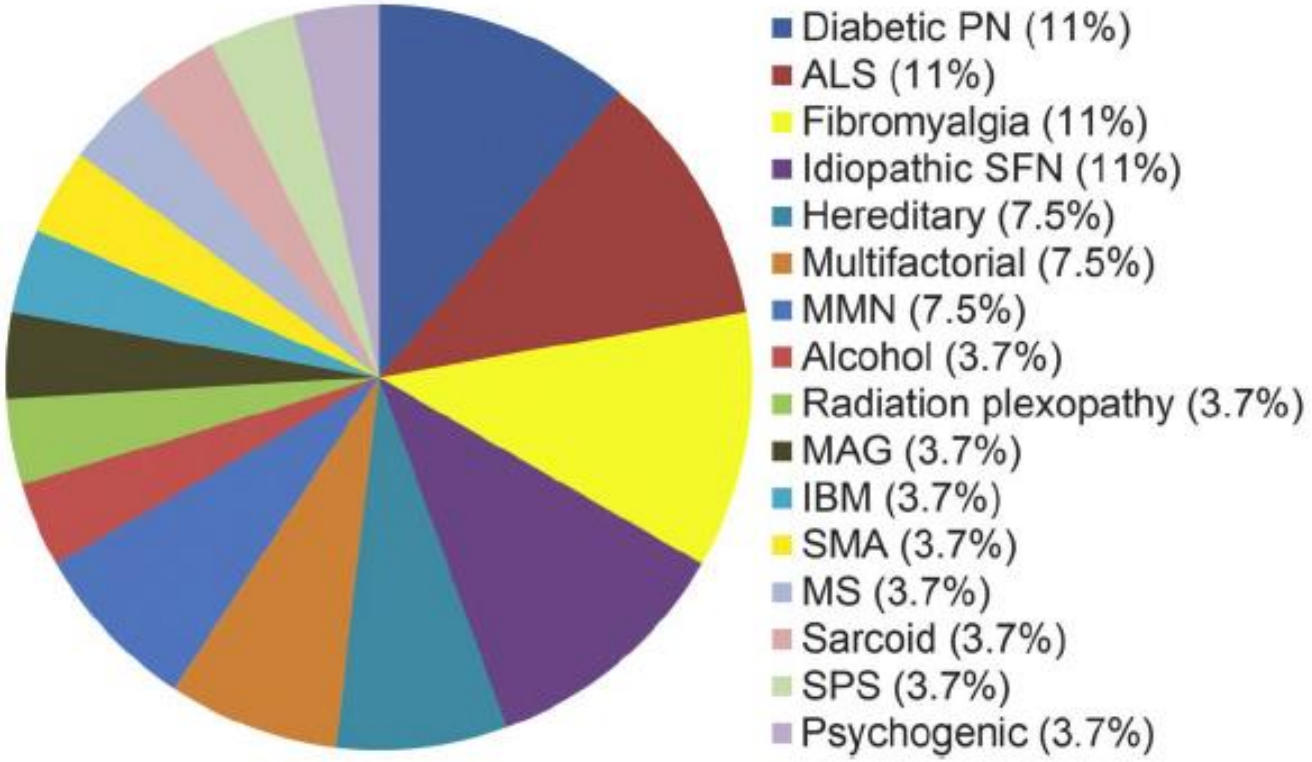
* In a retrospective study, about half of the 59 patients incorrectly carry the diagnosis of CIDP if reanalyzed accdg to the EFNS/PNS criteria.

* Reasons for misdiagnosis:
  * Overreliance on the subjective improvement with treatments
  * Liberal interpretation of demyelination based on nerve conduction studies
  * Overstated importance of borderline or mildly elevated protein

Allen & Lewis, 2015

Misdiagnosis

Figure Alternative diagnosis for patients without chronic inflammatory demyelinating polyneuropathy



How is CIDP treated?

- **Steroids**
- **Intravenous immunoglobulin (IVIg) or subcutaneous immunoglobulin****
  - **Some patients require maintenance IVIg**
  - **Hizentra (subcutaneous) approved in 2018**
- **Plasma exchange: remove antibodies or small molecules****
- Other medications that suppress the immune system
  - Mycophenolate, azathioprine, methotrexate, cyclosporine, tacrolimus
- Cyclosphosphamide or Rituximab (to deplete B lymphocytes) in refractory cases.
- Hematopoetic stem cell transplant?

** proven by clinical trial

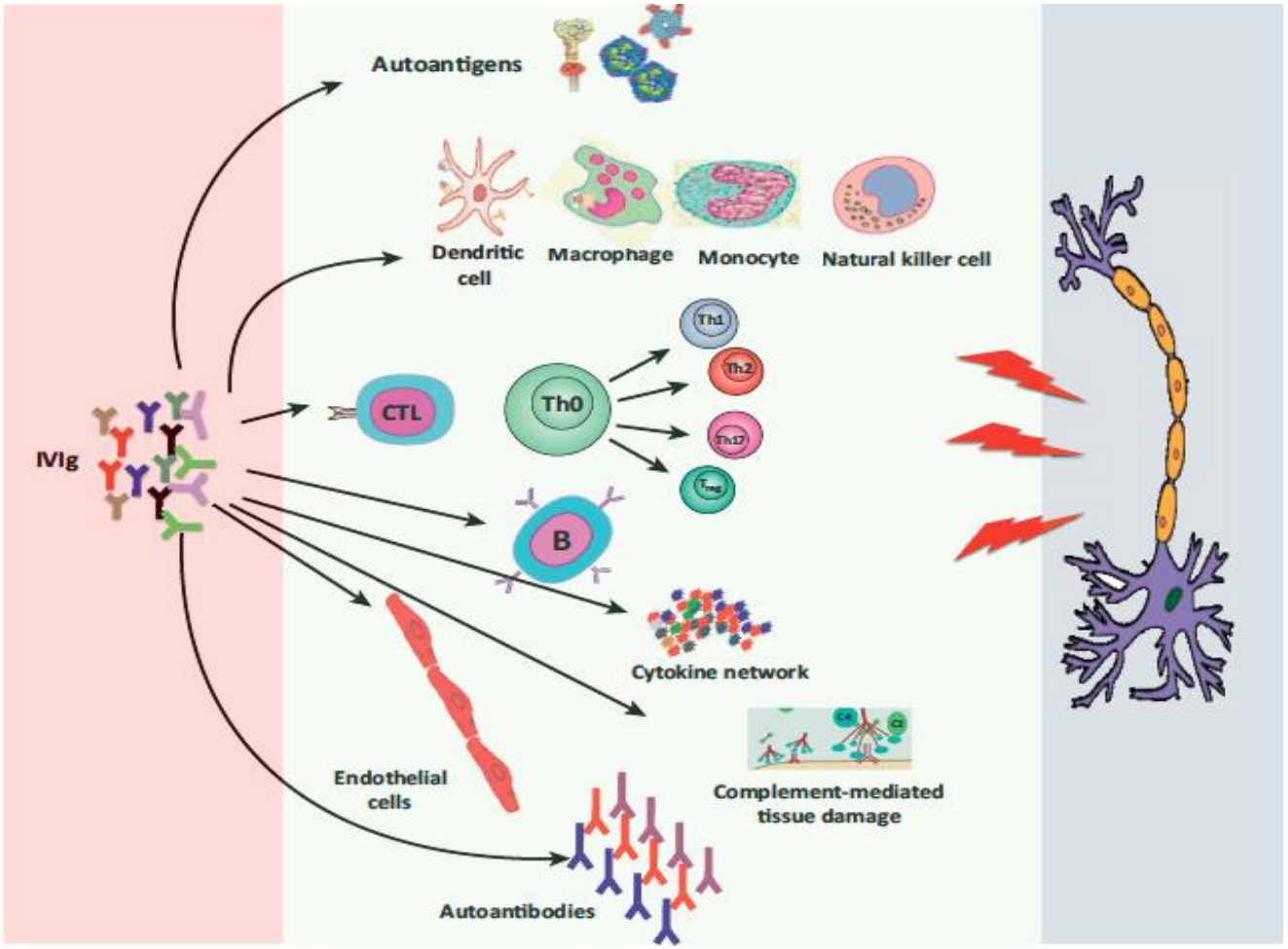
Steroids

* Suppress multiple genes that are activated in autoimmune diseases
* Advantage: low cost
* Potential side effects: diabetes, high BP, wt gain, insomnia, osteoporosis, gastritis, cataract, glaucoma etc
* No difference between daily Pred vs pulse high dose oral dexamethasone in terms of outcome
* Some centers use i.v. methyprednisolone (weekly)

Immunoglobulins (IV or SC)

* Acts on complement system, Fc receptors, compete with pathogenic antibodies
* Transient side effects in 49% (HA, flu-like Sxs)
* More serious side effects: aseptic meningitis, renal impairment, blood clots
* No consensus re optimal maintenance dose and frequency (0.4 to 1.2 g/kg every 2-6 wks).
* Data from the ICE trial of IVIg and the PATH trial of SCIg show that 58% and 37% of patients, respectively, did not relapse during treatment with placebo (means dose can be reduced or d/c in some pts after 6 mo)
* Psychological dependence on IVIg

Proposed mechanism of action of IVIG



Buttmann M, Hartung HP: Trends in Pharmacological Sciences 2013

Why am I not responding to IVIg or steroids?

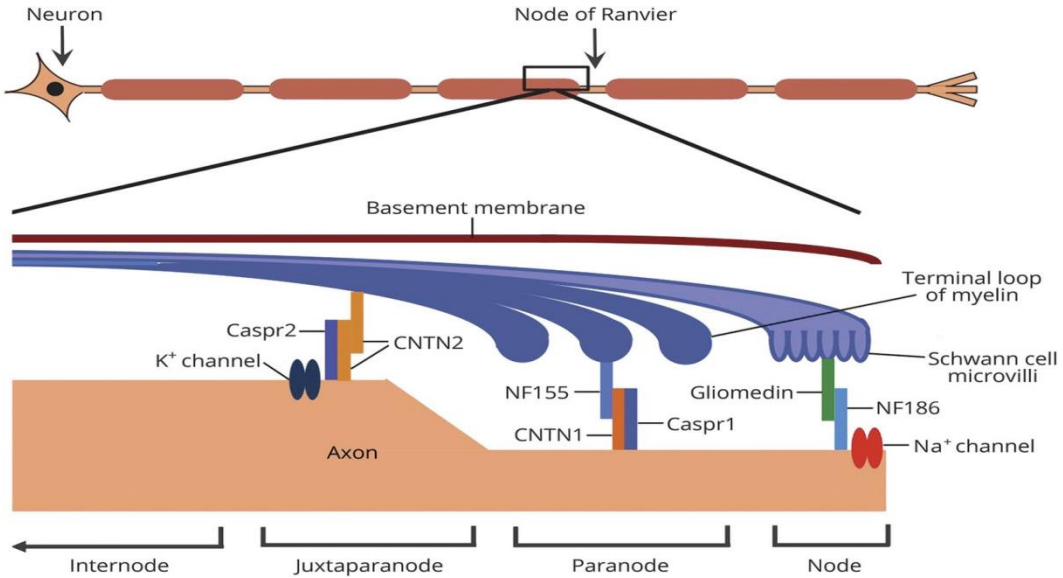
* Misdiagnosis- You don't have CIDP
* Some CIDP variants do not respond as well as others to IVIg
* CIDP illness associated with other medical conditions
  * Sjogren's and other rheumatologic conditions
  * Sarcoidosis
  * Hepatitis (B or C)
  * HIV
  * CIDP + diabetes
* Severe loss of axons/nerve fibers

CIDP variants

* Lewis Sumner syndrome- also asymmetrical affecting sensory and motor function; responds to the usual treatment for CIDP
* Pure motor CIDP- IVIg better than steroids; some deteriorates on steroids
* Sensory-predominant CIDP
* Distal acquired demyelinating symmetric neuropathy (DADS):
  * with IgM paraprotein- tends to be resistant to usual treatments; 50% with anti-MAG Ab
  * w/o IgM paraprotein- responds to usual treatments

CIDP variants- cont'd

* CIDP variants associated with antibodies against nodal or paranodal protein (neurofascins, contactin)
  * Some patients have significant tremors; others with gait imbalance
  * Some variants respond better to rituximab than IVIg



Koike et al., 2018

Other Chronic autoimmune neuropathies (CIDP mimics)

* Multifocal motor neuropathy- asymmetric weakness usually starting in the hands; responds very well to IVIg but may get worse with steroids
  * Associated with IgM anti-GM1 antibody
* Anti-myelin associated glycoprotein (MAG) neuropathy
  * presents with numbness, tingling and gait imbalance; some with weakness
  * Tends to be resistant to usual treatments
* POEMS- polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes
  * Usually high VEGF; or sclerotic bone lesion
  * Respond to lenalidomide (revlimid)

Living with CIDP

* Early treatment is important to keep the condition under control
* Response to treatments and the course of illness vary between patients
* CIDP patients often experience pain, fatigue and reduced quality of life
* Physical therapy, occupational therapy and assistive devices (AFOs, cane, walker)
* Frequent foot inspection for pressure ulcers or injuries
* Symptomatic treatment for tingling and pain
  * Gabapentin (neurontin), pregabalin (lyrica): act on a subtype of calcium channel that mediates pain
  * Duloxetine (cymbalta), nortriptyline, venlafaxine (effexor): increase the threshold for pain perception

Cannabinoids

* No controlled studies in CIDP
* May help neuropathic pain
* CBD and THC have some inhibitory effect on T lymphocytes or B lymphocyte function, but clinical data in autoimmune conditions such as multiple sclerosis are inconsistent.
* Side effects: increased heart rate, agitation, nausea, seizures, kidney injury, hallucinations, psychosis etc.

Practical tips

* Blood test monitoring if patients are on immunosuppressants to detect side effects early (diabetes, bone marrow suppression, renal dysfunction)
* Those on steroids need to be on medications to protect against gastritis or ulcer, take calcium and Vit D supplements to minimize osteoporosis, and have bone density measurements as well as regular eye check up for cataracts, glaucoma
* While on steroids, decrease carbs in the diet. Significant wt gain can impact mobility.

Practical tips-continued

* Exercise- Keep active as much as possible; focus on aerobics and flexibility; do passive range of motion or stretching exercises (particularly those wearing braces)
* Diet- No controlled studies. But some recommend diet rich in antioxidants, anti-inflammatory (avoid saturated fats) and low in carbs (if on steroids).
* There are two aspects to any disease: the illness itself and the coping mechanism. Do not hesitate to seek help if you are depressed.
* In general life expectancy is good and comparable to healthy controls. However, complications from treatments may occur.

How about vaccination?

* General rule- No live virus vaccine while on steroids or immunosuppressants
  * For shingles vaccine, use shingrix (recombinant viral protein) instead of zovirax (live attenuated virus)
  * Good resource: CDC website to check if a vaccine contains live virus or not.

* Flu vaccines are considered safe in recent studies (after 1976). However, in rare pts who develop GBS within 6 wks after prev flu vaccines, it may be prudent to withhold future flu vaccination

How about vaccination?

* About 1/100,000 patients who received vaccination against H1N1 influenza A in 1976 developed GBS
* Risk of developing GBS after seasonal flu vaccine and H1N1 vaccination campaign in 2009 is estimated at 1.6 cases per million vaccinations
* Influenza vaccination might reduce the chance of developing GBS after influenza infection
* Recurrence of GBS after vaccination unlikely
* Vaccination to be avoided in vaccination related GBS and GBS in the 3 month period before the vaccination

Willison et al., Lancet 2016

Prognosis

* Long term prognosis is generally favorable (5 yr follow-up) (Kuwabara et al., 2006)
  * 26% in complete remission (w/ normal nerve conduction studies), while 61% in partial remission (able to walk with or w/o immune treatments)
  * 39% still required immune treatments
  * 13% had severe disability (unable to walk)

* In a 5 year follow up study (Gorson KC, et al, 2010):
  * 11% classified as cured
  * 44% stable/active on therapy
  * 18% were untreated or refractory to treatment
  * Overall 75% of treated patients were stable off treatment or treatment responsive

Prognosis- cont'd

* Poor prognostic factors:
  * Older patients
  * Rapidly progressive course
  * CNS involvement
  * Severe secondary axonal involvement on EMG
    * Axons regenerate but very slowly
    * Remyelination and axonal regeneration may also be impeded by ongoing inflammation

Clinical trials

* Recent oral fingolimod trial failed
* SC Immunoglobulin (IgPro20) worked
* Other SC immunoglobulin Phase III study to start soon
* Potential trials using therapies to block recycling via increased FcRn binding, which leads to fast depletion of the autoimmune disease-causing IgG autoantibodies

Divino et al., 2018

Treatment utilization over the 2 yr follow-up

* In a retrospective study based on adjudicated claims, 83.2% of pts (from 7/1/2010 to 6/30/2014) initiated therapy in a median of 52 days.
  * 57.4% had steroids only (costs ~$7,900)
  * 27.5% had IVIg only (costs ~$165,000)
  * 8.2% had combination of IVIg and steroids
  * 4% had plasma exchange
  * Others: azathioprine, mycophenolate
* Frequent use of opioids (60.6%), anti-convulsants (45.7%) and anti-depressants (44.2%).

Divino et al., 2018

Conclusions

* CIDP is a common form of treatable neuropathy with a spectrumof clinical phenotypes.
* Probably heterogeneous disease from the immunopathogenic standpoint
* Correct diagnosis is essential. Incorrect diagnosis will result in treatments which will be costly and/or subject the patient to serious side effects of pharmacotherapy.
* Most of CIDP patients respond favorably to treatment
* Pharmacogenetic studies may provide insight regarding immunotherapy in individual patients
* If untreated, it may cause severe disability and shorten the lifespan.