



SUPPORT • EDUCATION • RESEARCH

**IWMF**

---

**International Waldenstrom's  
Macroglobulinemia Foundation**

# Peripheral neuropathy (PN)

- **damage or disease affecting nerves, which may impair sensation, movement, gland or organ function**
  - **chronic: long term, begins subtly and progresses slowly**
  - **acute : sudden onset, rapid progress and slow resolution**
- **sensory nerves, motor nerves, autonomic nerves**

# **Peripheral neuropathy (PN)**

- **The peripheral nervous system sends information from your brain and spinal cord (central nervous system) to the rest of your body.**
- **Peripheral neuropathy (damage to your peripheral nerves) can cause weakness/dysfunction, numbness and pain, usually in your hands and feet, and other areas of your body.**
- **Variable clinical presentation.**

# Signs and symptoms

- **sensory function “negative” symptoms:**
  - **numbness to touch and vibration,**
  - **reduced sensitivity to temperature change and pain,**
  - **reduced position sense causing poor coordination and balance, and gait abnormality**
- **sensory function “positive” symptoms:**
  - **tingling, itching, crawling, pins and needles**
  - **pain or skin allodynia (severe pain from normally non-painful stimuli, such as light touch).**

# Signs and symptoms

- **motor function “negative” symptoms (loss of function):**
  - **impaired balance and coordination**
  - **weakness and tiredness**
  - **heaviness and gait abnormalities**
- **motor function “positive” symptoms (gain of function):**
  - **cramps**
  - **tremors**
  - **muscle twitches (fasciculations)**

# Signs and symptoms

- **autonomic nerve dysfunction:**
  - **poor bladder control**
  - **abnormal blood pressure or heart rate**
  - **reduced ability to sweat normally**
- **pain in the muscles (myalgias)**
- **neuropathy may cause muscle loss, bone degeneration, and changes in the skin, hair, and nails.**

# **Etiology of PN**

- **Diabetes Mellitus**
- **Alcohol Abuse**
- **HIV**
- **Autoimmune \***
- **Toxic \***
- **Hereditary**
- **Environmental**
- **Idiopathic**

# Prevalence of PN

- **Paraproteinemic neuropathies (single monoclonal gammaglobulin)**
  - **Osteosclerotic myeloma (POEMS) 50-85%**
  - **WM 30-50%**
  - **MGUS 5-37%**
  - **Amyloidosis (AL) 10-20%**
  - **Cryoglobulinemia 7-15%**
  - **Multiple myeloma 3-14%**
  - **Lymphoma 2-8%**



# Mechanism of neuropathy

- **Mono, multi, cranial neuropathy & radiculopathy**
  - **direct infiltration**
  - **nerve/root compression**
  - **hyperviscosity**
  - **bleeding diathesis**
  - **Cryoglobulinemia**
- **Symmetric polyneuropathy**
  - **Amyloidosis**
  - **chemo/drug related toxicity**
  - **M-protein reactivity with nerve (*IgM*)**
  - **unknown**

# Anti-neural antigens of IgM

## Antigens

## % PN

- **Anti-MAG** **50%**
- **Sulfatide** **6%**
- **GQ1b+Disyalo** **2%**
- **GD1a** **3%**
- **GM2** **2%**
- **GM1** **<2%**

# Diagnosis of PN

- **History and physical exam**
- **Initial labs: CBC; Renal & Liver function; Bone chemistry; B2 microglobulin; LDH; NT-proBNP; Cryoglobulin testing; Serum free light chains; SPEP; Immunofixation; HIV serology; Hepatitis B & C serology; Urinalysis including UPEP; Bone marrow biopsy; CT chest, abdomen, pelvis**
- **Other labs: Serum B12 and folate; HGA1C; Anti-mag antibodies; Anti-ganglioside antibodies; Lyme disease serology; CSF; EMG; Nerve/skin biopsy**

# Nerve Conduction Studies

- **EMG (electromyography) recommendations:**
  - **Use to clarify the nature of the neuropathy and expand or curtail investigation;**
  - **Clinicians need to be very clear to request specific answers to questions when ordering the test;**
  - **Results of the EMG need to be viewed in context with the clinical picture of PN**
  - **Minimize risks to the patient (pacemaker, defibrillator, etc ...)**

# Treatment of PN

- **Patients not impaired in their daily life:**
  - **symptomatic therapy for tremor and paresthesias**
- **Significant or progressive disease:**
  - **Immunosuppressive or immunomodulatory treatment: rituximab and/or rituximab combinations, and then second line agents**
  - **Watch for IgM flare – plasma exchange ?**
  - **IVIg, steroids, plasma exchange of little use according to newer recommendations.**
  - **Avoid neurotoxic agents**

# Therapy of anti-MAG IgM PN

- **Past treatment examples:**
  - **Rituximab (62%)**
  - **Plasma exchange (45%)**
  - **Chlorambucil (40%)**
  - **Steroids (39%)**
  - **Cyclophosphamide (47%)**
  - **IVIg (18%)**
  - **Interferon  $\alpha$  (27%)**
  - **Fludarabine (52%)**
  - **Other therapies (14%)**

# **Pain symptoms**

- **Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.**
- **Chronic pain is a complex phenomenon where the intensity and impact of the pain is not always directly related to pathology.**

# Treatment strategy

- **the underlying cause of pain should be treated whenever possible**
- **oral medicines are key components of pain management**
- **some medicines should be given regularly ("by the clock")**
- **therapeutic regimes need to be individualized**
- **monitor and evaluate for therapeutic and side effects**
- **Nerve stimulators, nerve blocks**



# Pharmacological therapy

- **anticonvulsants**
- **antidepressants**
- **benzodiazepines**
- ***N*-methyl-d-aspartate (NMDA) receptor antagonists**
- **nonsteroidal anti inflammatory drugs (NSAIDs)**
- **opioid therapy**
- **cannabinoids**
- **topical agents**

# **Individualized therapy**

- **we are all different in many respects and patients who suffer from PN will need to try numerous combinations of therapies before finding the one that works well to control symptoms.**
- **the underlying cause of pain should be treated whenever possible and safe to do so.**

# Reference Articles

- **8<sup>th</sup> International Workshop in Waldenstrom Macroglobulinemia (IWWM8) reference article: Investigation and management of IgM and Waldenstrom-associated peripheral neuropathies: recommendations from the IWWM-8 consensus panel**
- **British Journal of Haematology; guideline. 2017; doi:10.1111/bjh.14492**
- **UpToDate Literature Review March 2018**

# Open Discussion

- **How has PN impacted you?**
- **What have you tried? What has worked?**
- **What advice do you have for WM'ers with PN?**