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, numbness and pain, usually in your hands and feet. It can also affect 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.**

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**
- **Intitial labs: CBC; Renal & Liver function; Bone chemistry; B2 micrtoglobulin; LDH; NT-proBNP; Cryoglobulin testing; Serum free light chains; SPEP; Immunofixation; HIV serology; Hepatitis B & C serology; Urinalysis including UPEP; Bone marrow biopsy; CT cehst, abdomen, pelvis**
- **Other labs: serum B12 and folate; HGA1C; Anti-mag antibodies; Anti-ganglioside antibodies; Lyme disease serology; CSF; EMG; nerve 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 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 of 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 α (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 Article

- **8th 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**