WM and Peripheral Neuropathy

IWMF Virtual Ed Forum
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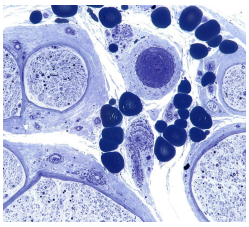
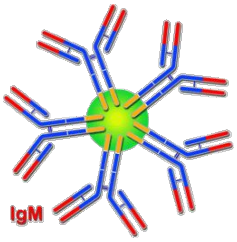
London, UK

WMUK
The UK charity for Waldenstrom's macroglobulinaemia



THE NATIONAL HOSPITAL FOR NEUROLOGY AND NEUROSURGERY



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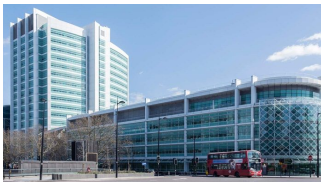
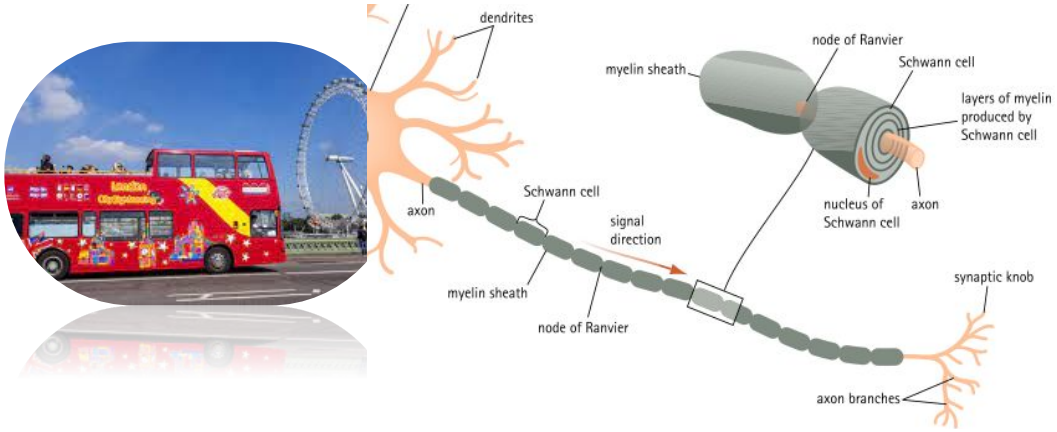
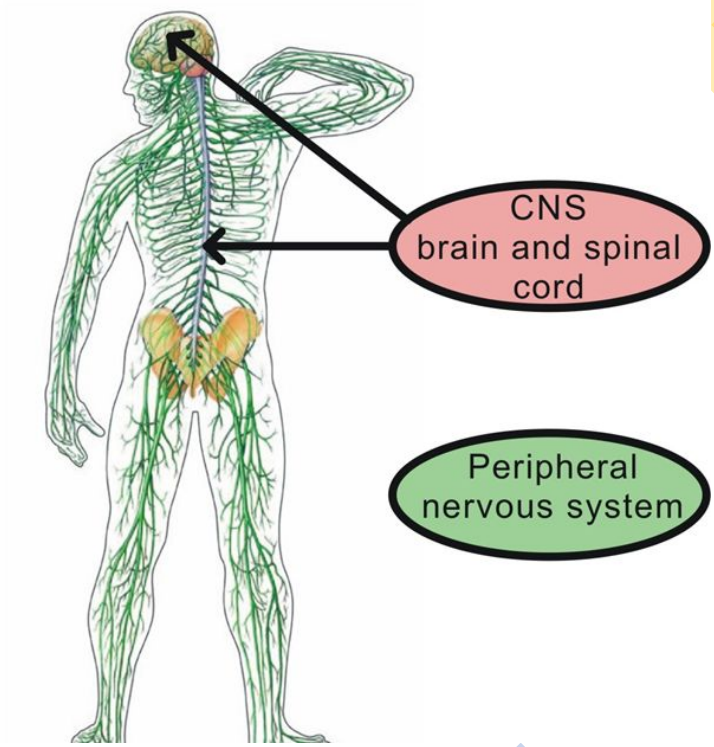


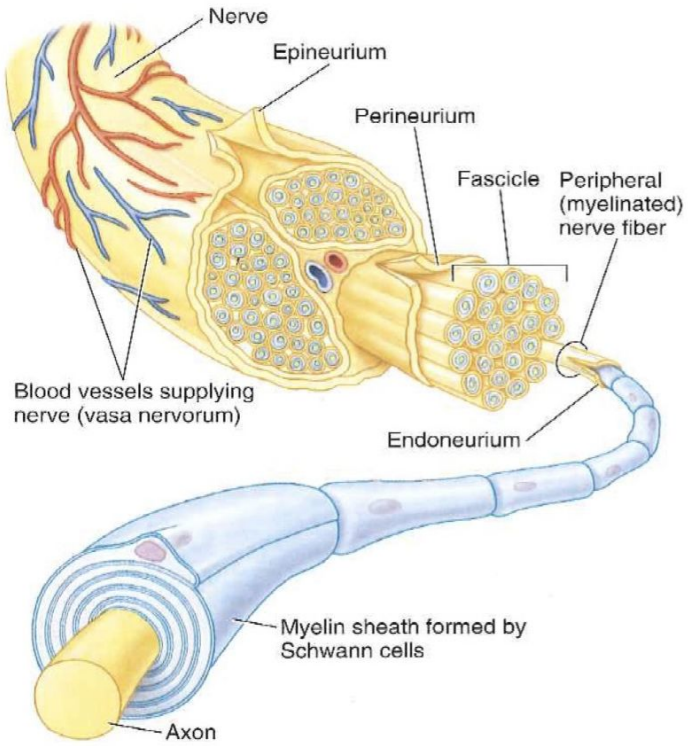
Quick Tour of the Nervous System



All information to and from the body must be coordinated and transmitted simultaneously and quickly. The brain requires extremely fast speeds to operate at even at the simplest level. How do the biological tissues of our body support such rapid coordination of the brain, limbs, and sensory input?
They do so with nervous system tissue that imitates electrical wiring.

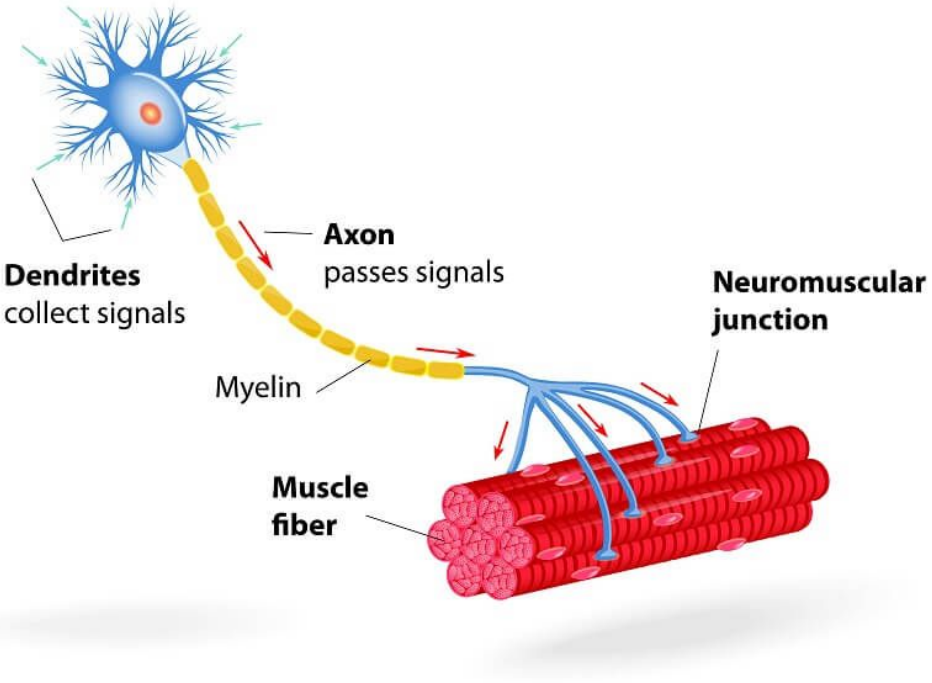


The Nervous System



The Anatomy of a Nerve

All large motor and sensory fibres are enclosed in **many layers** of myelin, which consists of the plasma membranes of specialized Schwann cells that wrap themselves around the axon during axonal outgrowth



Muscle contraction

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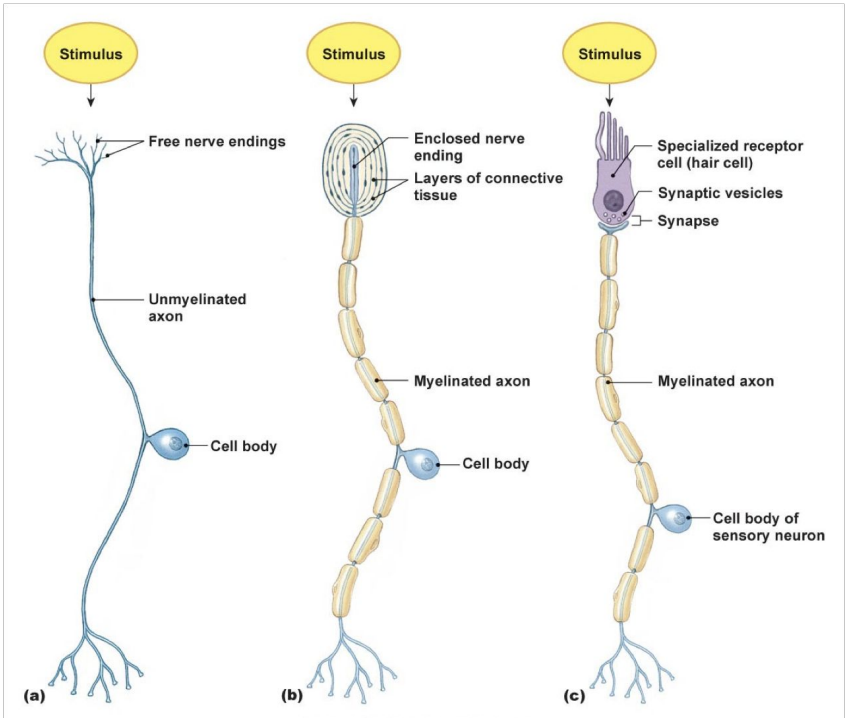
Movement

Motor Nerve

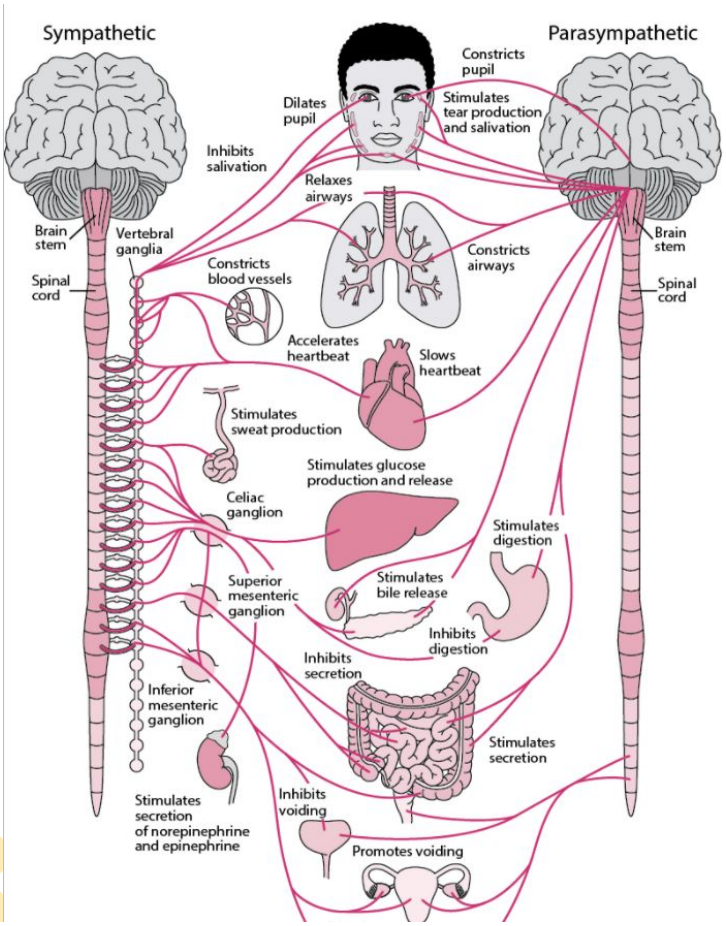
SENSATION:

Pain
Pressure
Soft touch
Temperature
Joint position sense



Sensory Nerve

Fight or flight

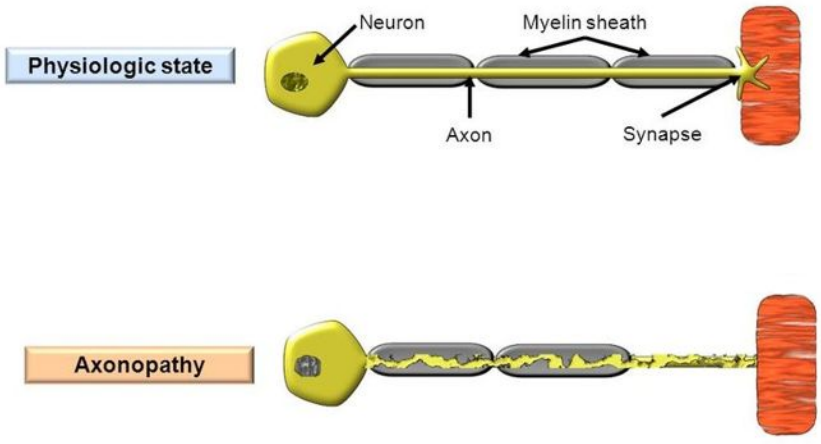


Rest and Digest

When things go wrong for the axon

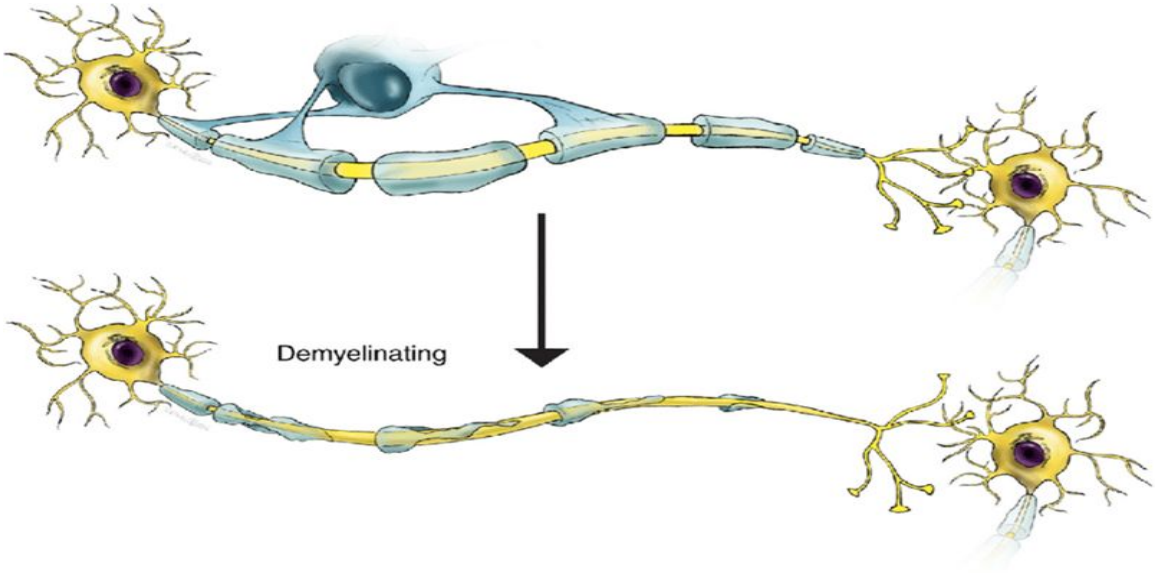
Neurons are specialised cells that receive and send signals to other cells through fragile and thin cellular extensions called axons.

These axons extend over distances long and short to reach their target, ultimately connecting neurons with other nerve tissue, muscle tissue, or sensory organs



Axonal Damage

When things go wrong for the myelin sheath



Demyelination

When things go wrong in the autonomic nervous system

you may experience one or more of the following symptoms. Some people experience one cluster of symptoms at one time, and another set of symptoms at other times.

The symptoms can be fleeting and unpredictable or triggered by specific situations or actions, like after ingesting certain foods or after standing up quickly.

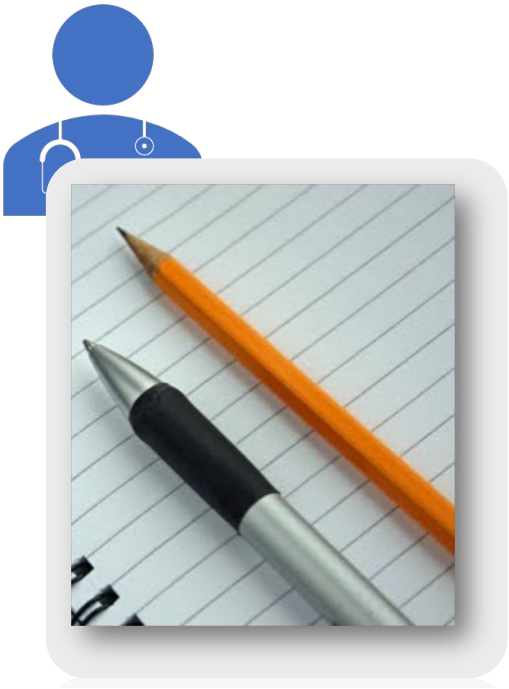
- Difficulty emptying the bladder
- Disturbing aches and pains
- Dizziness or light-headedness upon standing
- Erectile dysfunction
- Faintness (or even actual fainting spells)
- Fatigue and inertia
- Gastrointestinal symptoms
- Hypotension (low blood pressure)
- Lack of pupillary response
- Lack of sweat or profuse sweating
- Numbness and tingling
- Severe anxiety or depression
- Tachycardia (fast heart rate)
- Urinary incontinence

Symptoms of autonomic neuropathy

Important features to mention to your doctor

- When did the symptoms start?
- Have they come on gradually or quickly (days/ weeks/ months/ years)?
- Is there a timing link to any medication/ anti-cancer treatment?
- How are you affected- sensation strength, balance, tremor, pain?
- Is it the same on both sides or asymmetrical?
- What makes the symptoms worse- position, movement, lack of movement, fatigue, cold temperatures?
- What helps? Certain positions? Rest? Medication?
- How are the symptoms impacting on your function?

Doctor's Review



- In order to devise the appropriate testing strategy, a careful history is essential
  - Nature of symptoms, spatial distribution
  - Speed of onset
  - Rate of change
  - Effect on functional abilities
  - Motor/ sensory/ autonomic features

- Review of medication list
- Review of diet
- Alcohol and other toxins
- Medical history: diabetes?

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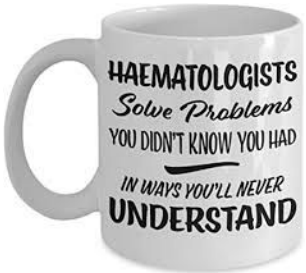
Clinical Examination



- Examination to confirm haematological picture: MGUS vs WM
  - Lymphadenopathy
  - Splenomegaly
- Examination to confirm neurological picture and provide a baseline for future comparison
  - Features of amyloid- bruising, oedema, cardiac insufficiency, postural drop in BP
  - Features of cryoglobulins- acrocyanosis, livedo reticularis, ulcers

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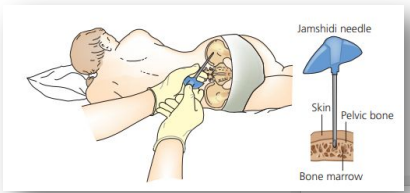
Is my WM causing my neuropathy symptoms?

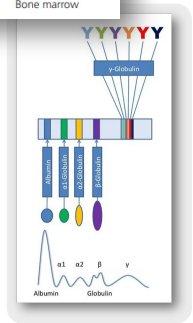
Investigations

General Laboratory Tests

- Tests may be done to seek out other (correctable) causes which can be treated
  - Diabetes: random glucose, HbA1c
  - Vitamin levels: B12, B6
  - Autoimmune screen: ANA, ANCA, rheumatoid factor, SS-A/Ro, SS-B/La, dsDNA
  - Infections: Hepatitis B and C and HIV serology, Lyme (Borrelia burgdorferi) antibodies
  - Sarcoidosis: Serum ACE

IgM-related tests Laboratory Tests



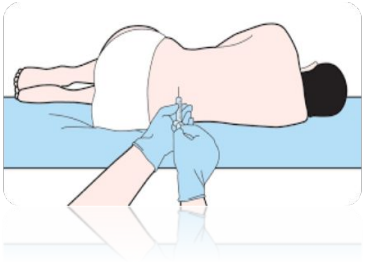


- MGUS vs WM tests: BM, imaging
- Neuroimmunology testing (anti-MAG and other nerve targets)
- Cryoglobulin testing: needs a blood test that needs to be kept warm until it reaches the lab
- Screening for amyloid biomarkers: NT-proBNP and urinary albumin can detect early amyloidosis in 97% patients
- Biopsy of tissues to see if amyloidosis is present.

Nerve Conduction Studies: Useful notes

- Nerve conduction tests (also known as EMG) are operator-dependent
- It is important for the correct information to provided to the neurophysiologist doing the test by the requesting doctor.
- The test can be uncomfortable as an electric current is applied and then the conduction is measured
- Even when neurological symptoms are prominent, the result may normal as NCS only pick up problems in large nerve fibres.
- Small fibre neuropathies (which often cause pain) are not picked up on NCS
- A single study gives little or no information as to whether the process is static or progressive: repeated studies over time may be needed

CSF: Cells Protein



- Cerebrospinal fluid (CSF) bathes the entire central nervous system.
- Sampling the CSF needs a lumbar puncture (LP)
- The CSF contains proteins and minerals that are within certain limits.
- Normal CSF does not contain any cells.
- When investigating a neuropathy examination of the CSF can add valuable information.
- CSF shows significantly **elevated protein (>1.0 g/l)** in up to 80% of inflammatory neuropathies
- If lymphoma cells are found, then there may be co-existing Bing-Neel syndrome
- Special tests called **flow cytometry** and **molecular (MYD88) testing** can help to identify lymphoma cells
- If you are blood thinners or a BTK inhibitor, they will need to be paused a few days before an LP

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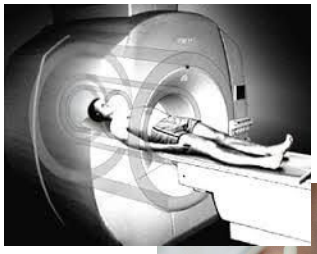
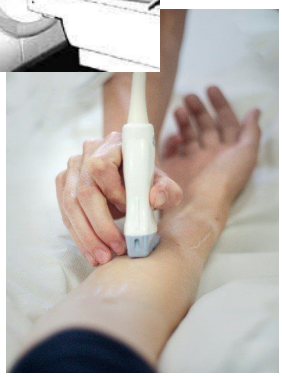
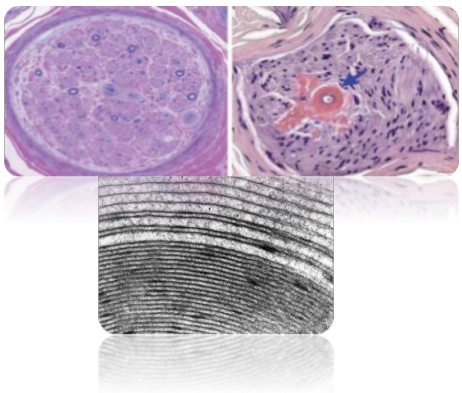
Imaging in the setting of neuropathy





- If nerve compression or infiltration is suspected
- If there are CNS features as well
  - *MRI with Gadolinium* is best targeting the brain and spinal cord +/- plexi
  - Needs to happen before an LP to avoid false-positive enhancement
- *Computed tomography* (CT) scans shows bones more clearly, narrowing of the spinal canal, tumors and other problems that may affect nerves.
  - May be used if a person cannot have an MRI scan
- *Muscle and nerve ultrasound* is a noninvasive technique for imaging nerves and muscles
  - Useful for looking at the carpal tunnel in the wrist, or signs of thickened nerves (such as amyloidosis)

Nerve Biopsy



- Practice varies across different centres
- Neurologists vary in their tendency to do nerve biopsies
- Generally only in specialist centres as nerve processing is highly specialised
- The result depends on several factors, including selection of patients, which nerve is selected to biopsy
- The sural nerve is a common site, but other locations are possible.
- If the damage is happening higher up (closer to the spine), there is more to lose from a biopsy
- Studies are performed to look for infiltration by lymphoma cells, amyloidosis or vasculitis- this may affect choice of therapy

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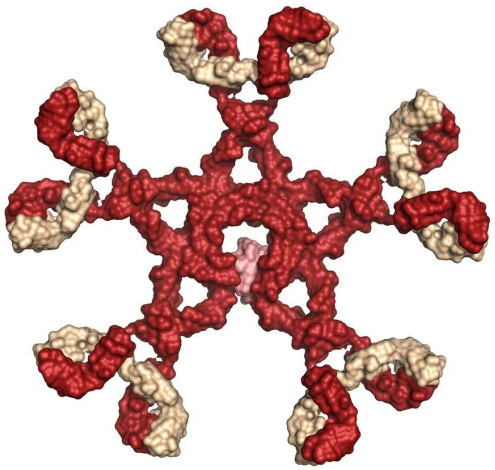
Neuropathies

MAIN MENU

VIEW THE MENU ▶

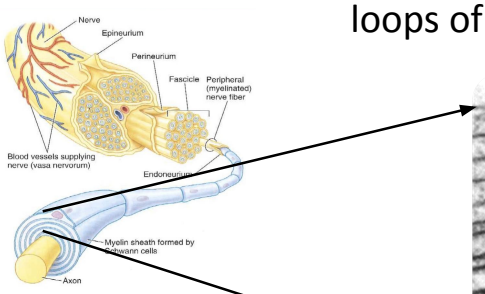
IgM and Neuropathy

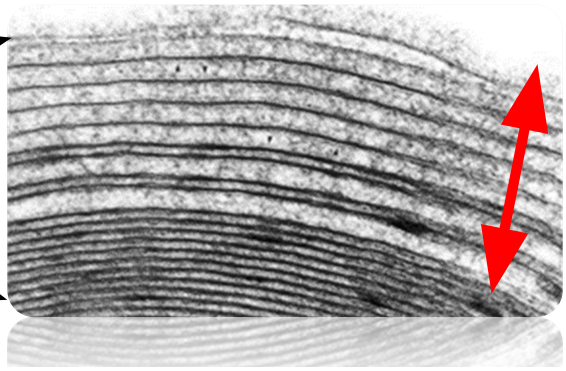
- Neuropathies associated with IgM paraprotein present variously as
  - Peripheral neuropathy caused by Anti-MAG antibodies
  - IgM-associated peripheral neuropathy with ganglioside antibodies
  - Peripheral neuropathy *without* anti-MAG antibodies
- Although these disorders that are distinct, the symptoms are often similar
- The prognosis of IgM-related neuropathy is variable but about 20% experience disability at 5 years after diagnosis
- NOTE!! Monoclonal IgM may be present but <u>not connected</u> to the neuropathy



Myelin Associated Glycoprotein

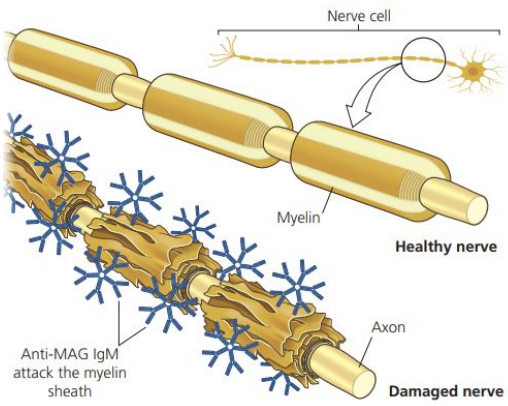
- The neuropathies associated with IgM have been extensively investigated.
- Anti-MAG associated neuropathy is the best studied and characterised
- The role of anti-MAG antibodies in mediating nerve damage has been well demonstrated and has prompted several studies on immune treatment options.
- Anti-MAG antibodies prevent MAG from holding together loops of myelin:





Widening of spaces between myelin layers

Anti-MAG antibodies:
Measurement



- The Bühlmann anti-MAG test is probably the most common way to measure anti-MAG antibodies in the blood
- However it is very sensitive and at low and intermediate levels of positivity may not be associated with typical anti-MAG neuropathy
- Different labs use different cutoffs for positivity.
- Bühlmann antibody levels are classified as
  - High (≥70000 BTU) : likely to be clinically significant
  - Medium (10000–70000 BTU) : less specific and may be irrelevant even if PN is present
  - Low (≥1000 to <10000 Bühlmann Titre Units; BTU)
- Anti-MAG levels are not a reliable measure of treatment response

Anti-MAG neuropathy treatment:

Who, when?

1. Treon SP 2010
2. Benedetti et al 2007

- Indicated for significant or progressive disability: Immunosuppressive or immunomodulatory treatment may be considered but rules and habits vary in different countries
- Better outcomes are likely if there is less nerve damage
- A significant drop in the anti-MAG antibody level may be important to get a good response but the depth of optimal haematological remission to achieve this is not known.
- Complete elimination of the clonal IgM is not practical or possible with current therapies (need to balance risks and benefits)
- Stability rather than improvement is the most likely outcome of treatment

Anti-MAG neuropathy treatment:

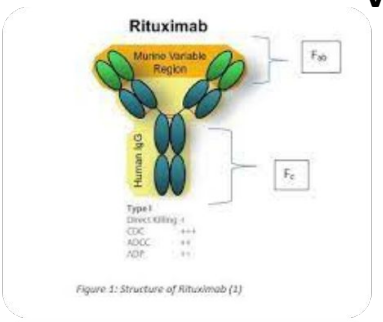


Figure 1: Structure of Rituximab (1)

- **Various treatments have been tried**
  - IVIG -limited short-term benefit (weeks), but this is of little clinical use.
  - Steroids alone are not effective, but may be beneficial in combination with other agents such as cyclophosphamide.
  - Other chemotherapy agents have been used singly or combined
  - Rituximab alone or in combination is effective
  - Bendamustine-Rituximab has shown a lasting response in patients with CIDP or paraproteinemic IgM neuropathies associated with a haem malignancy (but study only had 9 patients)
  - DRC (Dex, Cyclo, Ritux) is also effective
  - Factors predictive of a response and optimum dosage and schedules of treatment are unknown

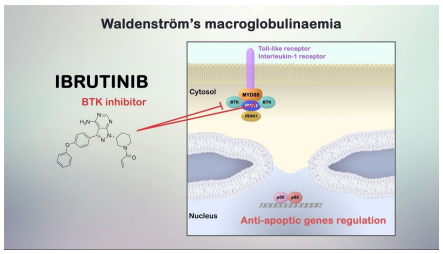
- Lunn & Nobile-Orazio 2016
- Niermeijer et al 2007
- Ghosh et al 2002
- Niermeijer et al 2006
- Massa et al 2020

Anti-MAG neuropathy
Ibrutinib

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

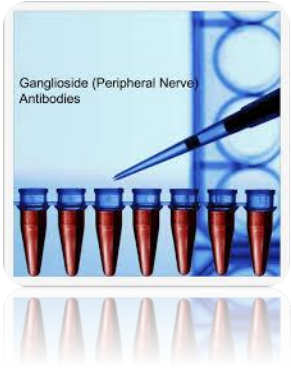
The Bruton tyrosine kinase inhibitor ibrutinib improves anti-MAG antibody polyneuropathy

- A report on 3 patients with anti-MAG antibody neuropathy treated with ibrutinib after previous Rituximab-based therapy.
- All patients had neurophysiologic evidence of sensory-motor demyelinating polyneuropathy
- All the patients reported an early and subjective benefit, consistent with the objective improvement, especially of the sensory symptoms as shown by clinical scales. Treatment was well tolerated.



Neurol Neuroimmunol Neuroinflamm. 2020 Apr 13;7(4):e720

Neuropathies without Anti-MAG



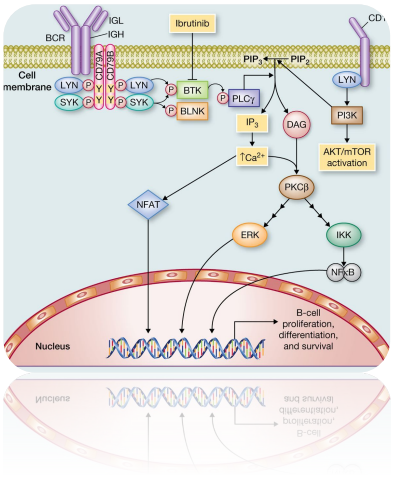
- Anti-MAG **negative** patients are a mixed picture of variants with different clinical and neurophysiological findings, and this makes it difficult to group these together for research studies.
- Moreover, they may or not have serum antibodies against other known targets, such as ganglioside and sulfatide, that associate with different neuropathy phenotypes
- The only exception is CANOMAD syndrome which is always associated with MGUS and anti-GD1b/GQ1b antibodies.
  - *CANOMAD syndrome (Chronic Ataxic Neuropathy with Ophthalmoplegia, M-protein, cold Agglutinins and Disialosyl antibodies*)
  - Patient have unsteadiness, reduced eye movements, and **cold agglutinins** in their blood

Waldenströms-associated neuropathy
Diagnosis

- Symptoms of neuropathy affect ~ 20% of patients with WM at diagnosis
- Up to 50% are affected at some time in the course of their disease[1]
- NCS typically show evidence of demyelination in anti-MAG positive cases.
- Axonal neuropathies or mixed axonal and demyelinating neuropathies seen, more commonly when anti-MAG is negative[2]
- When significant titres of anti-MAG antibodies are present, they are probably pathogenic in this setting
- If atypical clinical or electrophysiological features are present, consider other causes: amyloidosis, cryoglobulinaemia, vasculitis or direct tumoural invasion

1. Levine, et al 2006
2. Viala, et al 2012

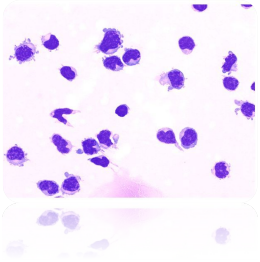
Waldenström's-associated neuropathy
Treatment

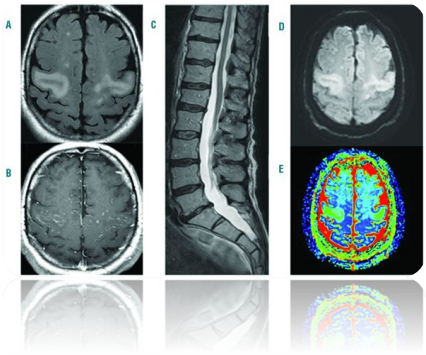


- **Treat underlying lymphoma as per standard of care**
- **Rituximab**
- **Bendamsutine and Rituximab (BR)**
- **Dex, Cyclophosphamide and Rituximab (DRC)**
- BTK inhibitors such as **Ibrutinib** have shown symptomatic improvement in WM associated PN that progressed after Rituximab[3].
- **Other BTKi (Acalabrutinib and Zanubrutinib)** are effective alternatives
- Proteasome inhibitors such as **Bortezomib** could make neuropathy worse but alternatives such as **Ixazomib** could be used

1. Alsina, et al 2012, Treon, et al 2014
2. Ioakimidis, et al 2009
3. Treon SP 2015

Bing-Neel syndrome





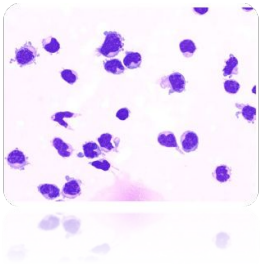
Rare disease manifestation of Waldenström's macroglobulinemia (WM)

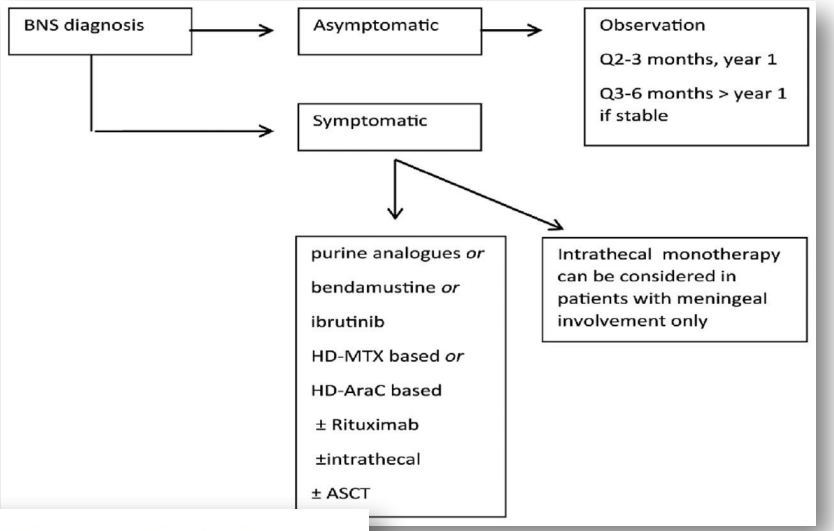
- May occur as first presentation of WM
- May occur when WM needs treatment or is in remission

- Due to invasion of the CNS by lymphoplasmacytic cells
  - May be detected in the CSF, meninges, +/- the brain tissue
- The clinical symptoms of BNS diverse
  - Gradually progressive over the course of weeks or months
- Often a considerable delay between the initial symptoms and the diagnosis.
- Diagnosis needs evidence of cells from the CNS
  - CSF, brain tissue, backed up with imaging results.

Bing-Neel syndrome

Treatment options





Guideline For The Diagnosis, Treatment And Response Criteria For Bing-Neel Syndrome

Monique C. Minnema, Eva Kimby, Shirley D'Sa, Luc-Matthieu Fornecker, Stéphanie Poulain, Tom J. Snijders, Efstathios Kastritis, Stéphane Kremer, Aikaterini Fitsiori, Laurence Simon, Frédéric Davi, Michael Lunn, Jorge J. Castillo, Christopher J. Patterson, Magali Le Garff-Tavernier, Myrto Costopoulos, Véronique Leblond, Marie-José Kersten, Meletios A. Dimopoulos, Steven P. Treon

Haematologica January 2017 102: 43-51; **Doi:**10.3324/haematol.2016.147728

Case Reports › Clin Lymphoma Myeloma Leuk. 2021 Jun 26;S2152-2650(21)00246-9. doi: 10.1016/j.clml.2021.06.017. Online ahead of print.

A Case of Bing-Neel Syndrome Treated Successfully With Ibrutinib Monotherapy Following Intensive Chemoimmunotherapy

American Journal of Hematology

E-ONLY ARTICLE | Free Access

High-dose therapy with autologous stem cells transplantation in Bing-Neel syndrome: A retrospective analysis of 14 cases

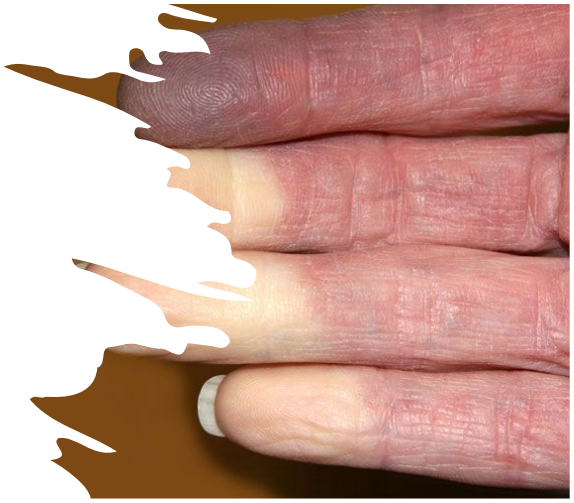
Laurence Simon, Richard Lemal, Luc-Matthieu Fornecker, Olivier Tournilhac, Véronique Leblond

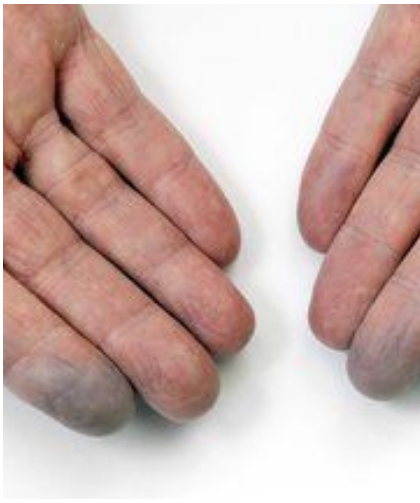
Case Reports › Hemasphere. 2018 Nov 30;2(6):e155. doi: 10.1097/HS9.0000000000000155. eCollection 2018 Dec.

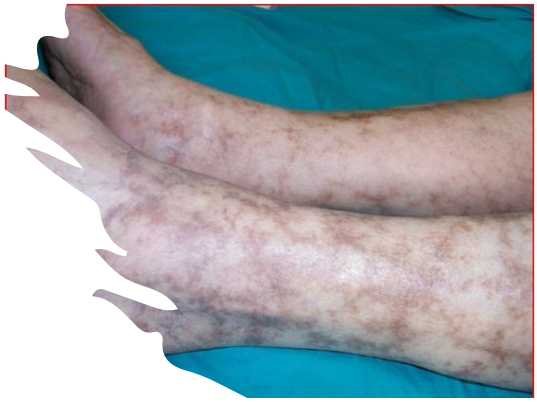
Efficacy of Zanubrutinib in the Treatment of Bing-Neel Syndrome

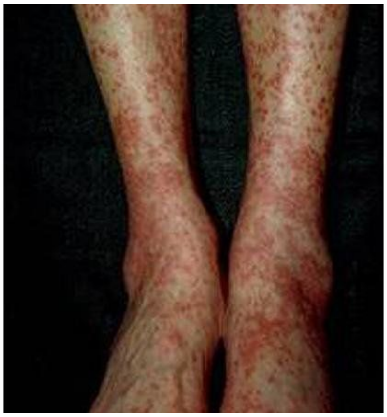
Cryoglobulinaemia

- Cryoglobulinemia is a form of vasculitis—a characterized by inflammation of the blood vessels, which can restrict blood flow and damage vital organs and tissues.
- In cryoglobulinemia, abnormal blood proteins called cryoglobulins clump together at cold temperatures, restricting blood flow and causing damage to skin, muscles, nerves, and other organs
- Type 1 cryoglobulinaemia is most commonly seen in IgM settings, like WM



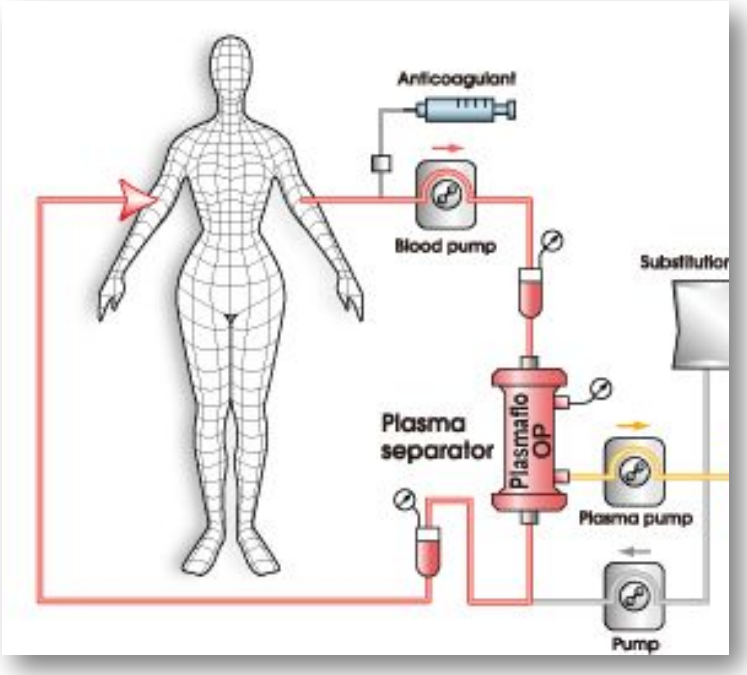




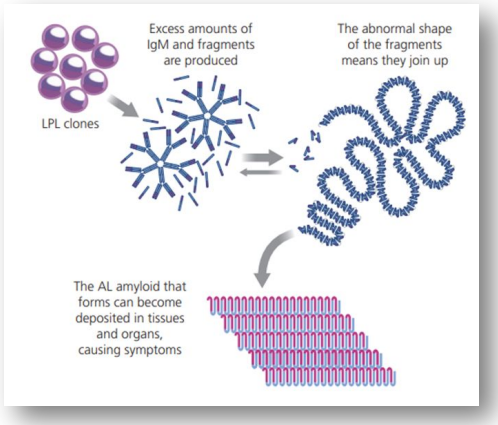


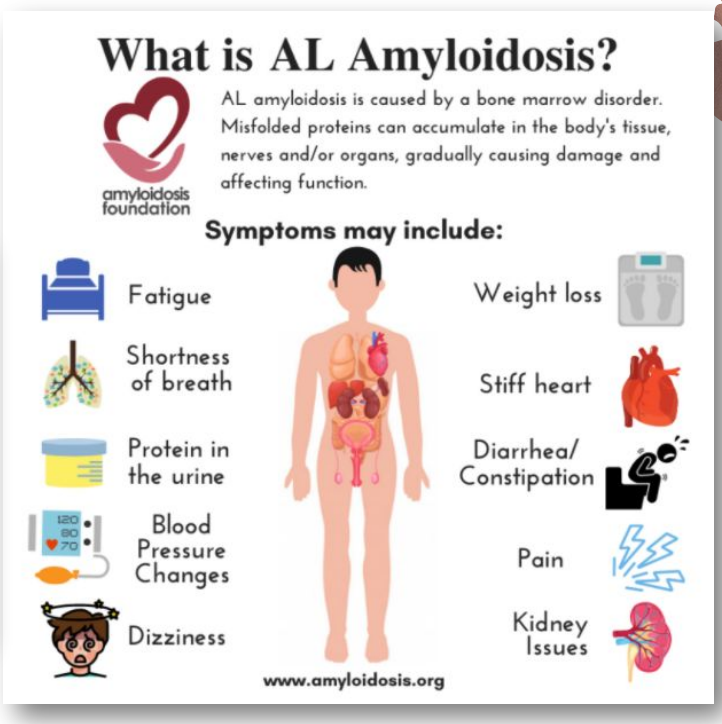
Cryoglobulinaemia

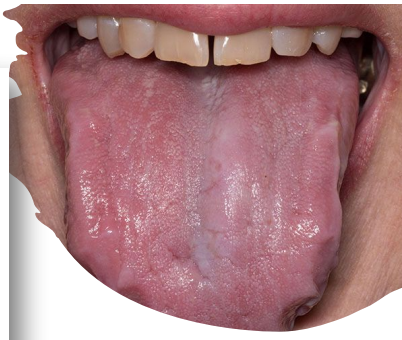
- Immunosuppressive drugs are the mainstay of treatment for severe disease where vital organs are affected. **Corticosteroids** such as prednisone, and immunosuppressants such as **azathioprine** and **cyclophosphamide**, are widely used.
- **Rituximab** is a common treatment option for this condition.
- **BTK inhibitors** may be legitimate options
- **Plasmapheresis** is an option when patients have life-threatening, or organ-threatening cryoglobulinemia.
- It is important to treat this condition promptly and aggressively to safe-guard tissues.

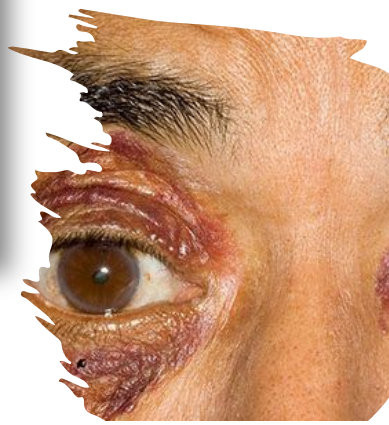


AL amyloidosis

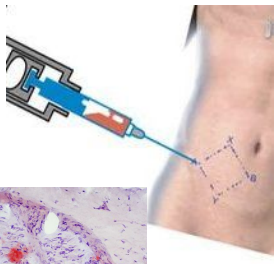


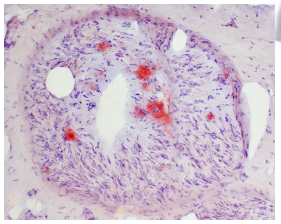


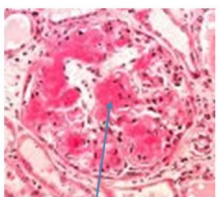




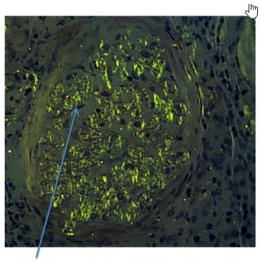
AL amyloidosis
diagnosis







Renal biopsy, stained with Congo Red.

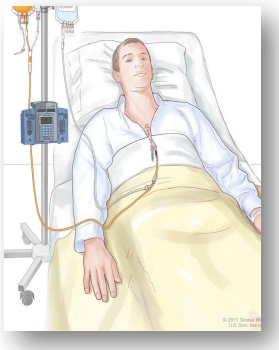


Under polarized light, the stain displays apple-green birefringence.

- Amyloid deposits can affect the nerves of the hands, feet and lower legs and may cause pain, numbness and tingling, loss of sensitivity to temperature.
- Nerves that control blood pressure, heart rate, bowel motility, erectile function, and other body functions can also be affected, causing a variety of symptoms including dizziness when standing too quickly, nausea and diarrhea. This is called autonomic neuropathy.
- Swelling may develop and cause symptoms as a result of the amyloid deposits. For example, patients may have carpal tunnel syndrome, where amyloid deposits in the wrist area can squeeze and irritate the nerve, causing tingling and numbness in the fingers and thumb.
- Ideally a tissue biopsy is required to confirm the diagnosis of amyloidosis using special staining techniques (Congo Red)
- Sometimes the diagnosis can be confirmed by finding AL amyloidosis outside the nervous system
  - Fat pad biopsy (from under the skin in the abdomen), from the bone marrow or other affected oragn
  - Urine protein
  - Cardiac echo and blood tests (NT-proBNP)

AL amyloidosis treatment: 2-pronged approach

1. Supportive treatment – treating your symptoms and organ damage



AL - Amyloidosis Foundation

AL amyloidosis treatment: 2-pronged approach

2. Source treatment – slowing down, or stopping, the overproduction of amyloid at the source of the disease.

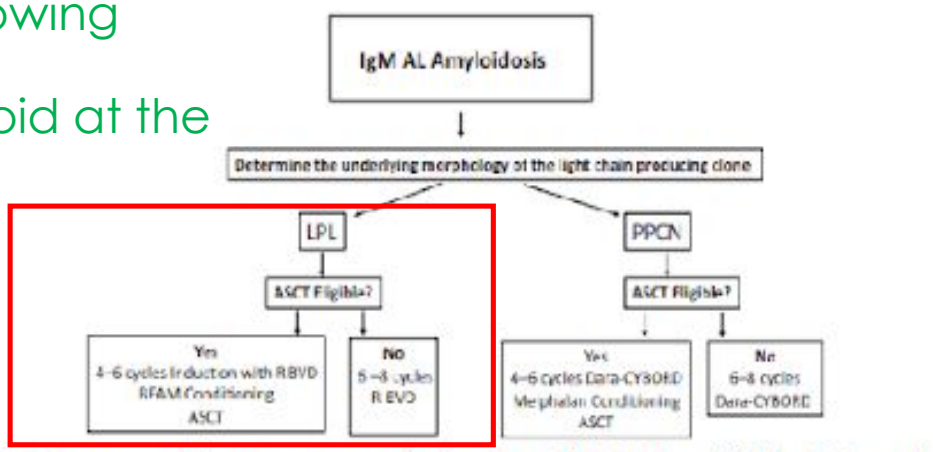
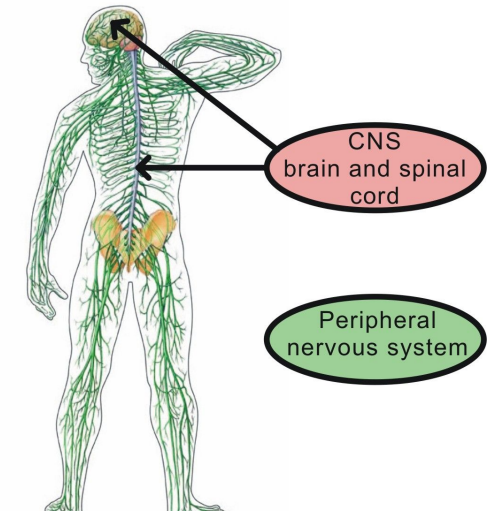


Fig. 2. Recommended treatment approach of patients with IgM AL amyloidosis. ASCT, autologous stem cell transplantation; BEAM, carmustine, etoposide, cytarabine and melphalan; Dara-CYBORD, daratumumab, cyclophosphamid, bortezomib, dexamethasone; LPL, lymphoplasmacytic clone; PPCN, pure plasma cell neoplasia; R-BVD, rituximab, bendamustine, velcade, dexamethasone.

Wechalekar et al. Systemic Amyloidosis due to Low-Grade Lymphoma
Hematol Oncol Clin N Am 34 (2020) 1027–1039



SUPPORT • EDUCATION • RESEARCH
IWMF
International Waldenstrom's Macroglobulinemia Foundation

WMUK
The UK charity for **Waldenstrom's macroglobulinaemia**

Conclusions

- IgM and WM can affect the peripheral and central nervous systems in different ways
- Effective therapies are available- prompt and accurate diagnosis is important to enable timely treatment

An important double act!