

gain information

anti-MAG paraproteinaemic demyelinating neuropathy



What is anti-MAG paraproteinaemic demyelinating neuropathy?

Anti-MAG paraproteinemic demyelinating neuropathy (anti-MAG PDPN) is one of the rarer diseases of the peripheral nerves which are included under the inflammatory neuropathy group of disorders. It occurs in about 1 per 100,000 of the population. However, within the group of patients with anti-MAG PDPN the majority are men and typically the disease begins in the mid 60's. Of course, it may occur in women and also appear both earlier and later in life, although cases under the age of 45 are very rare.

Patients with anti-MAG PDPN have fairly typical presenting symptoms and signs for their doctor or neurologist. Some doctors may never have come across the condition.

Initial complaints are of sensory change in the feet, often a numbness with additional tingling, pins and needles or a 'bound-up' feeling in the feet and ankles. This is usually slowly progressive both with change in the character of the sensation and also the area affected; the sensation gradually rises up the lower legs. In association with the sensory change, and sometimes occurring before it, a sense of unsteadiness is not uncommon and patient may begin to stagger, walking with an irregular broad based gait. The majority of patients will also develop a tremor of the hands. Power tends to be affected rather late in the condition, if at all, and early loss of strength in the feet might make a neurologist question the diagnosis.

Although it is never possible to distinguish one disease from another on clinical grounds alone, typical anti-MAG PDPN has enough typical distinguishing features to make it recognisable in most cases.

What causes anti-MAG neuropathy?

Myelin associated glycoprotein (MAG for short) is a molecule within the insulating sheath of the nerves, otherwise known as myelin. MAG helps the coiled insulating sheath stick together properly. We all have antibodies in our blood. Antibodies are there to help in the fight against infection and all antibodies have a specific target. Patients with anti-MAG PDPN have antibodies in their blood which are programmed to recognise MAG instead of targeting their normal infectious type targets. Anti-MAG antibodies bind to the MAG on the myelin sheath and result in damage which makes the myelin insulation less efficient. Myelin damage is called demyelination. It results in some short-circuiting of electrical impulses in the nerves, giving the symptoms above. In the longer term the damage results in permanent damage to the wires of the nerves (axonal damage).

All patients with anti-MAG PDPN have too much of one type of antibody called a paraprotein. This paraprotein antibody is always of the IgM class. IgM antibodies are usually our immediate defence against infection. After a few days, the immune system usually converts over to making IgG antibodies that have many more functions and are more specific for their target. In anti-MAG PDPN patients the IgM antibodies have been matured to be more specific for MAG and they do not

convert to IgG antibodies. What is more, they are all thought to be produced by a single clone of white blood cells (also known as B-cells).

This excess of one type of IgM is called a paraprotein. Paraproteins are quite common in the population as a whole (about 1% of people aged 50 and 3% of those aged 70). Many have no target and most do nothing other than exist in the blood with no damaging effects. We do not know why patients should develop paraproteinemic IgM antibodies to MAG with such frequency. Mostly the paraprotein disorder (or gammopathy) is entirely benign in its behaviour. There are no malignant cells to find in the bone marrow or elsewhere and the damage by the antibody to the cells stays fairly minimal. This is called a monoclonal gammopathy of undetermined significance (MGUS). Sometimes the gammopathy has slightly more aggressive characteristics (although in the context of all blood disorders they are generally at the benign end). In this case levels of the paraprotein increase significantly, abnormal cells are found in the bone marrow and the condition is termed Waldenström's Macroglobulinemia (WM) after the doctor who described it.

How is anti-MAG PDPN diagnosed?

Any diagnosis starts with a doctor taking a history and performing an examination. The history features that are usually reported are:

- Slowly progressive sensory disturbance occurring fairly symmetrically in the lower limbs
- A developing sense of imbalance, often reported as if from the feet (that is, not 'dizzy')
- A tremor of low frequency of the hands, usually on activity and not at rest. This can be the most disabling feature.
- Sometimes a sense of weakness of the feet resulting in a slowing of walking and occasionally trips and falls. Noticeable weakness is usually only present after many months or years
- A condition that gets worse very slowly
- Other than the tremor, usually very few or no symptoms affecting the arms and hands early in the condition
- No problems with speech, swallow, bladder, bowels or blood pressure
- Unless there are other illnesses already present, the patient is otherwise usually fairly well

A neurologist will usually perform an examination to clarify the symptoms. The examination usually finds:

- Abnormal perception of vibrations in the feet and legs, often right up to the chest
- Some reduction in the ability to feel pin pain or temperature over the feet and lower legs only
- Some unsteadiness on walking tests
- Tremor of the hands
- Usually little else of note

A doctor will then request some tests to help confirm the diagnosis:

- Blood tests to confirm that there is an IgM paraprotein in the blood, and that it has anti-MAG activity (note not all anti-MAG paraproteins cause disease – its presence does not automatically indicate that it is causative of the condition)
- Electrical tests (usually called Nerve Conduction Studies (NCS) and electromyography (EMG). These have characteristic changes in many patients with anti-MAG PDPN
- Sometimes a lumbar puncture to collect spinal fluid is performed.

- Blood tests may be performed by a haematologist to make sure that the paraprotein is benign. Often a urine test is performed to look for part of the paraprotein there too.
- Sometimes a haematologist may request a bone marrow test and some X-rays of the skeleton if there WM or other haematological diagnosis needs to be excluded
- MRI scans are generally not required
- Nerve biopsies are generally not required

Will I need to see a haematologist?

It is not essential to see a haematologist, but at some stage this is highly likely and seeing someone at the beginning of your journey may be worthwhile simply to say 'Hello' and make a note of the baseline characteristics of the condition to compare at a later stage if necessary. About 1 in 5 initially benign MGUS conditions change into a more progressive condition such as WM over the space of 20 years. A doctor is likely to want to check the paraprotein level annually to ensure it is not changing. If there are any early features of the paraprotein that might need assessing a haematologist will often assess you and possibly do the tests above.

What are the treatments?

Anti-MAG PDPN is a slowly progressive condition, often causing irritating symptoms and little or no disability. Frequently it requires no treatment other than monitoring. The early sensory symptoms are usually not reversible with treatment and balancing the potential adverse effects of treatment against the benefit they may or may not have should be discussed with your doctor. In many cases, it is acceptable to wait.

Symptomatic treatments can be very effective.

- Unsteadiness can be significantly helped with a walking cane.
- Tremor can be helped by one of a number of drugs, including propranolol, clonazepam, gabapentin, topiramate or botulinum toxin. Other interventions for severe tremor may be available in some centres.
- Good supportive footwear sometimes with a footed support and often help with balance and any foot pain.
- Tingling, pins and needles and pain can often be helped with gabapentin, pregabalin, amitriptyline or duloxetine. Pain is infrequent.
- Unfortunately, although numbness is one of the major symptoms it does not usually respond to symptomatic or therapeutic treatments

Therapeutic drug treatments are not right for everyone, may have side effects, might be delayed until it is evident the disease is progressing and may only stop the condition progressing rather than reversing it altogether

- Rituximab remains possibly the most effective drug at the time of writing. Rituximab is itself an antibody that targets many, but not all, of the white blood cells that produce the paraprotein antibody. It is given as a short infusion 2-4 times over 4 weeks. When effective it may halt progress of the condition and be effective for up to a year, sometimes longer. Recurrent dosing is sometimes performed where your doctor thinks this is necessary. Sometimes rituximab is given in combination with other treatments (below)
- Intravenous immunoglobulin (IVIg) – there is some evidence that this is useful in the short term, but its effect is often lost after a few infusions. It is purified from human blood and I

not without potential side effects. It will not cure the condition and thus if it is effective recurrent and long term infusions will be necessary.

- Cyclophosphamide – this is a chemotherapy drug given in infusions every few weeks. It is often used in combination with rituximab or steroids. At the doses usually used it does not cause hair loss (although this is a risk), but can cause significant nausea controlled with drugs) and fatigue. There are risks of severe infection.
- Steroids (prednisolone, prednisone, methylprednisolone and others) – are not usually effective alone in typical anti-MAG neuropathy, but may be used in combinations as above.
- Chlorambucil – although this used to be used frequently, there is no good evidence of its effectiveness and other better agents are now available
- Chemotherapies for the haematological disorder. Where WM is present (or more rarely another sort of progressive blood disorder) drugs used to treat haematological cancers might be used. These are continuously in development but fludarabine, bortezomib, carfilzomib, ibrutinib, bendamustine and others are used alone or in combinations. Your haematologist will tell you about these drugs if necessary.
- New therapies are continuously being developed and this list is not exhaustive.

What will happen to me in the longer term?

Most people with anti-MAG PDPN will be mildly affected and symptoms will progress very slowly over years to decades. Most find ways of ignoring or evading their symptoms and simple measures like those described above are sufficient.

Despite what is written elsewhere it is very rare for patients with anti-MAG PDPN to lose their walking abilities or need a wheelchair for mobilising even after many years of disease.

If treatment is required (which it is not all many cases) it can result in stopping progression, but it very seldom reverses the symptoms, especially the sensory changes of numbness.

Occasionally the underlying haematology condition (MGUS or WM) changes and required separate treatment in its own right. Your haematologist will work closely with your neurologist to try and avoid drugs that might result in damage to the nerves if at all possible; this is not possible in every case.

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