MGCS

Related conditions Infosheet

This Infosheet explains what Monoclonal Gammopathy of Clinical Significance (MGCS) is, how it differs from MGUS, and how it is diagnosed and managed. It also covers the condition Monoclonal Gammopathy of Renal Significance (MGRS).

What is MGCS?

Monoclonal **G**ammopathy of **C**linical **S**ignificance, or 'MGCS', is a rare condition where there is an abnormal protein in the blood, and the protein is causing specific complications in different parts of the body. MGCS is not a cancer.

MGCS is similar to a condition called Monoclonal Gammopathy of Undetermined Significance (MGUS). The abnormal protein (called a paraprotein) in the blood occurs in both MGCS and MGUS. The protein is produced by abnormal plasma cells in the bone marrow.

How is MGCS different from MGUS?

In MGCS, unlike in MGUS, the paraprotein causes one of several specific complications. It most commonly affects the kidneys, the nerves or the skin. MGCS is a fairly new term, and is not always used.

For more information about MGUS, see the MGUS Infosheet from Myeloma UK

Plasma cells and the bone marrow

Bone marrow is the spongy centre of bones where blood cells are made. This includes a type of white blood cell called plasma cells. Normal plasma cells help fight infection by producing antibodies (also known as immunoglobulins).

Antibodies

Antibodies are Y shaped proteins and are made up of four parts – two identical heavy chains and two identical light chains (see Figure 1).

There are five types of possible heavy chain: G, A, D, E and M. Antibodies using these heavy chains are called IgG, IgA, IgD, IgE and IgM. There are two types of light chain: kappa (κ) and lambda (λ).

Normal antibodies are part of the immune system. They bind to bacteria and viruses and flag them for removal.

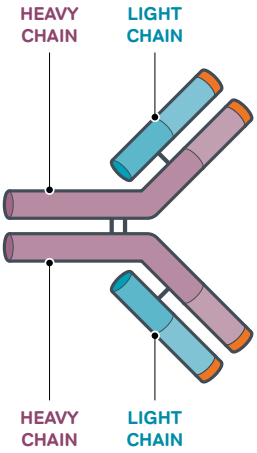

Figure 1. Antibody showing its two heavy chains and two light chains

Paraprotein

In MGCS and MGUS, plasma cells in the bone marrow become abnormal and release an increased amount of a single type of antibody. This is known as a paraprotein and it has no useful function.

Paraprotein can also be called M protein, monoclonal protein or abnormal protein (this protein is not related to dietary protein in any way).

Types of MGCS

MGCS is named according to the type of heavy chain the paraprotein is made from:

- IgM MGCS
- Non-IgM MGCS – that is, IgG, IgA, IgD or IgE MGCS
- Light chain MGCS – where there is no heavy chain at all, only light chains

Who can develop MGCS?

It has been estimated that 1 in 10 or fewer people with MGUS develop symptoms indicating MGCS. This is equivalent to about 1 in 300 people aged 50 years or older having MGCS.

An exception is that peripheral neuropathy develops in a third or more of people with IgM MGUS.

Studies indicate that MGCS is more likely to develop in older people (most often people in their sixties), and it is more common in men than in women.

MGUS is more common in people from black ethnic groups than in white or Asian people. It is also more common in people who have a close relation with MGUS or myeloma (a blood cancer which also involves abnormal plasma cells). Therefore, more people from these groups are at risk of developing MGCS.

What causes MGCS?

The underlying cause or causes of MGCS and MGUS are not yet fully understood. They are thought to involve complex changes at the genetic level.

The cause of the complications in MGCS is damage to organs caused by paraprotein or light chains. The structure of the paraprotein and light chains are unique to each person with MGUS. Most paraproteins and light chains don't cause any problems in MGUS. But in a few cases paraproteins may interact with the kidneys or other organs. It is thought that these interactions may be important in the development of MGCS.

What are the symptoms of MGCS?

The symptoms of MGCS depend on the tissue or organ affected. Patients may experience one or several symptoms. People with MGUS may have one or more symptoms but not have MGCS, as the paraprotein may not be the cause.

The kidneys, nerves or skin are the most commonly affected organs in MGCS, although other organs can be affected. Possible symptoms are listed below.

Effects on the kidneys

MGCS can cause kidney damage when paraprotein or light chains affect the function of the kidneys. In these cases it may be called Monoclonal Gammopathy of Renal Significance (MGRS). Symptoms can include:

- Fatigue
- Changes to your normal blood pressure
- Gastrointestinal symptoms (nausea/vomiting)
- Frothy urine
- Swelling of the legs
- Breathlessness

A proportion of patients may be at risk of developing severe kidney disease or kidney failure, where the kidneys can no longer function at all.

Effects on the nerves

The effect on the nerves in MGCS is called peripheral neuropathy. Peripheral neuropathy means damage to the nerves that transmit signals such as pain and touch, or that sense our position and control movement. The effects can include:

- Pain
- Numbness, tingling or 'pins and needles'
- Unusual sensations such as being very sensitive to touch
- Weakness, tremor or lack of co-ordination
- Loss of dexterity, making some tasks such as doing up buttons more difficult

Effects on the skin

MGCS can involve different effects on the skin in different patients. These can include:

- Red pinprick dots or purple patches
- Itchy reddish rash (urticaria), which can occur with fevers, joint pain, anaemia and other symptoms
- Numb or blueish fingers or toes when they are cold
- Skin ulcers
- Hardened or thickened skin

Having MGCS can mean you are at a slight increased risk of several other medical issues. These include bone fractures, osteoporosis, blood

clots and infections. However, most MGCS patients will not be affected by these issues, and in some who do have them, there may be no connection with MGCS. You may be given some tests and/or treatment for these issues. People with MGUS are also at slightly increased risk of these issues.

How is MGCS diagnosed?

Sometimes MGCS is diagnosed when issues such as kidney problems or peripheral neuropathy are being investigated.

In other people, a paraprotein may be discovered by chance when tests are being done for unrelated reasons, and then the connection with symptoms may be made.

Patients may also develop kidney, nerve or skin symptoms after they have had MGUS for some time.

When a paraprotein is discovered, it is important to make sure it is not related to a more serious diagnosis such as myeloma. Some of the tests that are recommended may be done for this reason.

The diagnosis of MGCS is difficult and often needs teamwork from many experts. Your initial evaluation may involve a team of specialists, depending on the complications you have. This may include a haematologist (blood specialist), nephrologist (kidney specialist), neurologist (nerve specialist) and dermatologist (skin specialist). The following tests will be used to diagnose MGCS:

- Blood and/or urine tests will show:
  - A paraprotein level in the blood of 30 g/L or less
  - Low level of monoclonal protein in the urine
- A bone marrow biopsy and X-rays or scans are only carried out in some people during initial investigations. If they are done they will show:
  - Less than 10% abnormal plasma cells in the bone marrow
  - No bone damage
- Tests and examinations for complications will show one or more of the following:
  - Abnormal kidney function shown in blood tests
  - Protein and/or blood leaking through the kidneys into the urine
  - Peripheral neuropathy
  - Skin changes

You may have tests to identify the type of paraprotein and light chain. Other tests that may be needed, depending on the symptoms you have, include:

- A kidney biopsy (removal of a small amount of kidney tissue). This will show the damage that is taking place, and may identify how the paraprotein or light chain is affecting the kidneys
- A skin biopsy
- Nerve conduction studies (tests to assess nerve function), and/or a nerve biopsy

How is MGCS managed?

Your MGCS may be managed in several ways:

- Treatment of symptoms and complications as needed
- Treatment targeting the underlying abnormal plasma cells. This aims to reduce the amount of paraprotein and/or light chains. Whether this is done will depend on the balance between the severity of the complications, and the risk of side effects from treatment
- Regular monitoring of the MGCS, to pick up the very small number of patients who go on to develop a more serious condition

These different types of treatment and monitoring are explained in the following sections.

Treatment of symptoms and complications

The treatments you receive for symptoms and complications will depend on the part of the body affected.

Treatment of kidney disease (MGRS)

Treatment of kidney disease may include:

- Treatment to control raised blood pressure
- Treatment of anaemia
- Treatment and prevention of infections
- Treatment with diuretics (water tablets) to help reduce extra body water
- In severe kidney disease, dialysis may be needed, to remove waste products and excess fluid from the blood when the kidneys are not functioning well enough to do it. If you are having dialysis, the amount of fluid that you can drink will be restricted

- Some patients may become eligible for a kidney transplant, if the MGRS/MGCS has been treated and is in remission

Treatment of peripheral neuropathy

Treatment of peripheral neuropathy symptoms may include:

- Pain-relieving drugs. Drugs to treat pain caused by neuropathy are different from those used for other pain such as headaches. You may be given drugs such as gabapentin, pregabalin or amitriptyline
- Pain caused by neuropathy can be challenging to control. If the drug you have been prescribed is not controlling your pain, ask to be tried on a different one, or to be referred to a pain clinic
- Drugs to control tremor may be given if needed

Living with peripheral neuropathy

There are things you can do yourself to make living with peripheral neuropathy easier:

- Keep your hands and feet warm
- Be cautious about showers and baths if your feet are numb
- Take regular gentle exercise to improve circulation and balance
- Stop smoking
- Avoid falls by keeping gangways in your home clear and well-lit, and wearing well-fitting shoes
- Use adaptations to help at home if peripheral neuropathy is affecting your mobility and balance – an occupational therapist can advise
- Ice packs or hot water bottles (wrapped in a towel) may give temporary relief
- Techniques such as meditation, relaxation or gentle massage may be helpful
- If you drive, you are required by law to inform the DVLA if you have peripheral neuropathy. Visit gov.uk/peripheral-neuropathy-and-driving or call the DVLA on 0300 790 6806

Treatment of skin complications

Treatment of skin complications in MGCS may include:

- Topical treatments (such as creams applied to the skin)
- Avoiding exposure to cold

Treatment targeting the abnormal plasma cells

Your healthcare team will consider whether to give you treatment that targets the underlying plasma cells. This will depend on how severe the complications are and how much they are worsening. Your team will look at the balance between the side effects of treatment and the severity and risk to you of the MGCS symptoms.

You may be given treatment targeting the plasma cells if you are developing kidney complications caused by paraprotein or light chains.

There have been few studies of treatments specifically for MGCS. The treatments used are similar to those for myeloma and related conditions that involve abnormal plasma cells. How the drugs are used may be different, however.

The aim of treatment is to prevent worsening of symptoms. Improvement may occur but may take some time.

The treatment you receive will depend on the type of MGCS. For example, some drugs are avoided or used in reduced doses if you have kidney problems. Other drugs can cause peripheral neuropathy so may be avoided if you have this complication. Your treatment may include one or more of:

- **Chemotherapy** drugs such as cyclophosphamide and bendamustine
- **Steroids** such as dexamethasone and prednisolone
- **Other drugs** such as bortezomib (Velcade®), thalidomide, lenalidomide (Revlimid®), rituximab (MabThera®, Rixathon®) and daratumumab (Darzalex®)
- **Intravenous immunoglobulins**
- **High-dose therapy and stem cell transplantation (HDT-SCT)** may be used for some patients with serious kidney complications

If you are having a kidney transplant, you will need to have drug treatment before the transplant to reduce the risk of the MGRS returning afterwards.

Information about some of the treatments listed above can be found at **myeloma.org.uk/publications** or by contacting the Myeloma UK Infoline on **0800 980 3332**. Although the information booklets are for myeloma patients rather than MGCS patients, so how the drugs are used may be different, you may still find the information helpful

How is MGCS monitored?

The complications you have will be monitored regularly, but how often this is done will depend on the type of complications involved. Monitoring will be done to check the response to any treatment. Your healthcare team will also check for any worsening of symptoms that might mean treatment needs to be started (or re-started if you have already had treatment).

A very small number of people with MGCS may go on to develop another, more serious, condition, such as myeloma. For this reason, it is important to have blood tests at intervals to check for any change in your condition. This will ensure that if you need to start new treatment, this can be done as soon as necessary. There is more about this in the section "Can MGCS develop into another condition?" (page page 10).

When will my MGCS be monitored?

You may have blood and urine tests every 3–6 months for the first year, followed by checks every 6–12 months after that. Your tests may be done less often if you have mild symptoms, and if you have a very low risk of progression to serious disease.

You will also be monitored for any symptoms that could indicate a change in your condition.

What blood and urine tests will be done?

Your regular blood and urine tests will include:

- Measuring paraprotein in your blood and/or urine, and sometimes also free light chain
- Red and white blood cell and platelet counts
- Blood tests for kidney function, and urine tests to check for protein leaking through the kidneys
- Blood tests for bone disease

How is response to treatment measured?

Response to treatment is measured by:

- Improvement in blood test results (called haematological response)
- Improvement in organ function

Improvement in organ function is a slower process than improvement in blood test results. Sometimes full recovery of organ function may not be possible.

Paraprotein levels can rise and fall in MGCS – this is normal. However, if there is a steady or large increase in paraprotein, or if you develop new symptoms that are of concern, further tests may be carried out.

You may find our free patient diary useful to keep a record of your test results. The diary is for people with MGUS but may still be helpful for MGCS patients. It has more information about the tests that are done to monitor MGUS/MGCS.

Order your free **MGUS Diary** from Myeloma UK

What symptoms should I watch out for?

It is important to report any new or worsening symptoms, as soon as possible. Don't wait for your next routine appointment. Symptoms to watch for in particular are:

- General deterioration in health or ability
- Pain, particularly in your back or ribs
- Fatigue
- Having frequent infections, or infections that don't clear easily
- Unexpected bone breaks
- Swollen legs or abdomen
- Breathlessness
- Bruising or bleeding
- Numbness or tingling in the feet, hands or legs
- Unexpected weight loss

Who will monitor and treat my MGCS?

Your MGCS is likely to be monitored and treated by a team of people that may include:

- Haematologist (doctor specialising in blood disorders)
- Depending on the complications you have, the team may include other hospital doctors specialising in those areas
- Your regular tests may be organised by your healthcare team at the hospital, or by your GP

Can MGCS develop into another condition?

In a very small proportion of people, MGUS and MGCS can eventually develop into a more serious condition, such as myeloma, AL amyloidosis or lymphoma.

Myeloma, also known as multiple myeloma, is a type of blood cancer arising from plasma cells in the bone marrow. It causes symptoms and requires treatment. Each year around 1 in 100 people with MGUS will be diagnosed with myeloma or related conditions and will need treatment. It is not yet known what percentage of MGCS patients go on to develop myeloma or related conditions.

AL amyloidosis is a condition where an abnormal protein made of light chains builds up in different tissues or organs. It can develop in rare cases from MGUS. In other cases, renal problems or peripheral neuropathy can develop in patients who already have AL amyloidosis.

For more information see **Myeloma – An introduction** and **AL amyloidosis: Your Essential Guide**, from Myeloma UK

Lymphoma can develop in a small proportion of people with IgM MGCS and MGUS, and this is explained on page 12.

Is there any way to tell if MGCS will develop into myeloma or a related condition?

It is not yet clear which patients with MGCS will be in the very small number who eventually progress to myeloma or a related condition. There is no definitive test to show who will progress and who will remain stable long-term.

Certain factors have been found to be associated with an increased risk of progression in people with MGUS (although the risk is still very low). The factors are:

- An abnormal serum free light chain ratio – this is a measure of the ratio between the two different types of light chain (kappa and lambda) that can be produced. An abnormal ratio shows that there is an increase in the production of one type of light chain (produced by the abnormal plasma cells)
- Types of MGUS other than IgG type
- Higher paraprotein level (15 g/L or more)

People with MGUS who do not have any of these three risk factors (called low-risk MGUS) have an extremely low risk of progressing to myeloma – over 20 years, only around 2 in 100 people with low risk MGUS progress to myeloma or related conditions. The risk of progression is higher the more of the risk factors people have, but it is still very low overall. These risk factors may also apply to MGCS patients.

It is not yet clear whether MGCS patients are at more risk of progression to myeloma or related conditions than people with MGUS. In one study, patients with MGCS involving the kidney had a higher risk of progression to myeloma than people with MGUS. In a second study, patients with MGCS involving peripheral neuropathy had a higher risk of developing AL amyloidosis than people with MGUS. The overall risks of progression in these studies were still very low however.

The cause of progression from MGUS and MGCS to myeloma or related conditions is unknown but probably involves further changes at the genetic level. This is an area of active research.

IgM MGCS

IgM MGCS is where the paraprotein produced is of the IgM type. The symptoms can vary and may affect the kidneys, nerves or skin. Peripheral neuropathy is often involved. This type of MGCS can, although rarely, progress to a low-grade non-Hodgkin lymphoma (sometimes called Waldenström's macroglobulinaemia). The risk of progression of IgM MGCS is not certain, but the risk of progression of IgM MGUS is about 1 in 100 people per year.

Non-Hodgkin lymphoma is a different blood cancer from myeloma and the symptoms can include fatigue, anaemia, swollen glands and sometimes, sweats at night.

For more information, contact **WMUK (wm.org.uk)** or **Lymphoma Action (lymphoma-action.org.uk)**

Living well with MGCS

We know from speaking to patients that anxiety can be caused by knowing that you have a condition where there is a (very small) possibility of developing a more serious condition.

You may find you are anxious at certain times, for example in the period after your diagnosis, and also when your blood tests and follow-up appointments are due. This is not unusual for patients.

However, you can be reassured that very few MGCS patients progress to a more serious condition, and that your healthcare team are monitoring you and will take any action needed.

Sources of support

It's important to reach out for any help that you need, and there are many sources of support for MGCS patients. You can get support from:

- Your healthcare team – if you are concerned about your tests or about any new symptoms, you should speak to your healthcare team
- You can call the Myeloma UK Infoline on **0800 980 3332** or email **AskTheNurse@myeloma.org.uk** for information, advice or just a listening ear
- Family and friends – who you tell about your diagnosis (and when) is a personal decision. Those you do tell can be an important source of support
- Chatting with someone else who has MGCS – speaking to someone who understands can help. You can speak to others living with MGCS on the Myeloma UK Discussion Forum

Myeloma UK is here for everything a diagnosis brings. Get in touch to find out more about how we can support you by calling the Infoline on **0800 980 3332** or visiting our website **myeloma.org.uk**

Staying positive and getting on with life

It is important not to let worry about your diagnosis of MGCS take over. Instead, be aware of the symptoms to watch out for, and use the sources of support at times when you do feel anxious.

Summary

- MGCS is a condition where abnormal plasma cells in the bone marrow produce a protein called a paraprotein, and the paraprotein causes specific complications
- MGCS is not a cancer
- MGCS is similar to the related condition MGUS. In MGCS, unlike MGUS, the paraprotein causes symptoms or complications
- The complications are most commonly kidney problems, peripheral neuropathy (a problem with the nerves), or skin symptoms
- In a very small number of cases, MGCS can develop into other conditions, such as myeloma
- Patients with MGCS will be monitored for any change in their condition
- MGCS symptoms and complications are treated as needed
- The underlying abnormal plasma cells will be targeted with specific treatments in some cases

About this Infosheet

The information in this Infosheet is not meant to replace the advice of your healthcare team. They are the people to ask if you have questions about your individual situation.

For a list of references used to develop our resources, visit myeloma.org.uk/references

We value your feedback about our patient information. For a short online survey go to myeloma.org.uk/pifeedback or email comments to patientinfo@myeloma.org.uk

Other information available from Myeloma UK

Myeloma UK has a range of information booklets available covering all aspects of myeloma and related conditions. Download or order them from myeloma.org.uk/publications

To talk to one of our Myeloma Information Specialists about any aspect of MGCS, call our Myeloma UK Infoline on 0800 980 3332 or 1800 937 773 from Ireland.

The Infoline is open from Monday to Friday, 9am to 5pm and is free to phone from anywhere in the UK and Ireland.

Information and support is also available around the clock at myeloma.org.uk

Related conditions Infosheet:
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MyelomaUK

We're here for everything a diagnosis brings

Get in touch to find out more about how we can support you

Call the Myeloma UK Infoline on
0800 980 3332

Email Ask the Nurse at
AskTheNurse@myeloma.org.uk

Visit our website at
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Myeloma UK
22 Logie Mill, Beaverbank Business Park,
Edinburgh EH7 4HG
0131 557 3332
myelomauk@myeloma.org.uk
Registered Charity No: SC026116

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