What I tell my patients about **fibrillary glomerulonephritis and immunotactoid glomerulopathy**

Hannah Wilkinson MBChB MRCP Nephrology Specialist Registrar
Catherine Horsfield MBBS FRCPath Consultant Histopathologist
Nicky Kumar MBChB MRCP MD(Res) Consultant Nephrologist, Guy's and St Thomas' NHS Foundation Trust, London

Fibrillary glomerulonephritis (FGN) and immunotactoid glomerulopathy (ITG) are very rare diseases affecting the kidneys. The conditions are often described together, but most experts would agree that they should be seen as two separate entities. A list of terms that have been used since the conditions were first described in 1977 is shown in Table 1. Nowadays, we prefer to use the terms FGN and ITG.

What is glomerulonephritis?

The kidney is essentially a collection of filtering units. A single filter is called a 'glomerulus' and multiple filters are called 'glomeruli'. There are approximately one million glomeruli in each kidney. The glomeruli have an important role, which is to filter waste products from the blood. The waste products are then removed from the body in the urine. Nephritis means inflammation in the kidney and glomerulonephritis means inflammation in the glomeruli. Glomerulopathy is another term that tells us there is a problem within the glomeruli.

Why do fibrillary glomerulonephritis and immunotactoid glomerulopathy occur?

Both disorders result from the entrance of unusual proteins, called 'immunoglobulins', into the glomeruli. These proteins become trapped in the glomeruli and it is thought that they cause damage through two mechanisms; the proteins can either directly disrupt the process of filtration, or they can activate the immune system causing inflammation and damage to the glomeruli. Inflammation can then lead to a process of 'fibrosis', resulting in scarring in the kidney, usually over a prolonged period of time. Later in this article, there is an explanation as to why the proteins have occurred in the first place.

Table 1. Synonyms for fibrillary glomerulonephritis and immunotactoid glomerulopathy

Fibrillary glomerulonephropathy
Fibrillary nephritis
Fibrillary glomerulonephritis
Immunotactoid glomerulopathy
Amyloid-like glomerulopathy
Non-amyloidotic fibrillary glomerulopathy
Congo red-negative amyloidosis-like glomerulopathy
Amyloid stain-negative microfibrillary glomerulopathy

How common are fibrillary glomerulonephritis and immunotactoid glomerulopathy?

Both conditions are uncommon causes of kidney disease and are found in approximately 1% of all kidney biopsies performed. ITG is ten times rarer than FGN and both conditions can affect any age group, with the youngest reported patient with FGN being ten years old. Patients with ITG are typically older than those with FGN, with an average age of 60–70 years. Overall, FGN and ITG are more common in Caucasians, with FGN being slightly more common in females and ITG slightly more common in males.

How are fibrillary glomerulonephritis and immunotactoid glomerulopathy diagnosed?

Upon examination, there may be a few signs which indicate that the kidney is not filtering normally; for example, the presence of blood or protein in your urine or a blood test showing a raised level of creatinine (the waste product of creatine routinely excreted by the kidneys). This often triggers your GP to ask a kidney specialist to see you. The finding of protein in your urine is the most common feature of both these conditions. In fact, all patients with FGN and ITG will have some degree of protein in their urine. In approximately two-thirds of cases, there is a significant or 'heavy leak' of protein. High blood pressure and urine stick tests indicating blood in the urine are also found in around two-thirds of cases.

The kidney specialist is likely to recommend a kidney biopsy, which is a procedure to take a small sample of your kidney for examination under the microscope. The diagnosis of both FGN and ITG can only be made following a kidney biopsy, since it is not possible to distinguish between the two conditions on the basis of the blood and urine tests alone.

What might the histopathologist see on your kidney biopsy?

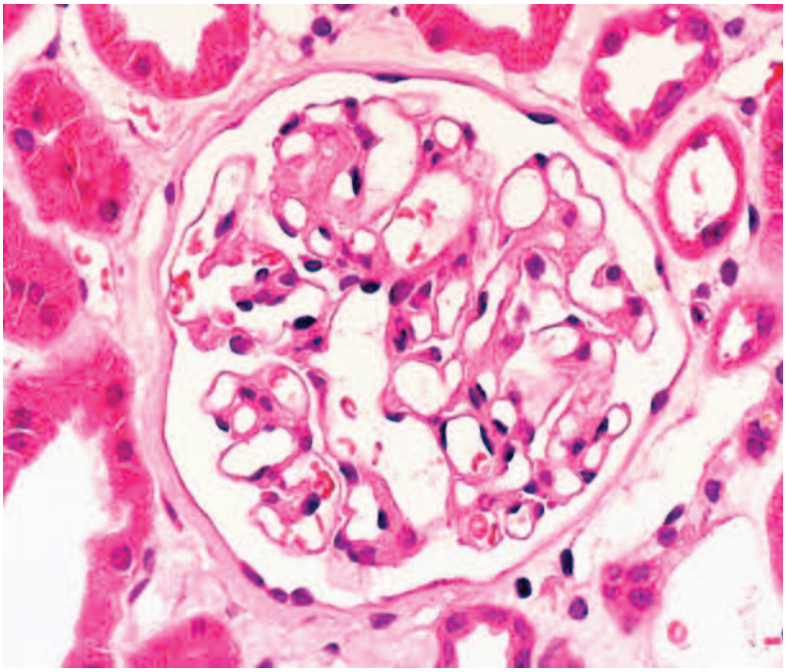
When your kidney biopsy is looked at under the light microscope, the sample can be magnified by 20–600 times the normal. By using an electron microscope, an even greater amount of detail can be seen.

Under light microscopy, the findings that can be seen are highlighted in the following figures: Figure 1 shows a normal glomerulus; Figure 2 shows a 'busy' looking glomerulus, due to an increased number of cells; Figure 3 shows a more pronounced abnormality with a massive increase in the number of cells and matrix material. It also shows how the walls of the capillaries (blood vessels) in the glomerulus have become thickened; Figure 4 shows the formation of 'crescent' shapes within the glomerulus, which is seen in about 25% of patients with FGN. The findings that can be seen under electron microscopy are highlighted in Figure 5.

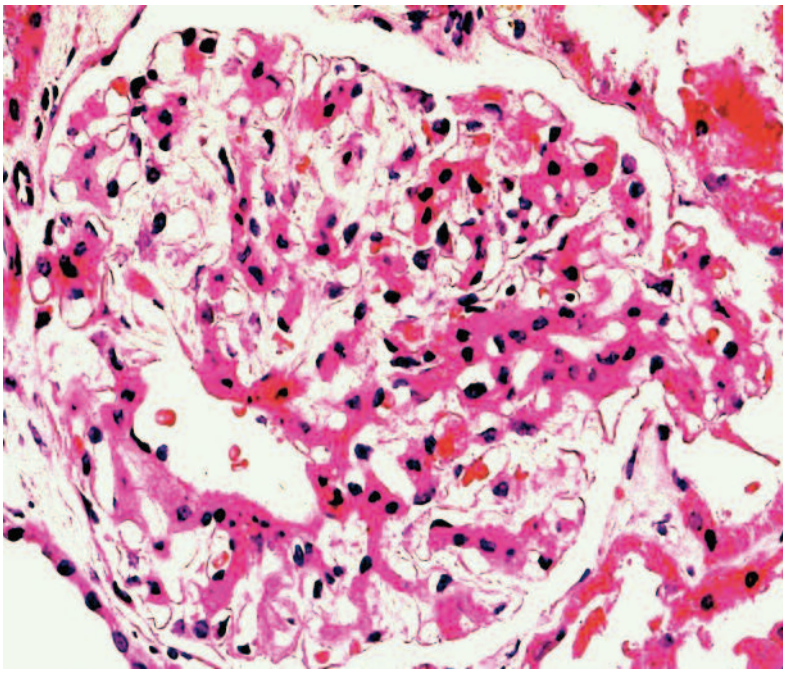
FGN is characterised by very small structures called 'fibrils', and the term 'fibrally' means a condition relating to fibrils. These are microscopic threadlike fibres measuring 10–30 nm in thickness, which are straight but haphazardly arranged. It is difficult to project this image; however, Figure 5 shows some larger structures that are 'tubular' – hollow like a pipe and usually over 30 nm in diameter. They tend to be lined up in parallel to each other, in small bundles and are typical of ITG. This is reflected in the name of the condition, as the word 'immunotactoid' can be broken down into 'immuno-', which refers to anything relating to the immune system and '-tactoid', which means a group of rod-like structures.

What are the associated diseases and how do I get tested for them?

Most cases of FGN and ITG arise spontaneously, with no underlying cause. However, in both disorders there has been an association with other diseases, such as chronic lymphocytic leukaemia (CLL), lymphoma, myeloma, hepatitis C and autoimmune conditions, such as lupus. As mentioned earlier, FGN and ITG occur as a result of immunoglobulins entering the kidney and damaging the glomeruli. Many of the diseases mentioned above are known to produce immunoglobulins. For example, in CLL (cancer of the bone marrow), the abnormal growth of a type of white blood cell (a lymphocyte) can cause increased immunoglobulin production. As a result of these associations, a variety of blood tests are often performed aiming to either exclude other conditions or determine the cause. The extra tests may include a full blood count, tests for autoimmune diseases, tests for viruses (such as hepatitis C) and sometimes a test on your bone marrow.



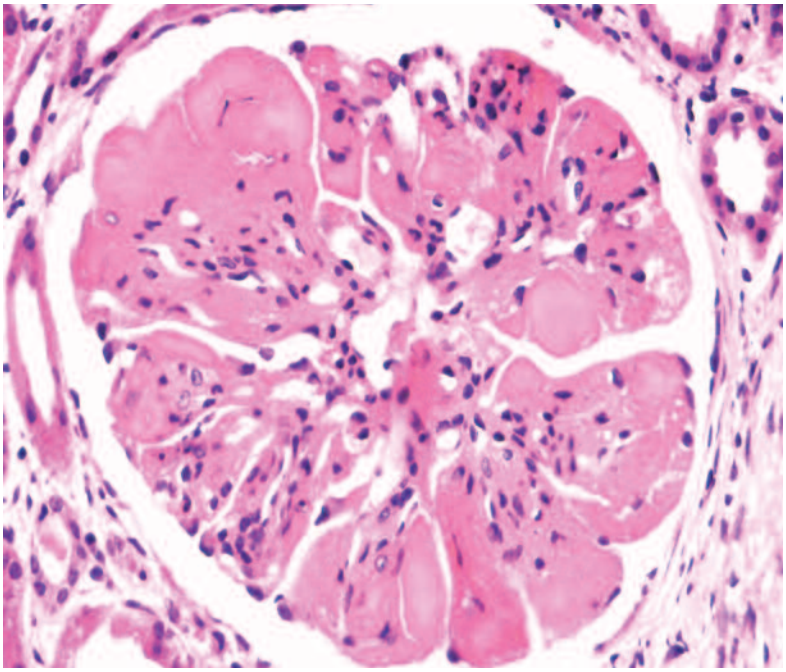
■ **Figure 1.** Cross-section of a normal glomerulus taken under a light microscope (LM) with haematoxylin and eosin (H & E) staining, magnification x 600



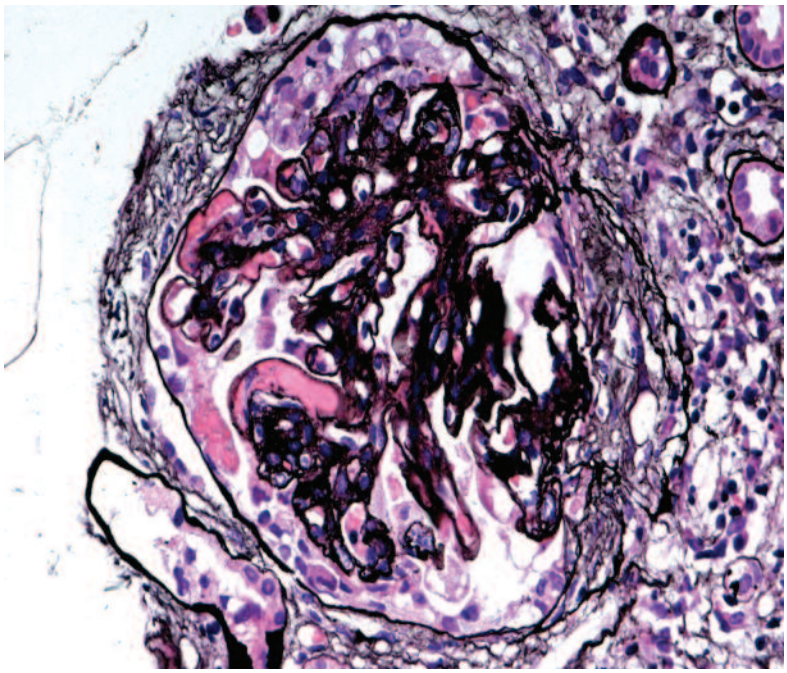
■ **Figure 2.** Some abnormality in the glomerulus, detected by the increase in number of cells. LM, H & E staining, magnification x 400

What symptoms might I get?

Some patients do not have any symptoms and an abnormality may be detected in your blood or urine upon routine testing for another condition, such as a diabetes screening. Almost all patients with FGN and ITG will lose protein in their urine and this often makes the urine appear frothy. The leak of protein in



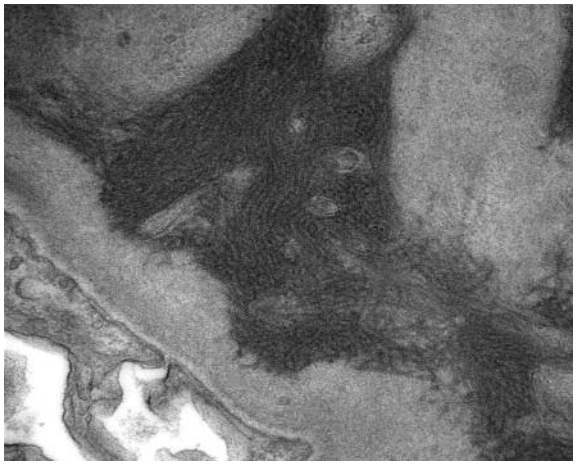
■ **Figure 3.** Section of the glomerulus with more pronounced abnormality. Futher increase in the number of cells and matrix is evident, as well as thickening of the capilleries. LM, H & E staining, magnification x 400



■ **Figure 4.** Distinctive crescent shapes in the glomerulus, present in approximately 25% of patients with fibrillary glomerulonephritis. LM, silver staining, magnification x 400

the urine (proteinuria) can lead to ankle swelling and sometimes a puffy face or eyes in the mornings. The protein loss can be so great that it causes nephrotic syndrome (protein leak in the urine), oedema (fluid retention) and low serum protein (albumin).

There is also an associated increase in blood cholesterol and an increased risk of blood clots and infection. Around half of the patients present with established damage (scarring) to the kidneys. By assessing the serum creatinine level, it is possible for your doctor to know approximately the extent of damage to your kidneys. When the creatinine level is very high, some of the symptoms you might experience include fluid retention (affecting the hands, face, feet, ankles or abdomen), breathing difficulties, loss of appetite, nausea, vomiting, tiredness, itching and high blood pressure.



■ **Figure 5.** Section of glomerulus under an electron microscope, showing the formation of larger tubular structures, typical of immunotactoid glomerulopathy. Magnification x 50,000

What are my treatment options?

At present, there is no proven effective therapy for either of these conditions; many therapies have been tried with limited success. If FGN and ITG are related to another disease, then effective therapy directed at the underlying disorder appears to have some beneficial effect on the renal disease. If there is little damage to the kidney and kidney function is relatively normal, with low levels of protein leak, usually a medication called an angiotensin-converting enzyme (ACE) inhibitor is advised in order to control blood pressure, reduce protein excretion and slow the progression of the disease. If there is heavy protein leak in the urine then treatment to prevent the complications of this will be needed, such as a statin to reduce cholesterol and possibly a blood-thinning medication (heparin or warfarin) if there is a risk of blood clotting. Diuretics, such as furosemide, can be administered to reduce fluid retention, and dietary and fluid restrictions may be put in place to reduce the fluid intake and prevent an accumulation of dangerous salts in the blood.

Some studies have suggested suppressing the immune system with steroids to halt the production of the abnormal protein; however, there have been no large trials testing this medication in these diseases. Other medications, such as rituximab, have been associated with complete or partial remission of proteinuria in some cases of FGN but not others. Patients presenting with rapidly progressive glomerulonephritis and advanced damage on their renal biopsy can be treated with high-dose steroids and cyclophosphamide.

How does it progress?

Approximately 40–50% of reported patients with FGN and ITG develop end-stage renal disease within two

to six years. When the kidneys fail, either their work needs to be taken over by dialysis (blood cleaning) or a kidney transplant is required to prevent dangerous accumulation of fluid and salts in the blood.

Is there a risk of the condition recurring after kidney transplantation?

There have been reports of disease recurrence after kidney transplantation. This tends to be a slower process than when the condition affected your own kidneys. Rates of recurrence are difficult to measure given the rarity of the disease and that most studies investigating this involve only a handful of patients ■

Declaration of interest
The authors declare that there is no conflict of interest.

Key points

- **Fibrillary glomerulonephritis (FGN) and immunotactoid glomerulopathy (ITG) are rare conditions that develop from the presence of immunoglobulins in the glomerulus. The immunoglobulins become trapped and cause damage by either directly disrupting filtration or by activating the immune system.**
- **Most patients will experience no real symptoms with FGN or ITG. In some, the loss of protein may lead to ankle swelling, or a puffy face or eyes in the morning.**
- **Blood and urine tests may show signs that the kidney is not filtering as normal, such as increased creatinine levels. However, these tests are unable to differentiate between FGN and ITG; a kidney biopsy is required.**
- **At present, there is no proven effective therapy for either FGN or ITG. If there is little kidney damage and low levels of protein loss, an angiotensin-converting enzyme (ACE) inhibitor may be prescribed. For a heavier protein leak, a statin (to reduce cholesterol) and blood-thinning medication (if at risk of blood clotting) may be needed. To reduce fluid retention, diuretics, such as furosemide, may be advised.**
- **In 40–50% of patients, FGN and ITG develop into end-stage renal disease within two to six years. When the kidneys fail, patients will need haemodialysis or a kidney transplant.**

■ *What I tell my patients about* ... is a patient information service specifically designed for renal units to use with their patients. You can now view this, and all of the previous *What I tell my patients about* ... articles, online and download them free of charge via **www.bjrm.co.uk/patient-information**

nkf
SUPPORTING KIDNEY PATIENTS

NKF, The Point, Coach Road,
Shireoaks, Worksop, Notts S81 8BW.
Tel: 01909 544 999.
Fax: 01909 481 723.
email: nkf@kidney.org.uk
www.kidney.org.uk

Over the past 16 years I have constantly argued that, for renal patients, transplantation is the 'gold standard' therapy, and that if we could make sufficient organs available and introduce sufficient changes to the transplantation infrastructure, then all suitable kidney patients should actively consider this route.

As a simple and non-scientific exercise, I took a detailed look at a committee that exists among renal patients. I plotted what has happened to its chairmanship since 2000 – a 14-year period. I considered a total of seven people who had held office. I will name these people A, C, D, F, G, H and I, in strict date order. All of these kidney patients were, or are, receiving renal replacement therapy (either transplant or dialysis) and were fit and well enough to take on the role of chairman when it was their time to do so.

Subject A was transplanted but developed a brain tumour and died in office. Subject C developed skin cancer and, when their transplant failed, could not be offered a second transplant – subject C has since died. Subject D received a transplant, as did subjects F and I. Following transplant, subject G developed skin cancer and died. Subject H is on dialysis, having elected not to be transplanted.

In summary then, the only dialysis patient in my sample is alive and well on dialysis, whereas three of the six transplanted patients have died – not particularly good odds when you consider that my exercise only spanned a 14-year period.

There are insufficient dialysis patients in this small sample to draw any meaningful conclusions as to whether dialysis or transplantation is a 'safer' option – we can all point to examples of patients doing well on dialysis and others doing well transplanted. What the exercise has done, however, is to cause me to wind back phrases such as 'gold standard' treatment. For kidney patients, there is no 'gold standard' treatment; the outlook remains a lottery and no matter which route is chosen, kidney patients remain desperate for better treatments ■

Timothy Statham OBE,
Chief Executive