What I tell my patients about membranous nephropathy

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Membranous nephropathy is quite rare among the general population but is one of the more common glomerular diseases seen in Britain. The glomeruli are the filtering units of the kidney and there are around one million in each kidney. They are carefully constructed so that the larger proteins in the blood, such as albumin, do not cross the filtering membrane of the glomerulus. The presence of albumin in the urine is a clear signal of glomerular disease. It is present in every patient with membranous nephropathy and the process affects all glomeruli in both kidneys.

Most patients develop swelling of their ankles. A patient will be referred to a nephrology unit after their GP recognises the connection between ankle swelling and proteinuria (see below). The account which follows reflects the practice in Glasgow Royal Infirmary, but is fairly typical.

First visit

I usually meet a patient for the first time before membranous nephropathy has been diagnosed. The nephrotic syndrome is the most common presentation and my first task is to explain the implications of this.

The nephrotic syndrome

Nephrotic syndrome is a condition which arises when the filters in the kidneys leak protein into the urine. Swollen ankles are the most common symptom which make patients notice the onset of the nephrotic syndrome. This is confirmed by investigations which show that the urine contains a lot of protein (proteinuria) and that there is a reduction of albumin in the blood (hypoalbuminaemia).

This combination of proteinuria, hypoalbuminaemia and swollen ankles is called the nephrotic syndrome. It may result from a variety of kidney problems, most of which are poorly understood. The swelling is a direct consequence of retention of salt and water by the kidneys, probably in response to the proteinuria. Treatment of this syndrome is divided into two parts: the relief of the main symptom, namely swelling, and, if possible, the treatment of the underlying condition.

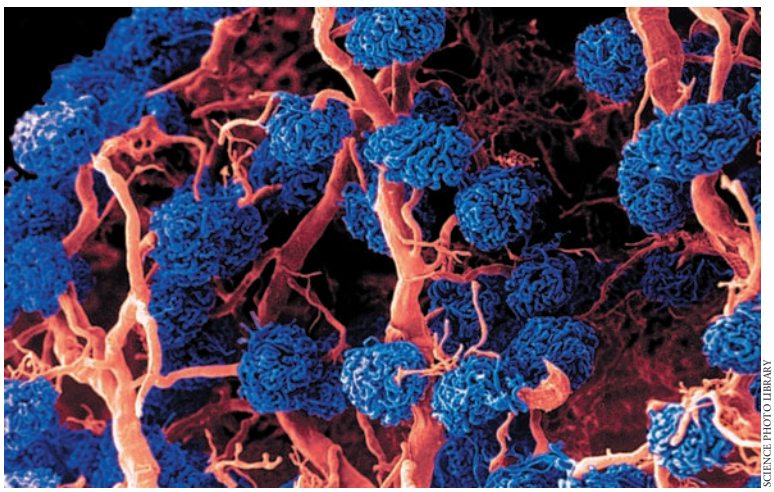
The swelling may be limited by the judicious use of diuretics (drugs which increase the output of salt and water through the kidney) and by limiting the oral intake of salt and water. At the first visit, the extent of the swelling, the patient's blood pressure and the treatment that has already been given is reviewed. Adjustments to limit the swelling and to control the patient's blood pressure will then be made.

There are several causes of the nephrotic syndrome and a renal biopsy is required to distinguish between them. A biopsy involves a short, 24-hour admission to hospital. The patient lies on his/her front and the kidney is identified by ultrasound. Local anaesthetic is infiltrated between the skin and the kidney and then a needle is advanced and a core of kidney is removed. This may be done two or three times and takes about 20 minutes. The patient is rested until the following morning when he or she is discharged. Treatment depends on the result of the biopsy; therefore it is an essential test.

Second visit

This visit takes place once the biopsy has been examined and the diagnosis made. It may also provide information on the extent of the disease. Patients are given their diagnosis at this visit, and the available options are discussed.

The diagnosis of membranous nephropathy is usually clear-cut because of the characteristic changes found in the biopsy when the tissue is examined by specialised microscopic techniques including electron microscopy and immunofluorescent studies.



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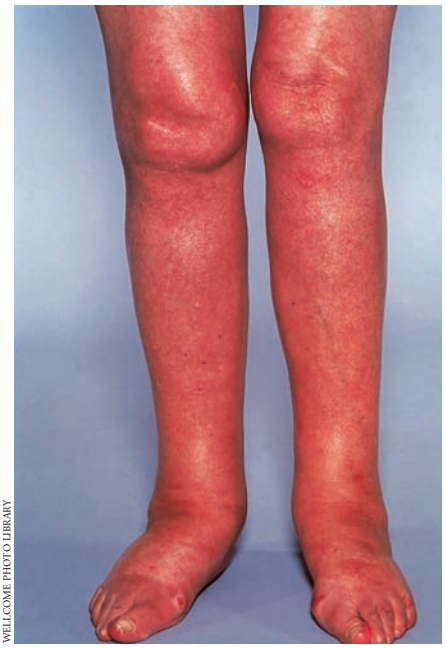
Glomeruli (shown in blue, blood vessels in red) are the filtering units of the kidney

After giving a patient his/her diagnosis, I usually write the name down for patients so that they can research membranous nephropathy if they wish. Membranous nephropathy affects people of all ages and men are twice as likely as women to suffer from the condition. A cause can be identified in about 20% of patients. This may include an infection, such as some forms of hepatitis, an autoimmune disease called systemic lupus erythematosus, tumours, or drugs – particularly those used to treat rheumatoid arthritis (gold and penicillamine).

Most patients with nephrotic syndrome have high blood pressure

At this visit I will ensure that these causes have been excluded. For the purposes of this article, I will assume that the diagnosis is idiopathic membranous nephropathy (IMN), which means that no cause can be identified.



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Swollen ankles are a characteristic symptom of nephrotic syndrome

If the diagnosis is easy to make, the prediction of what will happen to a patient is not. In a series of untreated patients in Britain, about 50% will go into remission (reduction in the amount of proteinuria) over ten years and the other half will develop progressive renal failure or may even die.

There is nothing at this stage to indicate what will happen to the patient, although those with less protein in their urine will have better prospects. Any reduction in a patient's proteinuria will help to improve their outcome. The other important observation is that once a patient starts to lose renal function, it is very unusual for spontaneous remissions to occur.

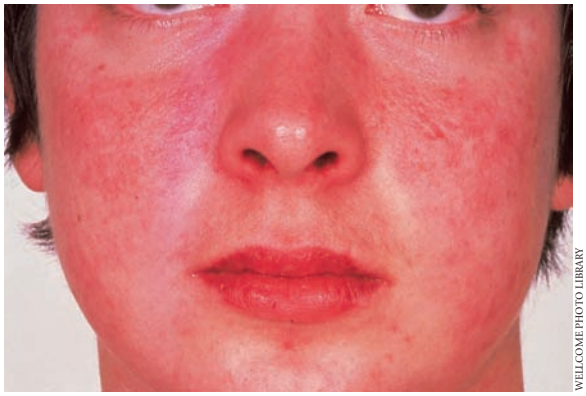
There are treatments available which can improve the chances of remission but they carry the risks of side-effects. These treatments are usually reserved for those with a bad prognosis – in other words, those with declining renal function. This is because it is not advisable to give these treatments to patients who may go into remission spontaneously. In the meantime, treatment can be given to reduce the swelling and to control blood pressure.

Swelling will decrease if less fluid is taken in than is lost to the body (mainly as urine). A balance has to be struck between removing the excess fluid causing the swelling and maintaining the circulating volume. This is the volume of blood pushed around the arteries of the body by the pumping action of the heart. If too much fluid is removed, low blood pressure, dizziness (particularly on standing), nausea and even a decline in renal function may result. The extent of the swelling can be monitored by regularly measuring the patient's weight. Over half a person's weight consists of water and the swelling adds to that weight. A target weight is given to the patient and they will be asked to adjust their treatment to maintain it. If the weight is too high, the dose of diuretic can be increased and/or fluid intake reduced. If it is too low, the patient may drink more and/or reduce the dose of diuretic. In this way, the patient may assume responsibility for some of their own treatment.

Most patients with nephrotic syndrome have high blood pressure (hypertension). Controlling this may reduce the extent of proteinuria. One class of antihypertensive drugs, called angiotensin-converting enzyme (ACE) inhibitors, are particularly adept at controlling blood pressure and reducing proteinuria. These drugs (and probably the angiotensin-receptor antagonists which have a very similar method of action) carry an advantage over all other similar drugs in preserving renal function in patients with heavy proteinuria. One of these drugs should be used at the highest dose that the patient can tolerate. It will be even more effective if salt intake is dramatically reduced. Dietitians can give advice on how this can be done.

Third visit

On the third and subsequent visits, the patient's weight, blood pressure and renal function are monitored. In our unit, we have a computerised record system which converts the result of an easily performed blood test into a figure which approximates to the percentage of kidney function remaining. The changes occurring with



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A 'butterfly' rash symptomatic of systemic lupus erythematosus – a potential cause of membranous nephropathy

time can be shown to the patient on the monitor so that they can easily follow his or her progress. Adjustments to treatment are discussed and the patient is encouraged to make some decisions between visits, as already outlined.

The nephrotic syndrome is associated with high cholesterol levels which, together with high blood pressure and proteinuria, increase the risk of problems with blood vessels such as heart disease or strokes. Therefore, it is important to reduce the risk of circulatory complications.

Unfortunately, there are no studies that define the effectiveness of various treatments in nephrotic patients, but it is assumed that lessons learned from trials of other groups of patients apply to them. A group of drugs known as statins reduce the blood's cholesterol level by as much as 40%, which gives a considerable level of protection. Other measures which may help are taking low-dose aspirin and controlling blood pressure. Patients who smoke are advised to give up.

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Cholesterol-rich foods such as these need to be avoided by patients with membranous nephropathy

Subsequent visits

The factors already discussed are reviewed and modifications are made to achieve the desired outcomes. If a steady decline in renal function occurs, the various treatments that are available are discussed. Two radical approaches to treatment have recently been reported in the form of rigorous clinical trials. To be deemed successful, these trials must show that the programme under consideration has achieved a certain standard of safety and effectiveness above that of conventional treatments. It can then be said to be a 'gold standard' treatment.

The Italian programme

A very good study in Italy has shown that intensive treatment with immunosuppressive drugs (drugs which regulate the action of the body's immune system) over a six-month period in patients with near-normal renal function increases the likelihood of remission and reduces the chances of kidney failure. It is not a cure in the same way that antibiotics cure infections, but the treatment programme significantly improves the results among a certain group of patients.The beneficial effects appear to last for at least ten years.

Two radical approaches to treatment have recently been reported

The drug used in the Italian programme is a steroid called prednisolone which is given in large doses for months one, three and five of the six-month programme. This is given in alternation with a drug called chlorambucil on months two, four and six.

Treated in outpatients, patients are given prednisolone in large doses directly into their bloodstream on the first three days of each of the odd months. For the rest of the month, they will take prednisolone tablets in a dose of 40 mg/day. However, there are a number of side-effects associated with this drug. It can make the blood pressure more difficult to control, increase appetite, change the patient's mood, promote osteoporosis (a loss of bone tissue predisposing to fractures) and bring out a diabetic tendency. It can also aggravate the tendency of the ankles to swell. Most of these effects are quickly reversed when the course is finished.

Chlorambucil prevents cells from growing and dividing and is known as a cytotoxic drug. It is most harmful to cells that multiply rapidly. In particular, it prevents the growth and division of cells in the bone marrow where blood cells are produced. This tends to deplete the blood of cells needed to combat infection. It may also make patients feel tired, suppress their appetite and cause nausea and, rarely, vomiting. Chlorambucil is given on months two, four and six. The treatment as a whole can induce stomach ulcers, so patients are advised to take anti-ulcer drugs such as ranitidine or omeprazole. Due to the toxic effects, many British nephrologists have preferred to use either a less toxic but unproven programme, or to reserve the Italian programme for those that have shown a loss of kidney function and who are at risk of developing kidney failure. They feel that the toxic risks are acceptable in these patients because of the increased risk of renal failure.

This use of the Italian programme has not been accepted as common practice, but there have been reports which have shown that it can reduce

proteinuria and the rate of loss of kidney function, albeit in conjunction with the side-effects described above.

The Canadian programme

There is one other treatment which has been proven to show beneficial effects. The trial was carried out in Canada and was unusually small, involving only 17 patients. It concentrated on patients undergoing progressive loss of renal function. The treatment given was cyclosporin, another immunosuppressant drug which is most frequently used to prevent the rejection of transplanted organs.

Given over a period of a year, this treatment significantly reduced both proteinuria and the rate of loss of kidney function in the group of patients receiving the treatment when compared to the untreated group. Cyclosporin also has side-effects the most serious of which is, ironically, to cause a loss of kidney function if given at the wrong dose. It can also cause tremor, some hair growth on the body, enlargement of the gums and anaemia. However, in this small trial, the patients had very few problems as a result of receiving this drug.

The outlook for patients with membranous nephropathy is improving all the time

The doctors' dilemma

There are other treatments for which there is some evidence to suggest that they are safe and effective, but they have not been proven by clinical trials to be of a 'gold standard'. This means that we are in a dilemma. Proven treatments are available but they are toxic, and there is some reluctance to use them except in patients facing renal failure.

The Renal Association, a body of British nephrologists, has designed a randomised, controlled trial (RCT) in an attempt to solve this problem. An RCT is the best method of establishing the effectiveness of a particular treatment, when compared with conventional treatment. Patients are told about the trial and its objectives. If they agree to participate, they are randomly allocated to one of the groups. Each trial is designed to show which is the better treatment, over a defined period of time, using a defined measure such as the level of renal function or proteinuria. The objective of this trial is to determine whether the Italian programme, the Canadian programme, or simply providing supportive treatment produces the best outcome over five years. The study has been funded by the Medical Research Council and is now under way, with patients recruited from about 30 centres.

Patients with IMN who have lost 20% of their renal function can enter the trial. Those that decide to join the trial are randomly allocated to one of three groups receiving either the Italian programme, the Canadian programme or supportive treatment. No one knows which treatment the patient will draw. This is reasonable because we do not know which is the best treatment.

The patient will receive the treatment and be reviewed at least every three months. Changes in proteinuria and kidney function will be recorded. The trial is designed to require as little extra from the patients as possible. He or she will be followed up for a maximum of five years or until the 'endpoint' is reached. This occurs if, and when, renal function declines by a further 20%.

After the patient leaves the trial, any treatment can be given. This means that all patients can receive treatment, if their clinician wishes, at quite an early stage in the progress of the disease. At the end of the trial, the results will be compared in the three groups to see which was most effective at reducing proteinuria and preventing the loss of renal function. In this way, it is hoped that we will learn which treatment is best for patients with IMN who have declining renal function.

In the case of the patients that I see in Glasgow, each patient is given an information sheet and asked to decide whether they would like to be considered for the trial. If they agree and sign the consent form, they are entered in the study. If they do not wish to join the study, it would probably be because they wanted to receive one of the three protocols that appeared most desirable to her or him. I would then introduce that treatment and continue to review the patient ensuring that the swelling, blood pressure and cholesterol were controlled adequately, while monitoring changes in the performance of the kidneys.

The outlook of patients with membranous nephropathy is improving all the time with the introduction of new drugs such as ACE inhibitors, cholesterol-lowering drugs such as the statins, and the new protocols which can reduce disease activity ■

Key points

- **Symptoms can spontaneously disappear in about half of patients who are affected by idiopathic membranous nephropathy.**
- **Control of swelling and blood pressure is the mainstay of conventional treatment.**
- **Those who begin to lose kidney function should be treated more vigorously.**
- **A Medical Research Council trial has been set up in an attempt to find the most effective form of treatment.**