



Monitoring kidney problems in TSC

Introduction

About 80% of people with Tuberous Sclerosis Complex (TSC) develop some abnormality in the kidneys.

Most of these abnormalities (or lesions) are either angiomyolipomata (AMLs) which are benign growths containing fat, blood vessels and muscle-like cells, or cysts (small fluid-filled spaces), or both together. Up to 20% of people with TSC can develop high blood pressure. Very occasionally some people develop kidney failure due to replacement of the normal kidney by cysts or AMLs. Another rare kidney problem is the development of a carcinoma. The two together probably occur in less than 5% of TSC sufferers.

AMLs occur in 60% - 80% of sufferers. They start to appear during childhood, by age 5 or 6, although they won't usually be causing any symptoms. They cause problems in about 20% of women and 10% of men with TSC. AMLs can cause bleeding into the urine or internally, pain in the tummy and anaemia. Almost all AMLs which cause bleeding are larger than 3.5cm in diameter, and many people feel it is worth looking for these in order to be forewarned before any problems occur. However, we don't know what proportion of people with AMLs larger than 3.5cm will suffer a bleed, and this is one of the questions we are hoping to answer through the National Register of Kidney Problems (see page 7).

Cysts are fluid-filled spaces and there may be one or several in each kidney. They occur in 20% of people with TSC. They do not usually cause symptoms but can predispose to high blood pressure and are sometimes associated with urine infections, when there can be pain on passing urine, the need to pass urine frequently day and night, bed-wetting and fever.

High blood pressure can cause headaches but is usually symptomless.

Kidney failure occurs in 1% of people with TS, usually due to polycystic kidneys (see below). If the kidneys are not working properly, there might occasionally be symptoms such as swelling of the legs, new onset need to pass urine at night, shortness of breath, poor appetite, weight loss or not growing properly (in children), or itching of the skin. All of these symptoms can occur for other reasons. In anyone who is persistently unwell for no apparent reason a kidney problem should be considered.

Polycystic kidneys

Some people get confused between the 2 types of cyst that can occur in TS: simple cysts and another condition called Adult

Polycystic Kidney Disease (APKD). APKD is a different genetic disorder which mainly affects the kidney and in which the cysts gradually enlarge and become more numerous, eventually causing kidney failure. It occurs in the 5% of people with TSC who have damage to both their TSC-2 gene and their PKD-1 gene, which are next to each other on the tip of chromosome 16. In the 5% of people with TSC who have APKD as well, renal function declines over a period of time and may eventually result in kidney failure.

The simple cysts that occur in 20% of people with TSC are much fewer, grow more slowly or not at all and do not cause kidney failure. Sometimes they have been known to disappear altogether.

Having said all that, thankfully most people with a TSC kidney abnormality have no symptoms at all. Many doctors, however, feel it is sensible to carry out routine monitoring for kidney problems in anyone with TS, even if they do not feel unwell.

How to monitor the kidneys

The best ways of looking for possible kidney problems are:

1. Measure blood pressure

This is high in up to 20 % of people with TSC. It is important to treat both to prevent the problems of high blood pressure (i.e. strokes and heart disease) in later life, and to protect the kidneys from blood pressure damage. Although they may suffer headaches, people usually do not know when they have high blood pressure; it should therefore be measured at least once a year in people who have TSC.

2. Blood tests

These should include:

- Plasma creatinine and urea, which give quite a good idea of baseline kidney function.
- Haemoglobin to look for anaemia.

These tests can be done on a single blood sample and ideally should be carried out once a year. However, in children who might find it traumatic and in whom kidney ultrasound and urine dipsticks are known to be normal, 2-3 yearly would be reasonable. If plasma creatinine is interpreted properly (i.e. any small change is important and a progressive change extremely so), then it will tell a doctor whether kidney function is normal or changing and repeat tests will show at what rate. Emla cream rubbed on the skin two hours before the blood test

will make it painless. More involved tests such as chromium EDTA GFR (which involves injection of a tiny amount of radio-isotope then 2 further blood tests 2 and 4 hours later) or a creatinine clearance which involves a complete collection of 24 hours' urine plus a blood test), are sometimes helpful in growing children.

3. Urine tests

Testing the urine for blood and protein can be done very quickly with a special indicator stick on a sample of a few millilitres. If there is any blood or protein in the urine this most commonly means the person has a urine infection. Sometimes it is due to kidney disease including minor bleeding from an AML (even when the urine is not obviously red).

If there is reason to worry about an infection (because of protein or blood in the urine, or pain on passing water, or a temperature, or just general distress in a young child), a special urine stick will show white cells or nitrites if there is an infection. Then an MSU (mid stream urine) needs to be sent to the local hospital. This will confirm an infection and identify the bacteria causing it. An MSU is tricky to obtain from a young child. It involves catching some urine after the person has already passed a few millilitres, so that the first few drops wash the outlet from the bladder clear of any unimportant skin bacteria. Sometimes it is necessary to start treatment without a satisfactory MSU.

4. Imaging

An **ultrasound** will show up any cysts or angiomyolipomata (AMLs). It is the same test used to look at babies in pregnant mothers. It takes 10-15 minutes and is not painful or unpleasant. The person having it needs to keep fairly still to get good pictures. A little bit of jelly is normally put on the skin over each kidney and a small probe moved about on the skin. The patient can usually see the pictures on the TV monitor, which helps. An ultrasound will show whether there is anything abnormal in the kidney and how big it is. It will not always distinguish between AMLs and the very rare carcinoma. Therefore if an atypical AML is found it may be necessary to carry out a **CT** or **MRI scan** as well, and occasionally a biopsy of the lump. Thereafter, if the tests confirm an AML, its size can be followed with repeated ultrasounds. The main disadvantage of regular kidney imaging as part of routine monitoring is that it may occasionally pick up these atypical AMLs with little fat in them, raising the suspicion that they may be a carcinoma. Any difficult problems like this should be referred to an expert centre e.g. a TSC clinic.

An **angiogram** is an X-ray where a very small tube (a fine bore catheter) is inserted through the skin into an artery in the groin. It is then slid up to the kidney arteries and dye is squirted into them. Nowadays with modern equipment it is a minor procedure. Adults have local anaesthetic injected into the groin to stop it being painful. Children still often have a general anaesthetic to stop them being frightened. The procedure takes 30-45 minutes and the person is able to go home after 2-3 hours. It shows the blood supply to each kidney very well and is used to

show the blood supply to an AML. An AML can be embolised (i.e. have its blood supply cut off) at the time of the angiogram. This is done by advancing the catheter into the blood vessel feeding the AML and injecting various things (plastic coils, foam or superglue) into the blood vessel, blocking it off. Doctors would consider embolising an AML if it was or had been bleeding, or causing a lot of pain or progressively enlarging beyond 4 cm in diameter. When arterial embolisation is carried out the procedure takes about an hour and the patient needs to stay in hospital for 2-7 days afterwards. This is because usually there is some pain and fever afterwards, and occasionally bleeding.

A **renogram** is a picture of the kidneys taken after injecting a small amount of radio-isotope (either **DTPA**, **DMSA** or **MAG-3**) that is concentrated by the kidneys. The patient needs to lie still on a reinforced glass bed for 15-20 minutes. The camera is under the bed and builds up a picture as the radioactivity passes through the kidneys. Renograms give very useful information about the function and blood supply of the kidneys, any partial blockage to the flow of urine and any scars in the kidneys. Some kidneys contain so many AMLs that no normal kidney tissue can be seen with ultrasound, CT or MRI scans. Most of these kidneys have normal or nearly normal function. This can be shown by a blood test (plasma creatinine) and with a renogram, which shows how much each kidney contributes to overall kidney function.

Who, When and Where

It is not known how often people should be monitored for kidney problems. Ideally doctors would like evidence from a controlled study to guide them as to what tests are helpful and when – and that looking for problems will be of overall benefit. Unfortunately it is likely to be a very long time before we have definite evidence. Until then we need to be guided by common sense and informed guesswork.

The main reasons for monitoring are:

1. So that the patient and their family can be fully informed as to what is going on. It is much easier for most people to cope with things once they are known and can be put into perspective rather than making frightening guesses about the unknown.
2. To explain any symptoms or medical findings that might be due to kidney problems. Then if any treatment is necessary your doctor will know.
3. To pick up any problems that can be dealt with before they cause real harm e.g. high blood pressure, carcinoma, urine infections, or impairment of kidney function. We do not know if embolising AMLs larger than 3.5cm before they bleed would cause more harm than good. This is because we don't know what percentage will bleed, but it is useful to know about them because if they do bleed the patient and carers will be aware of the possibility and know what to do about it straight away. Also, AMLs bigger than 4cm, which are pro-

gressively enlarging, are very likely to bleed and should probably be embolised before they do.

In a very small number of people, monitoring will pick up a carcinoma that can be cured by early diagnosis and surgery. In a larger number (but still a small percentage) regular ultrasounds will show an AML with little fat that looks like a carcinoma. This will need a CT or MRI scan, and possibly a biopsy, to prove it is an AML and not a carcinoma. Sometimes this requires a general anaesthetic, which carries a small risk. Some people would rather run the risk of missing a rare carcinoma, than the slightly higher risk of being unnecessarily worried and investigated. This is reasonable if that is how they feel. If you are worried then discuss the pros and cons with your doctor.

I would recommend checking blood pressure and a blood and urine test every year (except in young children with normal kidneys – see above) and an ultrasound every 2-3 years, increasing to every year if an abnormality is found. The tests described above can be carried out in most large hospitals. If your doctor cannot get them done locally he will know of a hospital where they can be done.

The National Registry of Kidney Problems

A lot more research is needed into kidney problems, especially into how often each occurs and when, how they change over time, and what the best treatments are. In order to answer some of these important questions the TSA has set up a research project, which everyone with TSC is invited to join. Registry participants (or their carers) are asked to fill out a simple questionnaire once a year to collect information about their kidneys and information is also collected from their doctors.

If you would like to participate you can contact the Registry care of:

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Further information on TSC and the work of the Tuberous Sclerosis Association can be obtained from our website at: www.tuberous-sclerosis.org

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