



The Tuberous Sclerosis Association

This document can be found at www.tuberous-sclerosis.org

It reports on a presentation at a meeting of the TS Alliance in San Diego in July 2001.

Brain, Kidney and Lung Involvement in Tuberous Sclerosis

Brain

Dr Peter Black gave the first part of the presentation about brain involvement in TS. He is Professor of Neurosurgeon at Harvard University School of Medicine.

His talk focussed on the various brain manifestations in TS. Three of these – cortical tubers, subependymal nodules (SENs) and white matter hamartomas - are found in 90-100% people with TS, whilst SEGAs (i.e. Subependymal Giant cell Astrocytomas, otherwise known as brain tumours) occur in 6-16%.

Neurological abnormalities in TS include epilepsy, infantile spasms, developmental delay and behavioural problems. The brain is made up of 90% glial cell and 10% neurons, with the glia supporting the neurons, and seizures occur when the glia cells don't work properly.

Dr Black showed some beautiful 3 dimensional pictures of the brain to illustrate how cortical tubers in TS can interfere with various neurological functions. It is these cortical tubers which have leant their name to the condition, Tuberous Sclerosis. They consist of giant cells which carried on growing, plus abnormal neurons. These tubers probably stop calcifying by the age of 20, after which time they are unlikely to give new trouble. TS patients may have several tubers but a specific tuber may be the source of an individual's seizures. Sometimes it is possible to remove a tuber in an attempt to stop the seizures, but sometimes after removal (in about 5% cases) other tubers will begin to generate epilepsy. Cortical hamartomas are similar to tubers but are on the surface of the brain and it may also be possible to remove these surgically. SEGAs are glial and neuronal in character. Similar to the cortical tubers, they lie under the ventricle walls. They don't change very quickly and if they do appear it is usually during the first and second decade of life. If they grow and block the flow of the cerebro spinal fluid in the brain, then they cause hydrocephalus. We don't yet know what causes one SEN to grow into a SEGA and another not..

Lungs

Dr Joel Moss, chief of Pulmonary Medicine at the Critical Care and Medicine Branch of the National Heart, Lung and Blood Institute at the National Institutes of Health in

Bethesda, Maryland, then gave an overview of lung problems (or LAM) in tuberous sclerosis.

LAM (lymphangioma) is a rare lung disease that occurs almost entirely in women of child-bearing age, although one or two men have also been found to be affected. It can occur in the absence of TS (usually with associated non-malignant kidney tumours), when it is known as sporadic LAM. It consists of thin-walled cysts in the lungs and is diagnosed on biopsy by abnormal smooth muscle cells. LAM cells contain mutations in the TSC2 gene.

Clinical problems in LAM include:

- Pulmonary – cystic lung disease and respiratory problems
- Renal – AMLs and sometimes renal carcinoma
- Lymphatic – effusions
- Bone – osteoporosis and osteopenia (not usually symptomatic).

There are a number of tests and investigations which can be used to predict when a transplant may be necessary. These include lung function tests, when the patient breathes into a machine, LAM histology score to look at the amount of cysts and LAM cells, and a high resolution CT scan. The results of the CT scan and lung function tests seem to correlate pretty well.

About a third of LAM patients respond quite well to bronchodilators, as with asthma patients. There have been some reports of progesterone treatment being helpful, but the evidence is inconclusive. The effects of pregnancy on a woman with LAM is unclear, apart from the risk of a collapsed lung, and some LAM patients have carried their babies to term. Patients with LAM should be warned about the risks of flying, which increases the risk of a cyst bursting, resulting in a pneumothorax.

Some TS patients (men and women) may also have nodules on their lungs, and they can coexist with LAM. They are no problem clinically, although they may be mistaken for cancer.

Kidney Involvement

This presentation was given by Dr John Bissler.

Renal cysts affect about 72% TS patients. They are usually solitary and can occur whether you have a TSC1 or a TSC2 mutation. They can also occur in non TS patients, as do AMLs (below). There are about 500,000 nephrons in a kidney which filter into urine. Cells sometimes develop abnormally in the nephrons to cause a cyst. They tend to occur as a person gets older. They can be multiple and although rarely in TS, can be polycystic.

These cysts rarely cause problems, but they can cause kidney infections and these can be serious if you are prone to get them with fever.

AMLs affect about 70% TS patients, both men and women, and usually affect both kidneys. They occur independently of cysts, and it is possible to have both. They are composed of dysplastic blood cells (angio-), smooth muscle cells (myo-), and fat cells (lipo-). The blood cells, muscle cells and fat cells can vary in proportion.

They can occur in the cortex, the medulla or the sub-capsule. They can also affect the adrenal glands, liver, lung, spleen, pancreas, intestines, regional lymph nodes and vessel extension.

Treatment includes embolisation (inserting polyvinyl particles to stop the blood flow and dam the blood supply to the AML), partial nephrectomy to remove the AML or full nephrectomy to remove the entire kidney. The aim is to preserve as much renal tissue as possible.

AMLs are treated to prevent haemorrhage, to prevent the onset of renal failure, to protect surrounding tissue from infiltration by AML and to protect from possible malignancy as it grows bigger. Renal failure occurs in 10-15% TS patients, but this figure should fall as renal problems are now being treated more appropriately.

Larger AMLs have an increased risk of haemorrhage due to abnormal blood vessels feeding them. Aneurysms are arterial defects that can lead to bleeding – the risk of bleeding crudely correlates with size of AML.

Embolisation is sometimes followed by post-embolisation syndrome. This involves flank pain (which can be severe) and is caused by the body's immune response to dying tissue. About 80% will develop this syndrome, which can be reduced by the use of steroids.

There is a rare risk of malignancy in TS. An epitheloid AML is very rare, as is a sarcoma. The risk of renal cell carcinoma is also low but warrants periodic imaging.

Management of renal lesions in TS includes periodic imaging (ultra-sound or CT). The future may see anti-angiogenesis for rapidly growing lesions.

