

## Renal (Kidney) involvement in Behçet's Disease

Kidney disease is not usually a significant problem for patients with Behçet's. In the medical literature, of many thousands of patient's with Behçet's disease, only around 250 patients have been reported to have Behçet's-related kidney problems. The prevalence of kidney involvement in clinics with large numbers of Behçet's patients has been reported to vary from 0-55%. However, in most cases the involvement is not significant; patients experiencing kidney-related symptoms are in a tiny minority. Because Behçet's –related kidney disease is uncommon, our knowledge comes from case reports of single patients, and a few reviews of the experience of larger clinics, so it is difficult to be absolutely certain whether the Behçet's has caused the kidney disease, whether it is a side effect of treatment, or whether the kidney disease is an incidental finding unrelated to the Behçet's. However, it is likely that the following kidney disorders are associated with Behçet's disease:

- Amyloidosis (AA amyloid; deposits of proteinaceous material which interfere with kidney function).
- Glomerulonephritis (inflammation of the blood filtering apparatus of the kidney).
- Vascular (blood vessel) disease (inflammation or thrombosis/ clotting).
- Side effects of drugs used for treatment.

Serious kidney problems are more common in men, in people who have had other severe Behçet's-related problems for some time, and in people who have vascular (blood vessel) involvement, such as thrombosis (blockage) or aneurism (bulging) of arteries or veins, affecting other parts of the body.

### Amyloidosis

Amyloidosis is the laying down of inert proteinaceous material which can affect the function of the affected organ. It can occur in almost any area of the body, but certain organs, such as kidney, are more susceptible. Amyloidosis in Behçet's is almost always of the AA type and occurs following many years of poorly controlled inflammation. Some people of Mediterranean origin may be more genetically susceptible to this complication.

### Diagnosis of amyloid

Amyloid produces no symptoms in the early stages, although protein may be present on urine testing (proteinuria). If significant amyloid is present, nephrotic syndrome may occur, resulting in generalized swelling, large amounts of protein in the urine and low albumin (protein) in the blood. A biopsy (small sample of tissue for examination under the microscope) is necessary to diagnose amyloid. Fortunately amyloid can usually be

detected on rectal biopsy; a minor clinic-based procedure, avoiding the necessity for a kidney biopsy, which is usually a day case procedure, under local anaesthetic.

### **Prevention and treatment of amyloid.**

Amyloid can be prevented by good control of the Behçet's disease, with anti-inflammatory or immunosuppressive drugs (for example prednisolone, azathioprine, cyclosporine). The intensity of treatment required should be determined by the overall activity of the Behçet's disease and blood tests to check levels of inflammatory markers such as ESR and CRP.

In rare cases monitoring of blood serum amyloid A protein (SAA) may be required.

Colchicine may have additional anti-amyloid properties and in theory could be prevent the formation of amyloid.

Once established, amyloid is difficult to treat. However, further deposition of amyloid, and in some cases regression of established amyloid may be achieved by the above measures.

### **Glomerulonephritis**

Glomerulonephritis refers to inflammation of the glomeruli; the areas in the kidney where the blood is filtered to remove waste products, which are then excreted via the bladder as urine.

Glomerulonephritis of significance is rare. In one Turkish survey only 0.16% of 4121 patients attending a Behçet's clinic over a 23 year period, had glomerulonephritis (proven on renal biopsy).

### **Diagnosis of glomerulonephritis**

In the early stages glomerulonephritis has no symptoms, or nonspecific symptoms such as fatigue, commonly experienced by people with Behçet's without kidney involvement.

Blood pressure may be high. However, high blood pressure is common and not usually caused by Behçet's related kidney problems.

Persistent presence of blood and protein on urine dipstick testing occurs. Casts (clumps of red or white blood cells, accumulating as a result of inflammation) may be seen on microscopic analysis of urine. Presence of small amounts of blood and/or protein on urine dipstick testing is very common (2.5-4% in healthy volunteers, 10.8% in the large Turkish survey of Behçet's patients) and usually does not indicate a serious problem. However, persistent abnormalities should be investigated further.

Kidney biopsy, is required to make the diagnosis in most cases where glomerulonephritis is suspected. Kidney biopsy is the taking of a small sample of tissue from the kidney with a needle inserted through the skin. The sample is examined under the microscope for signs of inflammation.

### **Treatment of glomerulonephritis**

Immune suppression with corticosteroids (prednisolone) or immunosuppressive medication, as used for treatment of Behçet's elsewhere, is often required.

Control of blood pressure is important to avoid further damage to the kidneys.

Control of conditions unrelated to Behçet's, such as high cholesterol or diabetes is important.

Inflammation of other areas of the kidney (interstitial nephritis) has not been shown to be caused by Behçet's. However, some of the drugs used to treat Behçet's can cause interstitial nephritis.

### **Vascular (Blood vessel) involvement**

Behçet's can affect both arteries and veins. The consequences depend on the size and extent of the blood vessels involved.

**Large arteries:** Blockage (thrombosis) or aneurism (bulging) of the renal artery (the main artery to the kidney) may occur. Occasionally Behçet's can affect the aorta (the main artery leading from the heart) in the region of the renal (kidney) arteries, indirectly causing kidney problems. Kidneys help control the blood pressure. Narrowing of the renal artery causes high blood pressure, which can be difficult to control, and can cause more damage to the function of the kidneys, in extreme cases causing kidney failure. If only one side is affected, the normal kidney on the other side may nevertheless be damaged by the high blood pressure.

Aneurysms (bulging of the arteries) affect blood flow, cause pressure on surrounding structures, may develop blood clots (thrombosis or embolism) and may rupture. Any of these events may result in poor kidney function or high blood pressure, as described above.

### **Diagnosis of large blood vessel involvement.**

**Ultrasound studies** show the structure of the large blood vessels and can diagnose aneurysms and large thromboses. Ultrasound also measures the size of the kidneys, bladder and tubes (ureters). Doppler studies use ultrasound techniques to measure blood flow and give useful extra information.

**Arteriography** involves injecting a dye (contrast) into the artery and taking X-rays or CT scans to look for blockages or other abnormalities. Arteriography is more risky in people with Behçet's as thrombosis is more likely to occur. Newer techniques using injections into veins are safer and, together with CT or MRI scanning, can often give the information required and may avoid the need for traditional arteriography.

### **Treatment of large vessel involvement**

Depending on the problem, corticosteroids or immunosuppressive agents may be given to reduce the Behçet's activity.

Anticoagulants, such as warfarin, may be required to reduce the chance of further blood clotting.

Surgery may be required to relieve a narrowing or a blockage, or to remove an aneurism. Minimally invasive surgery, such as stenting (insertion of a tube to bypass the blockage or aneurism) inserted via an artery in the leg, under local anaesthetic, may be possible.

### **Small blood vessel involvement**

Small blood vessels internal to the kidney may become inflamed (vasculitis), or develop aneurysms or blockages. In this case it may be difficult to decide if the kidney problem is Behçet's or polyarteritis nodosa, another type of vasculitis. Presence of Behçet's-type symptoms affecting other parts of the body and the time course of events will help determine the diagnosis.

Treatment of Behçet's related renal (kidney) vasculitis (and of polyarteritis nodosa) is with corticosteroids (prednisolone) and other immunosuppressive agents.

### **Drug-related renal problems**

The following drugs can sometimes damage the kidneys:

- **Aspirin and other non-steroidal anti-inflammatory drugs (e.g. ibuprofen/nurofen, diclofenac, indomethacin.)**

If used regularly, in high doses. Intermittent or low dose treatment is unlikely to be a problem. People with preexisting kidney damage should avoid this type of medication unless advised otherwise by their doctor.

- **Cyclosporine**

Cyclosporine levels should be monitored regularly to avoid toxic doses. In people with preexisting kidney damage, the risks and benefits of cyclosporine should be carefully considered before use.

- **Cyclophosphamide**

High doses can cause severe bladder inflammation which can indirectly affect the kidney function. People on high dose treatment (usually intravenous) can be given MESNA, an additional treatment which protects the bladder against the effects of cyclophosphamide.

- **Tacrolimus**

May cause impaired kidney function (rarely). Blood creatinine should be monitored.

*Please note; this is not a comprehensive list of drugs which may affect the kidney. Sometimes drugs with a risk of kidney side effects may nevertheless be the best choice to treat Behçet's-related kidney disease.*

### **Dialysis and kidney transplantation in Behçet's disease.**

End stage kidney failure is extremely rare in Behçet's Disease, so only a handful of affected people are known to have required these treatments.

Haemodialysis (use of a kidney machine) has been used successfully, although people with Behçet's are likely to have more complications initially. It is necessary to create a connection between an artery and a vein ('fistula') where the kidney machine can be connected. This connection is more likely to thrombose (block) in people with Behçet's.

Peritoneal dialysis is feasible, although infection may be a problem.

Kidney transplantation has been successful, although extra measures may need to be taken during surgery to avoid clotting of the transplanted renal blood vessels.

On dialysis or after transplantation, Behçet's disease activity at any site is usually much reduced or absent.

***Dr Hilary Longhurst, April 2008***