The eye in renal disease

This article summarizes the ocular pathology that can be seen in conjunction with renal disease. Both the eye and the kidney can be the target of systemic disease processes, but the eye can also be affected as a consequence of either renal disease or its treatment.

The ocular and renal systems are targets of end organ damage in a wide variety of pathologies. They may occur simultaneously as the result of a common disease process, or ocular involvement can occur secondary to specific renal syndromes. Awareness of the spectrum of ocular complications that can occur in renal disease allows for early identification and treatment of potentially irreversible sight-threatening conditions, but can also sometimes offer useful diagnostic or prognostic information. This article reviews the shared ophthalmic manifestations of end-stage renal failure resulting from an array of renal pathology, as well as specific oculorenal syndromes that occur in congenital and hereditary developmental abnormalities.

Chronic renal failure

The ocular manifestations of renal failure can occur as a result of both the systemic sequelae of disease and iatrogenic complications of various treatment modalities, including opportunistic infection as a result of systemic immunosuppression for renal vasculitis.

Anterior segment of the eye

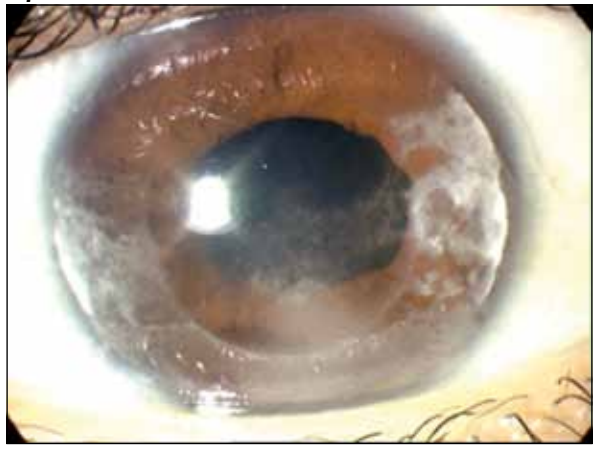
It has long been known that patients with chronic renal failure can develop ocular complications (Berlyne and Shaw, 1967). Secondary hyperparathyroidism leads to deposition of calcium within the cornea and conjunctiva (Klaassen-Broekema and van Bijsterveld, 1992). When marked, this deposition spreads across the cornea to cause band keratopathy, which can lead to significant ocular discomfort and impaired visual acuity (*Figure 1*). Treatment consists of removal under topical anaesthesia, either mechanically or using calcium chelators such as EDTA, but is an uncomfortable procedure and the condition is prone to recurrence. Calcium deposition within the conjunctiva causes chronic inflammation, which can then lead to further reactive changes such as pingueculae formation and superior limbic keratitis.

A significant number of patients undergoing haemodialysis develop chronic ocular irritation as a result of reduced tear production (Porter and Crombie, 1973) and alterations in the blink reflex (Resende et al, 2002). Treatment is usually straightforward, and takes the form of tear film supplementation with artificial tears. Haemodialysis has also been reported to induce rises in the intraocular pressure in predisposed patients (Choong and Menage, 1998; Tawara et al, 1998; Tokuyama et al, 1998), probably as a result of the removal of uraemic toxins and other solutes from the vascular compartment lowering serum osmolality more rapidly than ocular osmolality; this gradient is particularly steep in the eye owing to the presence of the ocular–blood barrier.

Posterior segment of the eye

Arterial hypertension is a significant and chronic cause of visual morbidity in patients suffering from chronic renal failure. The high volume and velocity of blood flow within arteries results in damage to the structure of the vessel walls, particularly in the small calibre vessels of the eye. Arteriolar narrowing leads to ischaemic retinal changes which produce cotton wool spots, flame-shaped haemorrhages, hard exudates and retinal oedema. In severe cases, optic disc oedema may develop. Damage to choroidal vessels may also occur, producing focal choroidal infarcts known clinically as Elschnig's spots (*Figure 2*). Although peripheral retinal changes may be asymptomatic, when these changes occur at the macula, patients can become aware of a decrease in visual acuity. Owing to the changes in the vessels walls as well as serum osmolarity, these patients are also at greater risk of developing both retinal arterial and venous obstructive disease which present as a sudden, painless loss of vision.

Figure 1. Band keratopathy, indicating a pattern of calcium deposition across the anterior surface of the cornea.



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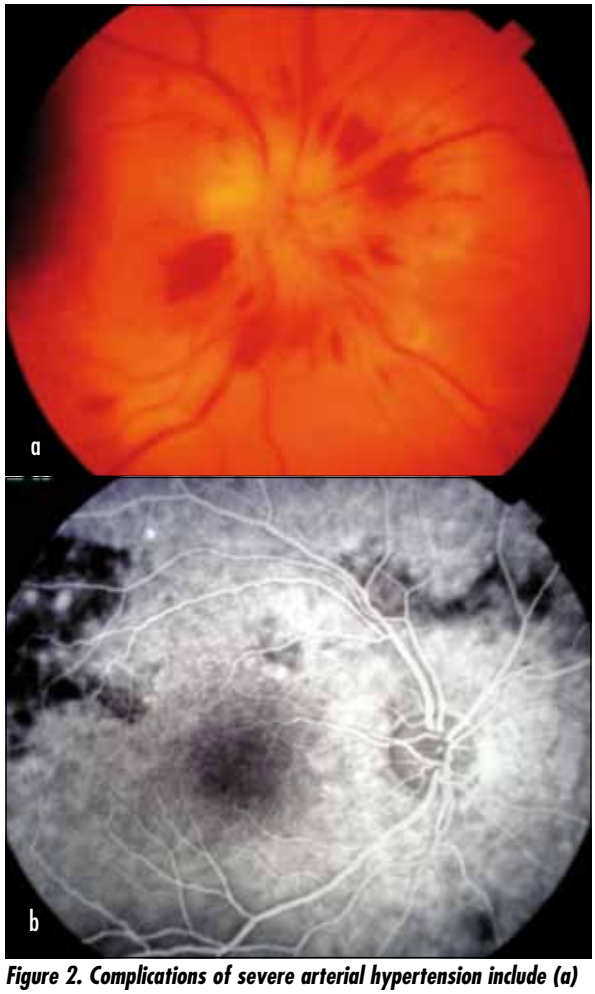


Figure 2. Complications of severe arterial hypertension include (a) swollen optic discs, and choroidal infarcts which can be visualized (b) as patches of non-perfusion on fluorescein angiography.

Diabetes mellitus also commonly affects both ocular and renal vascular beds, and patients with coexisting disease often develop an increase in retinal exudate when renal failure ensues (*Figure 3*).

Figure 3. Fundus photograph of severe diabetic retinopathy with much exudate (yellow areas) as the patient went into renal failure.

Patients on dialysis are particularly prone to the development of anterior ischemic optic neuropathy as a result of anaemia and hypotensive episodes during dialysis (Jackson et al, 1999; Basile et al, 2001). Patients typically present with an altitudinal visual field defect affecting the superior or inferior hemifield of vision in one eye (*Figure 4*). There is no effective treatment, but giant cell arteritis should be ruled out as a potential cause. Uraemic optic neuropathy is a reversible cause of optic nerve dysfunction which subsides if the uraemia is reversed before permanent optic nerve compromise is allowed to occur (Knox et al, 1988).

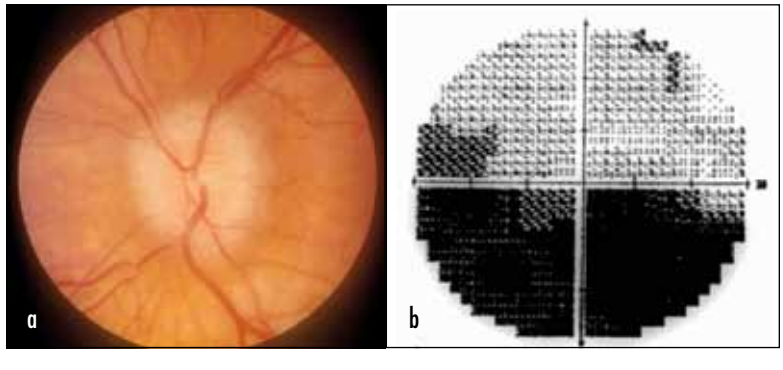
Systemic inflammatory disease

There are a number of systemic inflammatory diseases which target both the eye and the kidney, including Wegener's granulomatosis, systemic lupus erythematosus, scleroderma and polyarteritis nodosa.

Ocular involvement in Wegener's granulomatosis is estimated to occur in between 50 and 60% of patients, and typically takes the form of scleritis or orbital disease. The development of necrotizing scleritis is a hallmark of ocular Wegener's granulomatosis (*Figure 4*) (Joshi et al, 2009). It occurs in over 50% of patients and is a much feared complication, with 90% of patients developing complications such as keratitis, corneal ulceration, uveitis and glaucoma, which can lead to severe visual loss. Vision can also be compromised in orbital disease as a result of proptosis, with exposure keratopathy, corneal ulceration and perforation all having been reported (*Figure 5*).

Systemic lupus erythematosus is a systemic autoimmune disorder characterized by autoantibody formation. After secondary Sjögren's syndrome, retinal vascular lesions are the commonest ophthalmic manifestation of systemic lupus erythematosus and include cotton wool spots and retinal haemorrhages, usually as a result of arteriolar occlusion; the prevalence of these features ranges from 3–29% (Joshi et al, 2011). Systemic lupus erythematosus patients with raised antiphospholipid antibodies have a higher risk of developing occlusive retinal vascular disease (*Figure 6*).

Figure 4. a. Anterior ischaemic optic neuropathy presents with a swollen optic disc and loss of either the superior or the inferior hemifield of vision, as indicated by (b) the Humphrey automated visual field printout. Giant cell arteritis should be excluded as a cause.



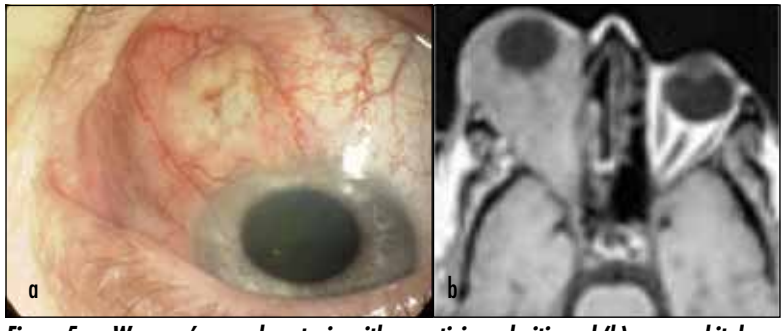


Figure 5. a. Wegener's granulomatosis with necrotizing scleritis and (b) gross orbital infiltration.

Polyarteritis nodosa can cause hypertensive retinopathy in patients with renal disease, retinopathy from the vasculitis itself and retinal arterial occlusive disease, including central retinal artery occlusion. Involvement of the posterior ciliary arteries can also result in anterior ischaemic optic neuropathy. Scleroderma or systemic sclerosis uncommonly causes retinal involvement, which is traditionally thought to be present in less than 5% of patients, although more recent studies have revealed that up to 34% of normotensive patients with systemic sclerosis can have hard exudates and vascular tortuosity (Joshi et al, 2011). Other reported retinal features include retinal haemorrhage, branch retinal vein occlusion and central retinal vein occlusion. The retinopathy of malignant hypertension can be seen in patients with scleroderma renal crisis, including cotton wool spots, intraretinal haemorrhages and optic disc oedema.

Tubulointerstitial nephritis and uveitis

Tubulointerstitial nephritis and uveitis is a rare disease which was first described in 1975 (Dobrin et al, 1975) and consists of anterior uveitis in association with tubulointerstitial nephritis. The ocular symptoms are forerunners of systemic symptoms in about 20% of cases and are usually bilateral and limited to anterior uveitis. The visual prognosis is good, but the uveitis is recurrent or chronic in at least half of patients, often persisting for several years and leading to ocular complications such as including posterior synechiae, cataract and raised intraocular pressure (Mandeville et al, 2001). The differential diagnosis includes sarcoidosis and Sjögren's syndrome.

Membranoproliferative glomerulonephritis type II

Membranoproliferative glomerulonephritis type II is a rare condition which also has ocular manifestations. These patients develop immune complex deposition within the glomerular basement membrane as well as the Bruch's membrane, retinal pigment epithelium and choriocapillaris of the eye (Duvall-Young et al, 1989). Deposits are scattered across the posterior pole and resemble drusen; severe loss of vision can occur in these patients if they go on to develop choroidal neovascular membranes that disrupt the retinal architecture and cause spontaneous macula haemorrhages (Troiano and Buccianti, 1998).

Ocular renal syndromes

There is a wide range of multisystem disorders that involve both renal and ocular pathology. As the life expectancy of individuals born with congenital abnormalities has improved, more syndromes are being categorized that show phenotypic abnormalities in both the ocular and renal system. A few of the more common syndromes are discussed in greater detail below.

von Hippel–Lindau disease

This is an inherited, autosomal dominant syndrome that leads to the development of benign and malignant tumours. It arises from germline mutations in the von Hippel–Lindau gene and has multi-systemic manifestations affecting the retina and CNS, as well as visceral organs including the kidney, pancreas, liver, adrenal glands and the broad ligament. Retinal capillary haemangioblastomas are the classic ocular lesion of von

Figure 6. Antiphospholipid syndrome with marked retinal haemorrhages and cotton wool spots.

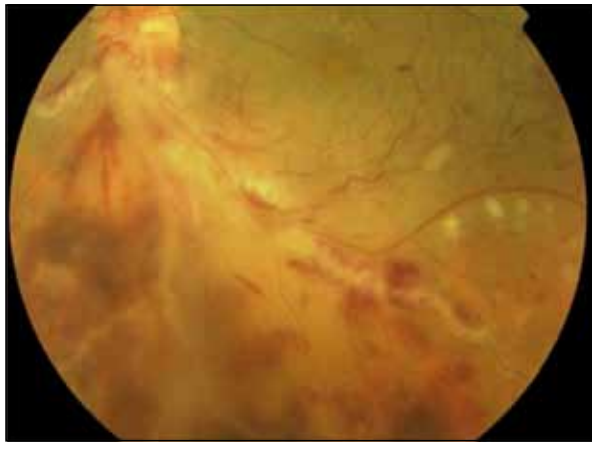
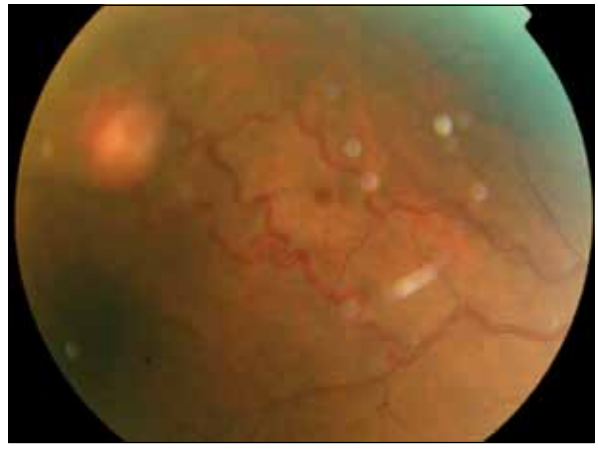


Figure 7. A retinal capillary haemangioblastoma in von Hippel–Lindau disease.



Hippel–Lindau; they usually arise in the first or second decade and are clinically evident around the third decade of life (*Figure 7*). Of all patients with von Hippel–Lindau, retinal capillary haemangioblastomas are the presenting manifestation in 43% of cases and ultimately develop in 59% of patients (Webster et al, 1999).

WAGR syndrome

The WAGR syndrome consists of Wilms' tumour, sporadic aniridia, genitourinary malformations and mental retardation (*Figure 8*). The majority of Wilms' tumours are sporadic and represent the most common malignant renal tumour in children. Sporadic aniridia is present in 1% of children with Wilms' tumour and therefore any newborn with non-familial aniridia should be referred for further genetic and medical examination (Jotterand et al, 1990; Warrier and Regueira, 1992).

Alport's syndrome

Alport's syndrome is a predominantly X-linked condition that results in a mutation of type IV collagen, causing a rare abnormality of the glomerular basement membrane. The disease is characterized by chronic renal failure with progressive haematuria, sensorineural deafness and ocular signs affecting the cornea, lens and retina. The severity of ocular manifestations is proportional to the severity of renal dysfunction, but no significant eye changes are seen in variants of Alport's syndrome without deafness (Thompson et al, 1987).

The visual prognosis for patients with this condition is generally good. Ocular manifestations include corneal changes such as anterior lenticonus and occasionally posterior polymorphous dystrophy along with retinal signs of scattered yellow perimacular flecks.

Cystinosis

Cystinosis is an autosomal recessive disease which results in the defective transport of cysteine out of lysosomes, leading to intracellular lysosomal accumulation and deposition of cysteine crystals within multiple body systems, including the kidneys and the eyes. Cystinosis remains the commonest cause of Fanconi's syndrome in the paediatric population, with renal tubule damage leading to excessive urine production and excessive thirst, resulting in deficits of water, calcium, potassium, magnesium and other substances in the body. It often leads to bone disease and stunted growth (Joosten et al, 2010). Ocular manifestations of cystinosis include crystal deposition within the cornea, starting in the periphery and becoming more widespread over time. Crystalline deposition also occurs in the conjunctiva, iris and retinal pigment epithelium. Patchy peripheral depigmentation of the retina is diffuse but symmetrical. Some patients can go on to develop atrophic macular scarring which carries a poor visual prognosis.

Fabry's disease

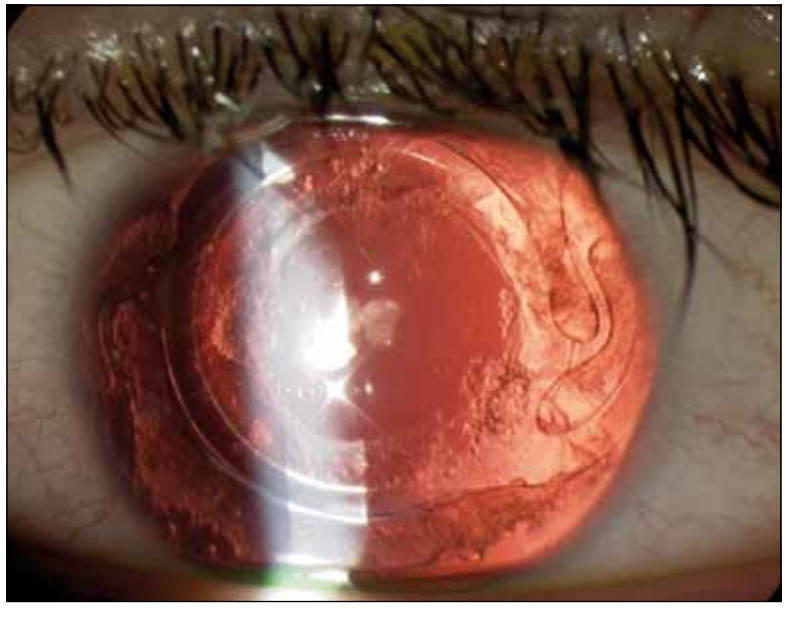
Fabry's disease is a rare X-linked glycosphingolipid storage multisystem disease that primarily affects the vascular endothelium. It is potentially lethal, and manifests in the third and fourth decades, but the advent of enzyme replacement therapy has improved the prognosis, although early diagnosis is vital to prevent irreversible end-organ damage. Ocular signs such as whorl-like lines emanating from a single corneal vortex can be detected in both hemi- and homozygotes at an early age and are diagnostic of the disease (Joosten et al, 2010). Other eye signs include distinctive lenticular opacities, and vascular tortuosity of the conjunctiva and retina. Ischaemic optic neuropathy and retinal artery occlusion have been reported as ocular complications of Fabry's disease (Sher et al, 1979; Parnes et al, 2008).

Side effects of drugs

Intraocular pressure can be increased by the administration of corticosteroids to so-called 'steroid responders', which is a potential issue for patients taking corticosteroids following renal transplantation. This is much more common for topical administration of corticosteroids than for systemic corticosteroids, so routine screening of patients taking systemic corticosteroids is not required, but care should be taken in some patients as there is an overlap between populations at risk of end-stage renal failure and glaucoma, i.e. African–Caribbean race, diabetes mellitus, advanced age and co-existing vascular disease. Other ocular side effects of the administration of corticosteroids include cataract formation (*Figure 9*).

Corticosteroids are also associated with dysfunction of the interior layers of the choroidal vasculature, the choriocapillaris, which can lead to accumulation of fluid within the potential space between the neurosensory ret-

Figure 8. A patient with aniridia who has had cataract surgery with implantation of an intraocular lens. The absence of iris tissue is clearly visible.



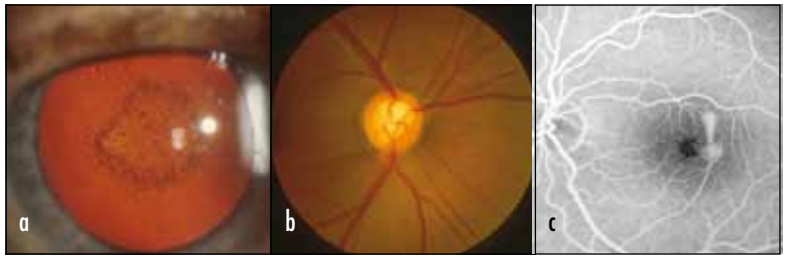


Figure 9. Corticosteroid-induced ocular complications can take the form of cataracts, particularly (a) posterior subcapsular cataracts, or raised intraocular pressure, which may lead to (b) glaucomatous optic neuropathy, if untreated in susceptible individuals. c. Rarely, steroid-induced central serous chorioretinopathy can occur, in which fluid leaks from the choroid through the blood–retina barrier and into the retina, causing visual distortion. This causes a classic 'smokestack' pattern of leakage on fluorescein angiography.

ina and the retinal pigment epithelium in a condition known as central serous chorioretinopathy (Friberg and Eller, 1990; Gass, 1992). It presents with a visual distortion in the affected eye and is treated by withdrawal of corticosteroids where possible, and occasionally by laser closure of the focal points of leakage.

In patients who have undergone renal transplantation, systemic immunosuppression can also cause them to be vulnerable to opportunistic infection. Common pathogens include herpes simplex, herpes zoster and cytomegalovirus (see associated article on the eye in virology, p. 672).

Conclusions

The eye can be involved in renal disease either because both organs are targets of the same disease process or because the ocular disease occurs as a result of renal involvement. There are specific oculorenal syndromes which also involve both organs. Clinical recognition of the overlap in pathology between renal and ocular disease can help to aid the prompt diagnosis and treatment of a patient population with a high degree of potential ocular and systemic morbidity. BJHM

KEY POINTS

- The ocular manifestations of renal disease can occur as a result of the disease itself as well as iatrogenic complications of treatment.
- Chronic renal failure is associated with several different ocular complications.
- There are a number of systemic inflammatory diseases which target both the eye and the kidney, including Wegener's granulomatosis, systemic lupus erythematosus, scleroderma and polyarteritis nodosa.
- Systemic immunosuppression can lead to important ocular complications, including opportunistic ocular infection.
- Clinical recognition of the overlap in pathology between renal and ocular disease can aid in prompt diagnosis and treatment.

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