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Deposition keratopathy

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Abstract

Material can be deposited in the cornea as a result of a wide range of systemic and ophthalmic diseases, as well as local and systemic therapies. Causes include local infection or trauma, systemic malignancy, a wide range of medications and a host of genetic and metabolic diseases. Some of these can be acutely life threatening, so generalists caring for both children and adults should have a basic awareness of the pattern and distribution of corneal deposits to facilitate timely diagnosis, investigation, management or onward referral to avoid significant morbidity or mortality. This article outlines causes of corneal deposits found in patients presenting to primary care, ophthalmic clinics or encountered on the wards to help generalists avoid missing serious pathology. It also provides insight into the natural history of underlying causative conditions and their possible treatments.

Key words: Band-shaped; Cornea; Corneal dystrophies; Corneal dystrophy; Fabry disease; Hereditary; Lipids

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Introduction

The ‘deposition keratopathies’ are a group of conditions characterised by the abnormal build-up of substances in the cornea. They have a wide range of ophthalmic, systemic and iatrogenic causes – the colour, pattern and location of deposits often giving clues as to the underlying pathology. If they are not identified in a timely fashion, these can be associated with significant morbidity and mortality, making their recognition important to the general clinician. Referral to the local eye unit can help with the prompt diagnosis of some of these rare inherited conditions where there is diagnostic uncertainty. While best visualised with a slit lamp biomicroscope, a basic examination can be performed at the bedside with adequate lighting or a direct ophthalmoscope. This article discusses the various causes of deposition keratopathies, their patterns of deposition and important considerations for further investigation and management.

Vortex keratopathy (corneal verticillata)

Vortex keratopathy is a bilateral corneal condition with a distinctive appearance of superficial, symmetrical, golden brown deposits emanating from a point in the inferior cornea in a curvilinear pattern (Figure 1). The limbus is spared, and vision is almost never affected. Vortex keratopathy is classically associated with Fabry disease, but it is more commonly encountered as a side effect of systemic medications, particularly amiodarone (Table 1) (Raizman et al, 2017). The diagnosis of vortex keratopathy is clinical, based on examination findings alone, and treatment is rarely indicated. Iatrogenic deposits often resolve when the offending medication is stopped.

Fabry disease

Fabry disease is a progressive X-linked disorder of glycosphingolipid metabolism caused by absent or deficient lysosomal α-galactosidase A activity. It is a systemic condition with renal failure, cardiovascular and cerebrovascular complications limiting life expectancy. Prenatal diagnosis is now possible and enzyme replacement therapy is widely used (El Dib et al, 2016). Vortex keratopathy is almost always seen in affected men and less commonly in female carriers. Other ocular manifestations include tortuosity of the conjunctival and retinal vessels, cataracts, optic atrophy and macular oedema (Germain, 2010).

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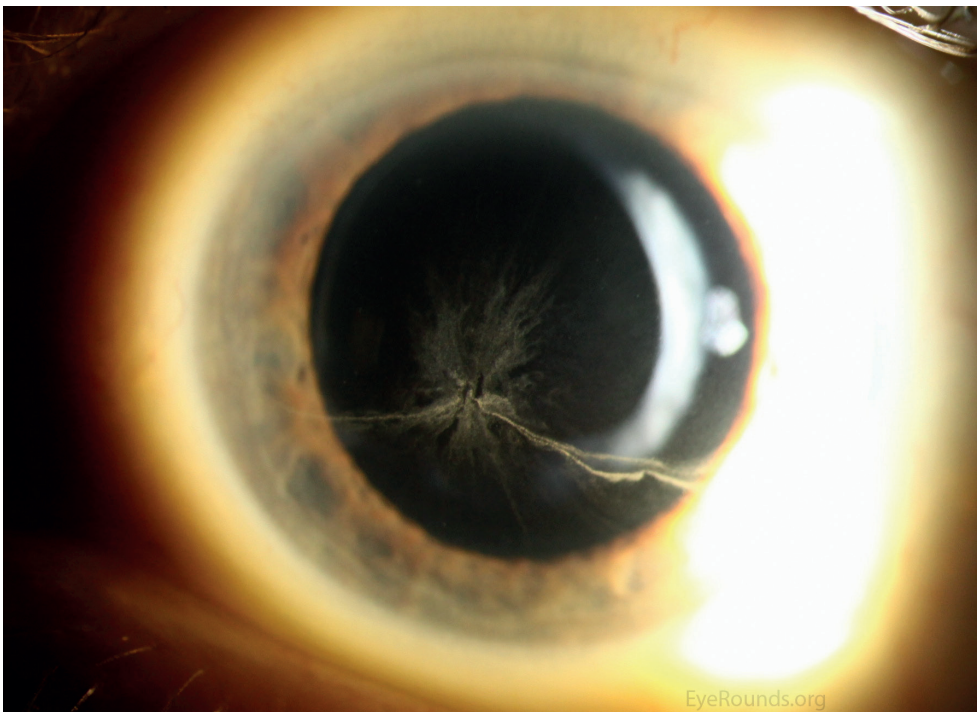

Figure 1. Vortex keratopathy.

Table 1. Drugs known to cause vortex keratopathy

Drug	Class	Indication
Amiodarone	Class III antiarrhythmic	Ventricular arrhythmias
Chloroquinine or hydroxychloroquinine	Antimalarials	Malaria, psoriatic arthritis, lupus
Chlorpromazine	Phenothiazine antipsychotic	Schizophrenia and other psychoses, intractable hiccups, nausea and vomiting in palliative care
Tamoxifen	Selective oestrogen-receptor modulator	Breast cancer
Indomethacin, naproxen, ibuprofen	Non-steroidal anti-inflammatory drugs	Moderate to severe inflammation in rheumatic disease and other musculoskeletal disorders, gout, dysmenorrhoea
Atovaquone	Quinone antibiotic	*Pneumocystis jirovecii* pneumonia
Suramin	Antiparasitic	Trypanosomiasis, onchocerciasis
Tilorone	Antiviral	Various viral infections
Perhexiline maleate	Anti-anginal	Angina

Adapted from Raizman et al (2017)

Medication-associated vortex keratopathy

Cationic amphiphilic drugs have been postulated to cause deposition keratopathy via the accumulation of phospholipids, drug precipitation, lysosomal sequestration or toxicity to the epithelium (Raizman et al, 2017). Corneal changes are both dose- and time-dependent, but can typically be seen within 1–4 months of starting the medication. The strongest association is with amiodarone, and occurs in up to 99% of patients receiving 200–1200 mg 5 days a week (Raizman et al, 2017).

Other causes to consider that may mimic vortex keratopathy include:

Hudson–Stahli line

Hudson–Stahli line is a benign interpalpebral epithelial iron line associated with ageing, typically seen at the junction of the lower and middle third of the cornea.

Healing epithelial defect

An epithelial abrasion can heal in a whorled manner caused by epithelial repopulation from limbal stem cells. This may briefly mimic the pattern of vortex keratopathy. Patients may have a history of eye injury and any changes are likely to be unilateral and transient.

Mucopolysaccharidoses keratopathy

The mucopolysaccharidoses are a family of disorders caused by deficiencies of enzymes responsible for the breakdown of glycosaminoglycans (mucopolysaccharidoses) (Table 2) (Denniston and Murray, 2018). The accumulation of various enzyme substrates results in a wide range of ophthalmic, facial and skeletal issues, along with varying degrees of intellectual impairment dependent on the deficient enzyme. Conditions are grouped into syndromes based on enzyme deficiency (commonly identified through urinalysis and assay blood tests) and presentation. Inheritance for all is autosomal recessive, with the exception of Hunter syndrome (MPS II) which is X-linked recessive, and most have corneal clouding with the exception of Hunter syndrome (MPS II) and Sanfilippo syndrome (MPS IV). Treatment options for all the mucopolysaccharidoses discussed in this article include enzyme replacement therapies, corneal transplant where corneal clouding is significant, and haematopoietic stem cell transplantation (Muenzer et al, 2009; Akyol et al, 2019a; Stapleton et al, 2019), although the latter is of uncertain benefit in patients with MPS IV (Akyol et al, 2019b).

Table 2. Disorders of glycosaminoglycan metabolism (mucopolysaccharidoses)

Syndrome	Deficient enzyme	Ophthalmic features	Systemic features
Mucopolysaccharidose I (Hurler, Scheie or Hurler–Scheie)	α-iduronidase	Cloudy cornea Pigmentary retinopathy Optic atrophy	'Coarse' facial features – enlarged head, lips, cheeks, tongue and nose Sleep apnoea Short stature Joint deformities Developmental delay Intellectual impairment
Mucopolysaccharidose II (Hunter)	Iduronate sulfatase	Pigmentary retinopathy Optic atrophy	Variable decrease in IQ Skeletal or facial dysmorphism
Mucopolysaccharidose III (Sanfilippo) type A–D	Heparan-*N*-sulfatase (type A)	Pigmentary retinopathy Optic atrophy	Intellectual impairment Neurodegeneration Mild dysmorphism
Mucopolysaccharidose IV (Morquio) types A and B	Galactose-6-sulfatase (type A) Beta galactosidase (type B)	Cloudy corneas Pigmentary retinopathy	Macrocephaly Short stature Bony or spinal abnormalities Hypermobile joints Mid facial hypoplasia, prominent mandible
Mucopolysaccharidose VI (Maroteaux–Lamy)	N-acetyl-galactosamine-4-sulfatase	Cloudy corneas	Coarse facial features as with mucopolysaccharidose I Normal intelligence
Mucopolysaccharidose VII (Sly)	β-glucornidase	Cloudy corneas Optic atrophy	Death in utero If surviving to childhood, as above with mucopolysaccharidose I including intellectual impairment

MPS IH: Hurler syndrome

This is the most severe subtype of MPS disorders in terms of clinical severity. It has features of skeletal and facial dysmorphism, severe intellectual disabilities and a reduced life expectancy (Williams et al, 2017). The deficient enzyme α-iduronidase leads to increased amounts of heparan sulphate and dermatan sulphate in the urine (Pavan-Langston, 2008). Ophthalmic features include corneal clouding (Figure 2), pigmentary retinopathy, glaucoma and optic nerve atrophy (Ashworth et al, 2010).

MPS IS: Scheie syndrome

This syndrome was initially thought to be a milder form of Hurler syndrome and designated as MPS V. However, it has been found to have a deficiency of the same enzyme affected in Hurler syndrome, α-iduronidase. The gene affected is at the same locus as the defective gene for Hurler syndrome, and therefore Scheie syndrome was reclassified within MPS I (Muenzer, 2011). The main difficulty in this syndrome is corneal clouding, with milder features of facial and skeletal dysmorphism than Hurler syndrome. IQ is usually less affected and lifespan is normal (Williams et al, 2017). In the eye, pigmentary retinopathy and optic nerve abnormalities have also been reported (Ashworth et al, 2010).

MPS IH/S: Hurler–Scheie syndrome

This intermediary syndrome is a genetic compound of its two eponymous syndromes, Hurler and Scheie. The phenotype comprises features of both syndromes, with an intermediate severity.

MPS IV: Morquio syndrome

The deficient enzyme is galactosamine-6-sulphatase in type A and beta galactosidase in type B, resulting in excessive excretion of keratan sulphate (Muenzer, 2011). Children with Morquio syndrome have some corneal clouding that is generally less severe than in MPS I (Ashworth et al, 2010). There are usually no features of facial dysmorphism or intellectual disability (Pavan-Langston, 2008).

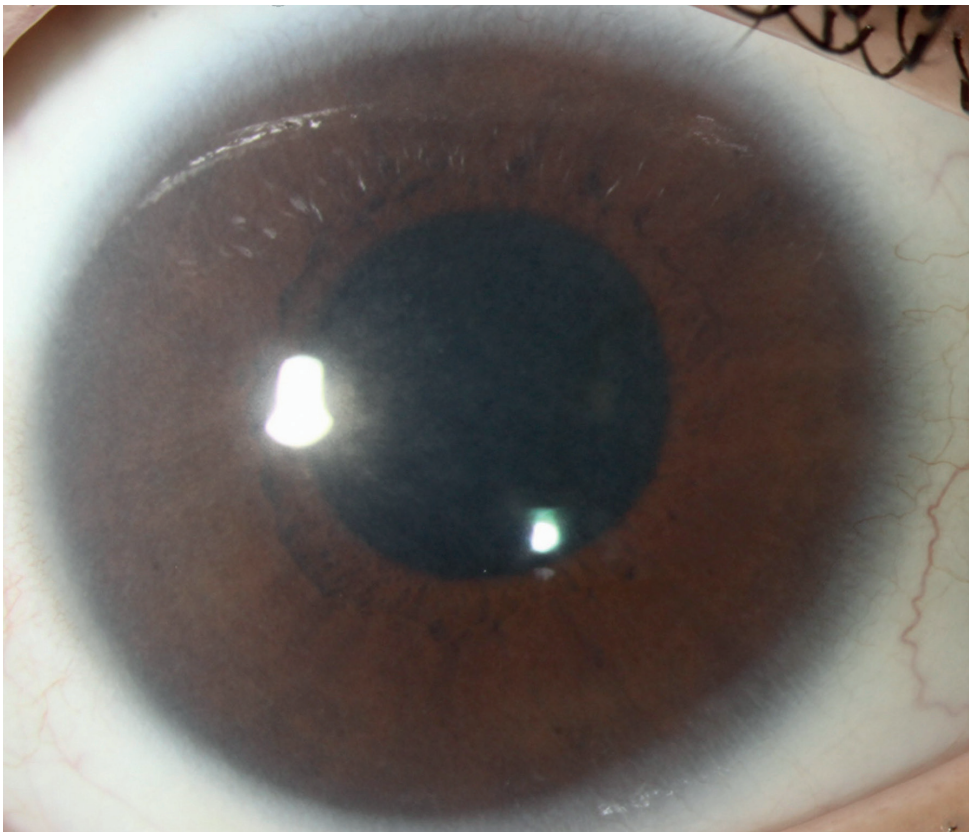

Figure 2. Corneal clouding in Hurler syndrome.

MPS VI: Maroteaux–Lamy syndrome

There are severe, intermediate and mild forms of this syndrome which has facial and skeletal dysmorphism (Pavan-Langston, 2008). There is a deficiency of N-acetyl-galactosamine-4-sulfatase and excessive dermatan sulphate in the urine (Muenzer, 2011). Corneal clouding is a significant feature of the syndrome, along with glaucoma and optic nerve abnormalities (Ashworth et al, 2010).

MPS VII: Sly syndrome

This is a rare disorder with all features of facial and skeletal dysmorphism, intellectual disability and corneal clouding (Pavan-Langston, 2008). The enzyme beta-glucuronidase is deficient, with dermatan, heparin and chondroitin sulphate all excreted in the urine (Muenzer, 2011). There may also be optic nerve abnormalities (Ashworth et al, 2010).

Macular corneal dystrophy

Corneal macular dystrophy is an ocular-specific mucopolysaccharidosis caused by an autosomal recessive condition leading to the abnormal deposition of keratan sulphate in the corneal stroma (Figure 3). It is the result of a mutation in the carbohydrate sulfotransferase (CHST6) gene. The deposits appear as ill-defined grey-white opacities with a background of diffuse clouding extending into the corneal periphery. There may be a gradual, painless reduction in vision and patients are susceptible to recurrent painful corneal erosions with photophobia (Denniston and Murray, 2018). Corneal transplantation remains the mainstay of treatment (Aggarwal et al, 2018).

Infectious crystalline keratopathy

Infectious crystalline keratopathy is a rare form of corneal infection that occurs in the context of local or systemic immunosuppression. Corneal epithelial injury from surgery, trauma or inflammation allows the entry of micro-organisms into the cornea where they form biofilms, with their sugars and proteins firmly adhering to local tissues. Immunosuppression (most commonly from topical corticosteroids but also reported with systemic administration) results in a dampened host immune response and minimal inflammation within the cornea or the

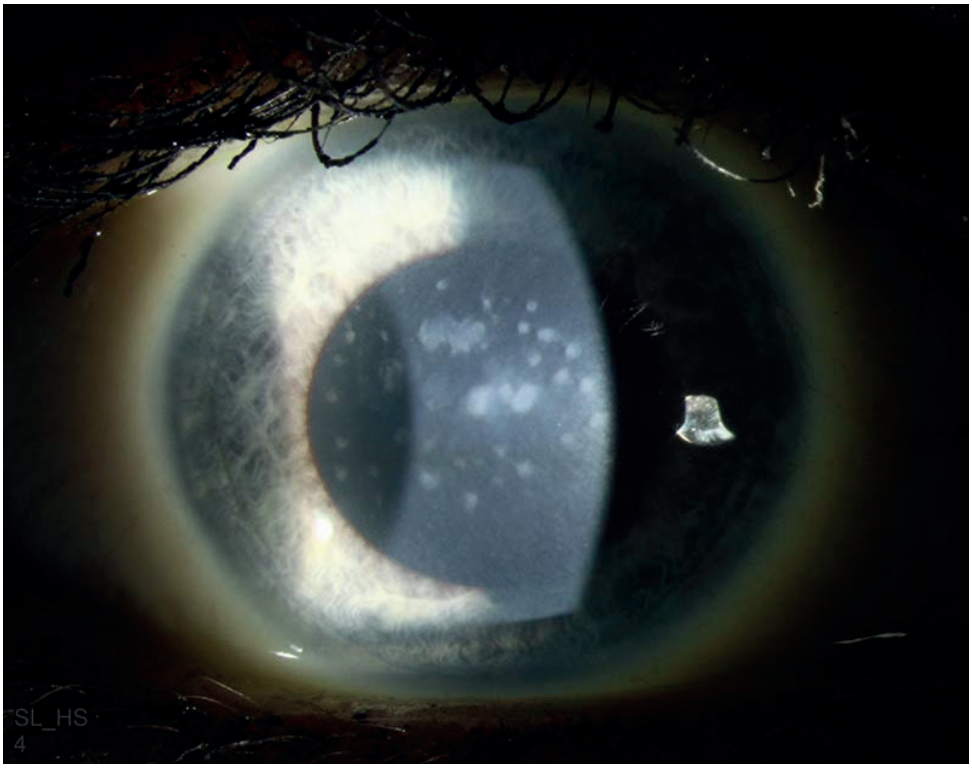

Figure 3. Corneal deposits in macular dystrophy.

eye itself (Porter et al, 2018). A slowly progressive infection ensues as the biofilm extends in between the stromal layers, producing branching opacities on examination (Figure 4). Offending organisms are listed in Table 3. These include Gram-positive cocci (eg *Streptococcus viridans* and *Staphylococcus epidermidis*), Gram-negative organisms (eg *Haemophilus influenzae*, Pseudomonas), fungi (candida) and acanthamoeba (Porter et al, 2018).

It has previously been suggested that infectious crystalline keratopathy is a misnomer as pathogens are commonly opportunistic and originating from the host, and there is no true crystal deposition – only a crystalline appearance (Watson et al, 1988). Treatment

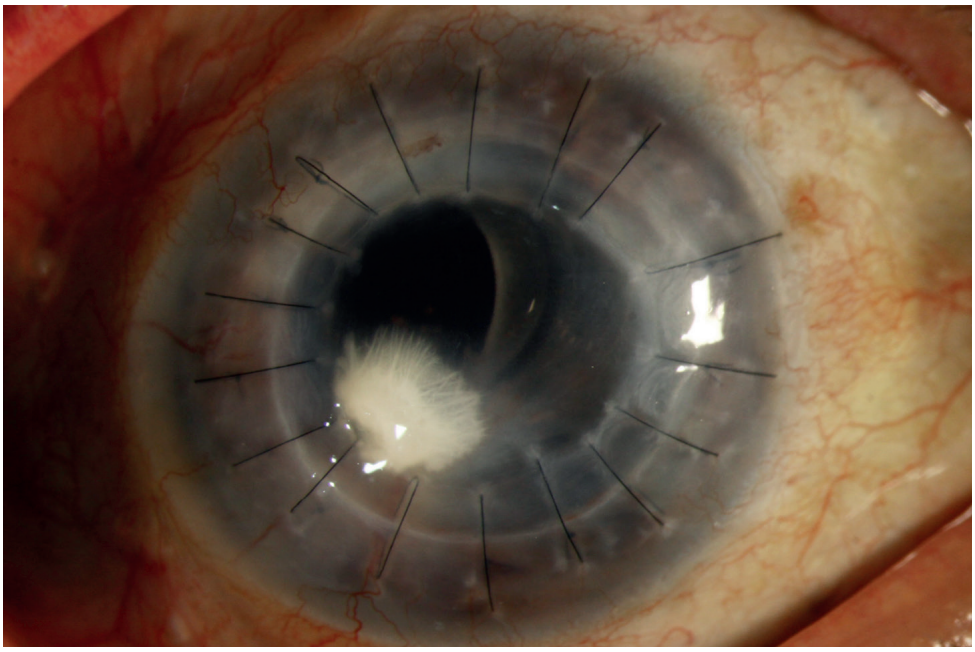

Figure 4. Infectious crystalline keratopathy.

Table 3. Causes of crystalline keratopathy

Infectious	*Staphylococcus epidermidis*
	Streptococcus pneumoniae
	Streptococcus viridans
	Streptococcus pyogenes
	Enterococcus faecalis
	Actinomyces
	Haemophilus influenzae
	Candida albicans
	Furarium solani
	Acanthamoeba
Non-infectious	Multiple myeloma
	Monoclonal gammopathy of undetermined significance
	Lymphoma
	Lymphoplasmacytic lymphoma
	Gout
	Cystinosis
	Primary lipid keratopathy
	Gold intake

involves intensive broad-spectrum antibiotics guided by cultures and sensitivities where available. Patients often require fortified preparations for extended periods, with further treatment options for resistant cases including laser treatment, antibiotics injected into the cornea itself or a corneal transplant to remove any infected tissue (Porter et al, 2018). Postoperatively, these patients often need close follow up and continuing topical antibiotics to prevent recurrence in their graft.

Non-infectious crystalline keratopathy

Crystalline keratopathy can also have a range of other causes (Table 3). Corneal deposits can occur in paraproteinaemias such as multiple myeloma, monoclonal gammopathy of undetermined significance, lymphoma and lymphoplasmacytic lymphoma. This is relatively uncommon but depositions have a highly variable location and pattern of distribution (Lisch et al, 2012).

Similarly rare is the deposition of urate crystals in the cornea in patients with gout. When this does occur, crystals tend to be white and located in the superficial corneal stroma or epithelium (Lin et al, 2013). Treatment of both paraproteinaemic and gout-related crystalline keratopathy is that of the underlying disease (Moshirfar et al, 2021).

Every reported case of cystinosis since the disease was first described in 1941 has had corneal or conjunctival involvement, such that this is often considered pathognomonic (Tsilou et al, 2007). Patients lack the *CTNS* gene on chromosome 17 which codes for a cell membrane protein responsible for transporting cysteine out of intracellular lysosomes. Lacking this, cysteine accumulates within cells including the cornea. While systemic treatment with cysteamine can reduce internal organ damage, topical cysteamine is also needed to help reduce visual impairment caused by excessive build-up of the crystals (Figure 5). Needle-shaped opacities can be found in each layer of the cornea progressively accumulating from the periphery inwards and in an anterior to posterior direction (Tsilou et al, 2007).

Long-term gold therapy for the treatment of rheumatoid arthritis leads to the deposition of fine particles in the corneal stroma. These tend to be purple or reddish in colour and concentrate inferiorly, with relative sparing of the periphery (McCormick et al, 1985). They are not usually visually significant and may reverse with cessation of treatment (Raizman et al, 2017).

Corneal deposition of lipid with a crystalline appearance can occur as a result of systemic lipoprotein disorders or spontaneously (primary lipid keratopathy), although this is rare (Alfonso et al, 1988). Non-crystalline deposition of lipid from other causes is much more common.

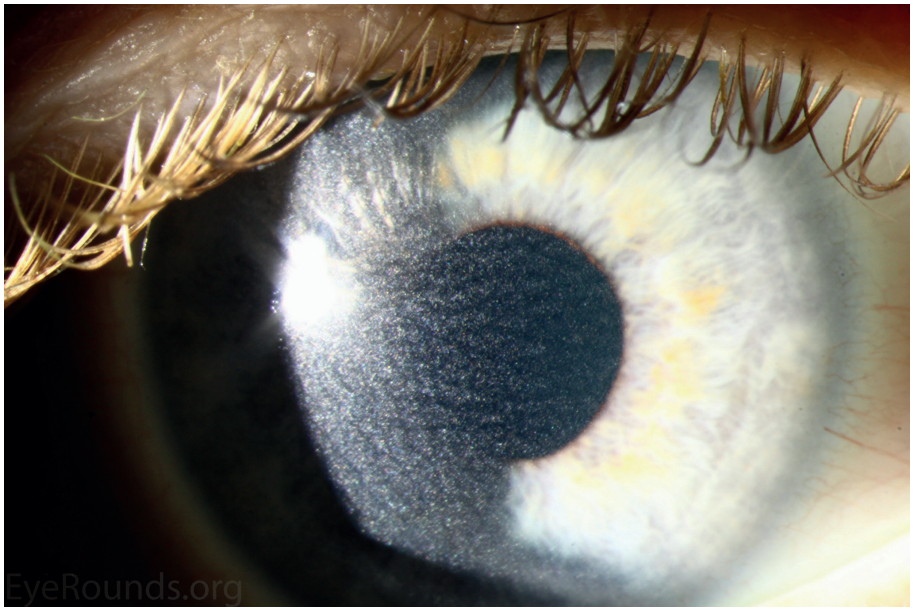

Figure 5. Cystinosis.

Lipid deposition

Corneal arcus describes lipid deposition in the peripheral cornea, starting temporally and nasally before eventually forming a complete ring, with a clear band of unaffected cornea between it and the limbus (Figure 6). Considered a normal part of ageing, it rarely warrants any further investigation, follow up or treatment when encountered in older patients. However, arcus seen in the young (arcus juvenilis) could be a sign of an underlying lipid disorder and further investigation is advised to exclude hyperlipidaemia (commonly type 2) (Denniston and Murray, 2018).

Corneal lipid deposition also occurs as a result of neovascularisation, a common endpoint of a number of corneal diseases such as infection, inflammation or trauma. This is termed secondary lipid keratopathy and is commonly precipitated by previous herpetic keratitis from simplex or zoster infection (Figure 7) (Marsh, 1988). Treatment involves treating the underlying cause and minimising inflammation with topical steroids. Corneal procedures may be of benefit if the deposits are still increasing in size despite medical treatment or visually significant and failing to resolve. Localised treatments target the new vessels 'feeding' the deposits; these treatments include argon laser and fine needle diathermy, now often combined with subconjunctival injection of anti-vascular endothelial growth factor (anti-VEGF) agents such as bevacizumab to minimise regrowth of new vessels (Marsh, 1988; Denniston and Murray, 2018).

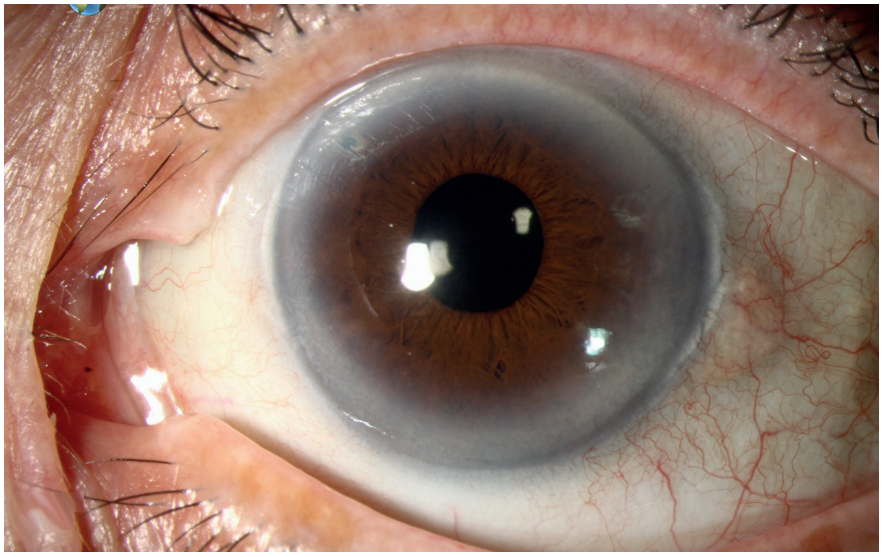

Figure 6. Lipid deposition arcus senilis.

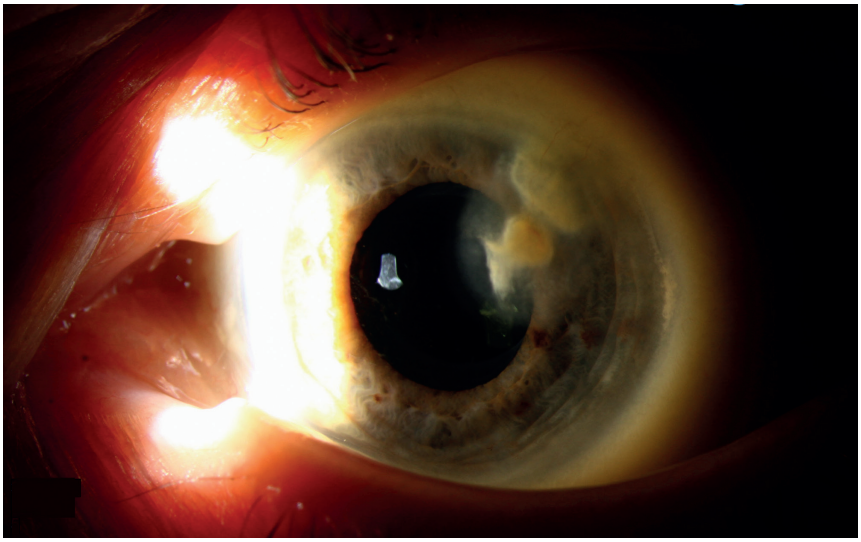

Figure 7. Secondary lipid keratopathy.

Wilson disease

Wilson disease is an autosomal recessive genetic disorder affecting copper metabolism. The affected ATP7B gene on chromosome 13 normally encodes a transmembrane protein involved in copper excretion in the bile. Its dysfunction causes impaired copper excretion and accumulation of copper in bodily tissues. The liver and brain are particularly affected, leading to hepatic failure and a wide range of neurological and systemic symptoms (Table 4). Deposition in the Descemet membrane of the peripheral cornea (Figure 8) results in a characteristic Kayser–Fleischer ring which is present in nearly all patients with neurological disease, half of those with hepatic disease and less than half of those with presymptomatic Wilson disease (Steindl et al, 1997). Rings are potentially reversible following adequate medical treatment of the underlying condition, but can recur if disease control worsens

Table 4. Features of Wilson disease

Hepatic	■ Hepatic failure ■ Cirrhosis ■ Hepatocellular carcinoma
Neurological or psychiatric	■ Akinesia ■ Rigidity ■ Tremor ■ Ataxia ■ Dystonia ■ Micrographia ■ Poor coordination ■ Drooling ■ Dysarthria ■ Dystonia ■ Spasticity ■ Migraine ■ Headaches ■ Insomnia ■ Seizures ■ Altered behaviour ■ Depression ■ Anxiety ■ Psychosis ■ Cognitive impairments
Ophthalmic	■ Kayser–Fleischer rings ■ Sunflower cataract ■ Night blindness ■ Strabismus ■ Optic neuritis ■ Optic atrophy
Other	■ Haemolysis ■ Osteomalacia ■ Osteoporosis ■ Pathological fractures ■ Cardiomyopathy ■ Arrhythmias ■ Hypothyroidism ■ Infertility ■ Kidney stones

(Ala et al, 2007). Corneal deposits similar to Kayser–Fleischer rings can be seen in other chronic liver diseases such as longstanding cholestasis (Ala et al, 2007).

Calcium band keratopathy

Calcific band keratopathy is corneal degeneration resulting the deposition of calcium phosphate salts in the superficial layers of the cornea, typically in the interpalpebral zone. The features include a grey-white plaque with fine, dusty deposits distributed in a horizontal band on the cornea, typically sparing the periphery (Jhanji et al, 2011). There are often lucent holes in the plaque which represent the corneal nerves traversing through it (Figure 9). The causes are listed in Table 5. Symptoms include irritation, photophobia, recurrent corneal erosions and, if the band keratopathy extends into the visual axis, glare and reduced

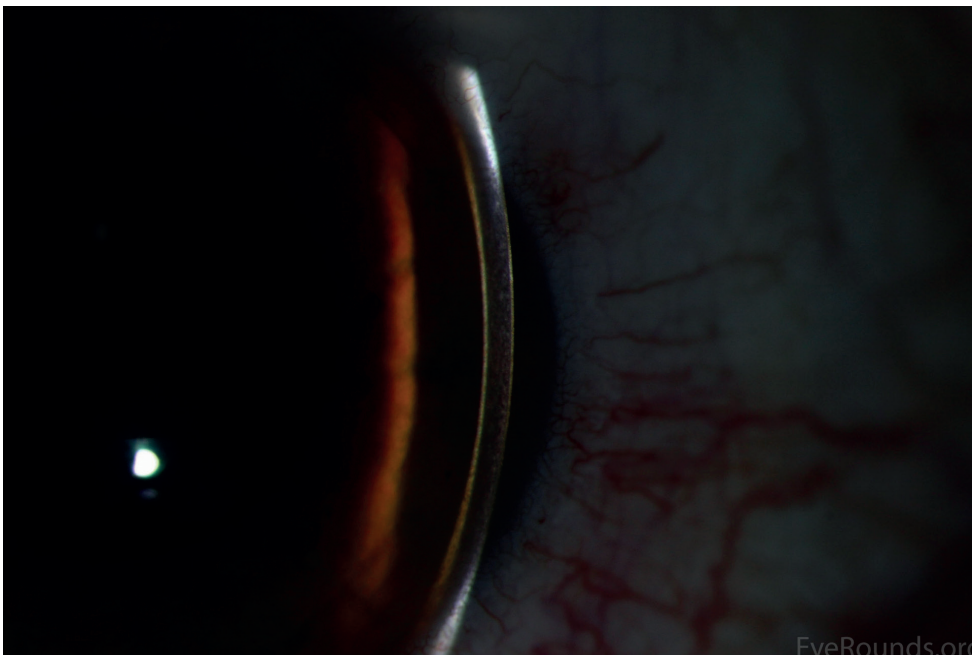

Figure 8. Wilson disease.

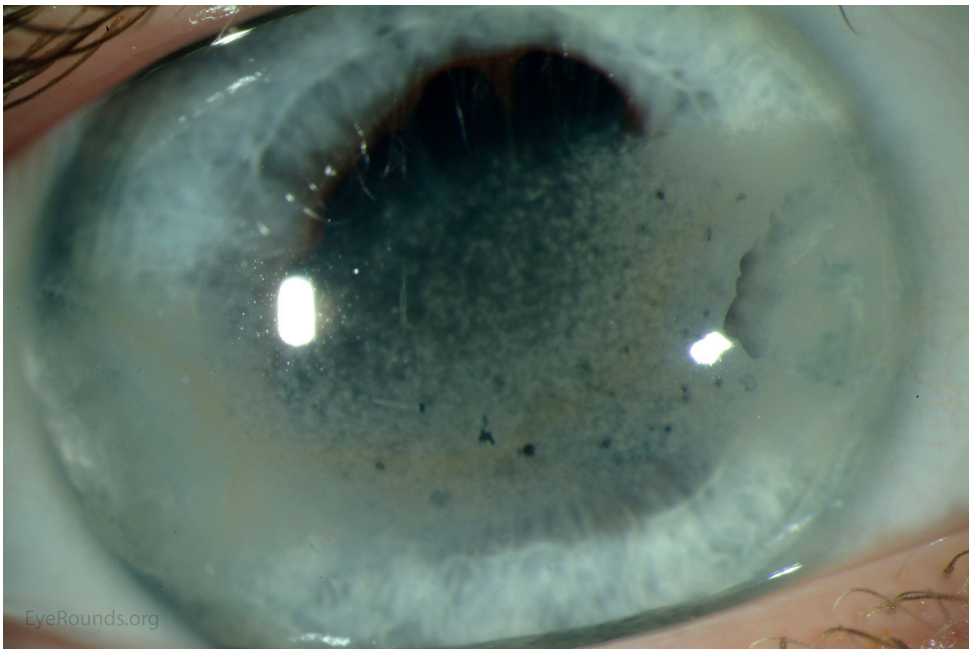

Figure 9. Band keratopathy.

Table 5. Causes of calcific band keratopathy	
Ocular	Chronic anterior uveitis
	Chronic keratitis
	Chemical exposure (eg mercury fumes), phosphate-containing eye drops (eg steroid preparations)
	Chronic corneal oedema
	Silicone oil in the anterior chamber (used as a treatment for retinal detachment)
	Phthisis bulbi
Systemic	Familial
	Senile
	Ichthyosis
	Hypercalcaemia
	Hyperphosphataemia
	Hyperuricaemia
	Chronic renal failure

vision. Often visually insignificant, reduced vision or pain may prompt treatment by mechanical removal, laser or, more commonly, chelation with ethylenediaminetetraacetic acid (EDTA) (Jhanji et al, 2011).

Conclusions

Deposition of substances in the cornea can have a number of ophthalmic and systemic causes. A thorough history and examination with special attention paid to the pattern, colour and anatomical location of deposits is key to ascertaining the cause, be it ophthalmic or systemic. Referral to an eye specialist may be required for a more detailed examination by slit lamp biomicroscopy. When seen initially in eye services, patients may require referral to general or specialist medical clinics to investigate or manage potential systemic causes. Treatment of the underlying cause is usually the mainstay of treatment with systemic disease, with patients rarely requiring topical ophthalmic therapy or surgery. These are often required for ophthalmic causes with corneal transplant the commonest treatment where indicated.

Key points

- Deposition keratopathies result from a wide range of systemic, ophthalmic and iatrogenic causes, with early recognition potentially preventing life-threatening illness.
- Corneal verticillata can be caused by Fabry disease but is more commonly iatrogenic, most commonly associated with amiodarone use.
- The mucopolysaccharidoses are a family of disorders caused by enzyme deficiencies resulting in a wide range of ophthalmic, facial and musculoskeletal signs and symptoms along with varying degrees of intellectual impairment, depending on the type.
- Ophthalmic causes for corneal deposits include bacterial biofilms, calcium or lipid deposits from chronic inflammation, and localised metabolic disorders
- Wilson disease is a disorder of copper metabolism leading to copper deposition in the cornea as well as the brain and liver, potentially resulting in significant morbidity and mortality if not treated in a timely fashion.

Curriculum checklist

This article addresses the following requirements from the Royal College of Ophthalmologists curriculum:

- PM13 - Systemic implications
- BCS8 – Therapeutics
- BCS16 – Genetics

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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