The eye in metabolic disease

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INTRODUCTION

Eye involvement is a feature of many metabolic diseases; early identification of ocular changes may aid diagnosis and management of the underlying condition. This review aims to describe common metabolic conditions where ocular findings can help the diagnosis.

MINERAL TRANSPORT DISORDERS

Wilson disease

This is an autosomal recessive disease with a prevalence of 1:30 000, caused by a deficient ATPase that transports copper into the Golgi apparatus (Bull et al, 1993) before it would normally be released to the plasma. This leads to copper overload in the tissues, mainly the liver, CNS, renal system and the cornea.

It usually presents in young adults as chronic hepatitis, but might present later with neurological problems including dystonia, dysarthria, dysphagia and tremor. Ocular findings are diagnostically important. Kayser–Fleischer ring is usually only visible by slit lamp examination (*Figure 1*) as a brown-green deposit in the periphery of Descemet's membrane. It is universal in neurological disease but is not pathognomonic and can be seen in patients with other liver diseases. 'Sunflower' cataract, on the other hand, is rare but characteristic.

Treatment involves chelation of excess copper with D-penicillamine, but Trientene and zinc may be effective; liver transplant may be necessary (Yarze et al, 1992). Ocular manifestations usually resolve with successful treatment.

Figure 1. Kayser–Fleischer ring in the cornea: brownish deposits in Descemet's membrane level.

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MITOCHONDRIAL CYTOPATHIES

This is a group of uncommon disorders characterized by mitochondrial dysfunction, where ocular findings are part of the clinical presentation.

Kearns Sayre syndrome

In Kearns Sayre syndrome, the patient presents in the late teens with chronic progressive external ophthalmoplegia (CPEO), pigmentary retinopathy and one of the following: heart block, cerebellar syndrome or high CSF protein. CPEO presents as ptosis, and muscle weakness and diplopia. The retinal dystrophy is mixed rod-cone with moderate visual loss unless optic atrophy is involved. Other features may include hearing loss, endocrine disorders and cardiomyopathy.

Treatment with coenzyme Q10 and succinate results in clinical improvement of respiratory distress (Shoffner et al, 1989). Whether this treatment has any effect on ocular manifestations remains to be seen.

MELAS syndrome

In MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes), the retinal dystrophy is more severe and macular involvement occurs earlier. CPEO, visual field defects, cortical blindness and hemiplegia are also common.

Neurodegeneration, ataxia and retinitis pigmentosa

NARP (neurodegeneration, ataxia and retinitis pigmentosa) is the result of a point mutation in the mitochondrial gene for subunit 6 of ATPase, usually a T→G 8993 transversion. This mutation is also a common cause of Leigh disease.

Leber's hereditary optic neuropathy

Leber's hereditary optic neuropathy is suspected in a young male presenting with gradual, painless loss of vision. Visual loss is profound and usually affects both eyes but not at the same time. Fundoscopy reveals telangiectatic peripapillary capillaries and pale discs. This condition is caused by a group of point mutations in the mitochondrial DNA and males are affected more than females. Some of these mutations have severe manifestations, but visual recovery can occur with the milder ones.

DISORDERS OF LIPID STORAGE

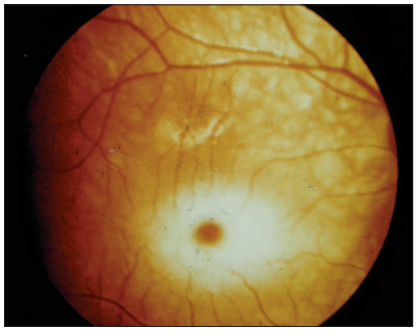
Sphingolipidosis

The cherry red spot (*Figure 2*) is common, although not diagnostically specific, in this group of diseases. The choroid red colour shows through the thin macular area against the white infiltrated retinal ganglion cells. Cherry red spot usually fades away as the retinal ganglion cells die and optic atrophy supervenes.

Niemann–Pick disease

In Niemann–Pick disease, sphingolipids are deposited in the reticuloendothelial cells, CNS and the

Figure 2. Tay–Sachs disease: the macula is pronounced against the pale background.



parenchyma of many organs. It is classified into two groups, both of which are autosomal recessive. In group 1, sphingomyelinase activity is reduced. This includes the neurodegenerative type A, and the hepatosplenomegalic type B. The ocular features are commonly a cherry red spot and optic atrophy.

Group 2, on the other hand, has normal sphingomyelinase activity but cholesterol intracellular transport is thought to be defective (Blom et al, 2003). It includes type C, which presents in neonates with liver disease of variable severity or in children with isolated splenomegaly. Early onset supranuclear palsy is characteristic to this group and includes vertical gaze palsy, loss of the voluntary vertical saccades and the fast phase of the optokinetic nystagmus. Type D is similar to type C but only seen in the Nova Scotian population.

Gaucher disease

Ocular examination may help distinguish between the different types of Gaucher disease (glucocerebrosidase deficiency). This condition results from a variety of mutations, and three types are identified. Type 1 presents with hepatosplenomegaly, anaemia and thrombocytopenia. Dark pingueculae laden with Gaucher cells are seen in the eye.

Type 2, on the other hand, is more severe as a result of brain involvement. Features may include psychomotor deterioration, spasticity and dysphagia. The typical ocular finding is horizontal gaze palsy. Fundus appearance is often normal but cherry red spot, optic atrophy or retinal haemorrhages can be seen.

Type 3 is moderate in severity with splenomegaly, slow brain involvement, strabismus and gaze palsy.

NEURONAL CEROID LIPOFUSCINOSIS

This is the commonest neurodegenerative disorder of childhood. Patients who present with a widespread loss of photoreceptor function with abnormal electroretinogram (ERG) and symptoms of cerebral deterioration may have cerebroretinal degeneration, grouped under the overall heading of neuronal ceroid lipofuscinosis. This used to be named Batten's disease but now is divided into five entities:

1. Infantile (Haltia–Santavuori disease): psychomotor deterioration by the second year, ataxia and microcephaly. Vision is reduced early as a result of retinal degeneration with diminished ERG and visual evoked potentials (VEP)
2. Late-infantile: seizures, rapid mental deterioration in early childhood, early retinal degeneration with extinguished ERG but abnormally high VEP.
3. Classical late (Jansky–Bielschowsky disease)
4. Juvenile (Batten): mental deterioration beginning around the age of 6 years, delayed onset of seizures, visual deterioration and bull's-eye maculopathy (*Figure 3*), reduced ERG.
5. Adult-onset (Kuf's disease): seizures, slow dementia, and no ocular manifestations.

No proven treatment yet exists for these diseases.

LIPOPROTEIN DISORDERS

Abetalipoproteinaemia is a fat malabsorption condition with acanthocytosis of red cells, retinal dystrophy, spinocerebellar ataxia, and low serum levels of cholesterol and beta-lipoprotein. Fat malabsorption leads to vitamin A and E deficiency, causing retinal dysfunction, and vitamin K deficiency, causing excessive bleeding.

It should be suspected in an infant presenting with steatorrhoea, ataxia, and other neurological signs. Night blindness and mixed rod-cone retinal degeneration present at any age but usually in late childhood (*Figure 4*). CPEO may be seen (Cogan et al, 1981) with bilateral ptosis, or signs of aberrant third nerve regeneration.

Treatment depends on fat restriction to minimize diarrhoea, with administration of high doses of vitamin A, E, and K. Combined treatment with vitamin A and E in the early stages can reduce the retinal degeneration, but the fundoscopic and functional changes still occur (Chowers et al, 2001).

MUCOPOLYSACCHARIDOSES

This is a group of progressive diseases affecting many organs including the eyes. They are caused by hydrolytic enzyme deficiency and mucopolysaccharide deposition in the tissues. Variable degrees of facial coarseness, skeletal changes and mental retardation are seen. Corneal clouding (*Figure 5*) is an important feature seen in all but mucopolysaccharidoses (MPS) II and III; it is often better seen with illumination from the side rather than on the slit lamp. Retinal degeneration and optic atrophy are seen in almost all types of

Figure 3. Juvenile Batten disease with pale optic disc and bull's eye maculopathy.

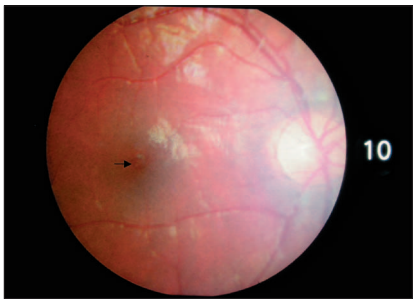


Figure 4. Abetalipoproteinaemia: notice the pale optic disc and the granular appearance of retinal pigment changes (arrow).

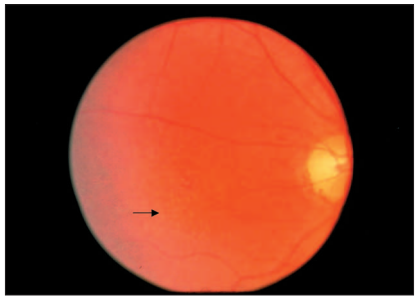
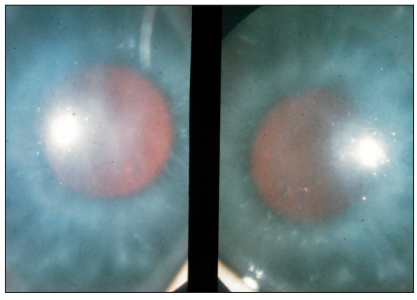


Figure 5. Corneal clouding in Hurler's disease.



MPS. Glaucoma is also common because of trabeculum obstruction by MPS-laden cells.

Management of MPS is mainly symptomatic, but it requires a multidisciplinary approach to care for all aspects of the disease. Severe corneal clouding may require penetrating keratoplasty if the retinal function is adequate.

GLYCOPROTEIN DISORDERS

Fabry's disease

This is an X-linked disorder presenting in childhood and affecting males. It is caused by deficiency of α-galactosidase-A, leading to accumulation of ceramide trihexoside in many tissues, but predominantly in vascular wall cells.

Ocular manifestations are common and include conjunctival and retinal vessel telangiectasia and tortuosity, cataract and, importantly, cornea verticillata. This is a typical appearance of whorl or vortex-like deposits in the cornea. It does not affect vision, but this can become affected by vascular accidents in the retina or the CNS. Medications including indomethacin, chloroquine, amiodarone and phenothiazines can cause corneal changes similar to cornea verticillata (*Figure 6*).

Mannosidosis

Mannosidosis is a lysosomal storage disorder caused by α-mannosidase deficiency, transmitted in an autosomal recessive fashion. Ocular examination may help differentiate it from MPS I (Hurler's) as corneal cloudiness is not prominent. Patients with type I disease have posterior cortical spoke-like lens opacities. They have severe systemic manifestation and die early. Type II is less severe systemically and has punctate cortical lens opacities.

PEROXISOMAL DISEASE

Complementation studies have shown that neonatal adrenoleukodystrophy, Zellweger syndrome and infantile Refsum's disease belong to the same spectrum of disease. Common to a variety of peroxisomal disorders is the finding of retinal dystrophy. Zellweger syndrome has a typical facial appearance and is very rare (1 in 100 000).

Refsum's disease

This is caused by phytanic acid alpha hydroxylase deficiency. All patients have elevated serum phytanic acid levels, which accumulates in a variety of tissues. It should be suspected in young adults presenting with night blindness, anosmia, peripheral neuropathy and ataxia. Retinal degeneration can be mild where the fundus appears granular with a subnormal ERG, but a more typical retinitis pigmentosa picture with non-detectable ERG is seen in more advanced stages (Berson, 1982) (*Figure 7*). Pupillary miosis is also seen.

DISORDERS OF TRANSPORT

Cystinosis is caused by defective cystine transport in the lysosomes. The infantile form has growth retardation, fair skin and hair and typical corneal deposits that appear as early as 2 months. The adult form has the corneal deposits (*Figure 8*) but no systemic involvement. Other ocular tissues might be involved including the conjunctiva, uvea, trabecular meshwork and retina. Photophobia and recurrent corneal erosions are prominent but the retinopathy eventually affects vision. Treatment depends on systemic and topical cysteamine (Jones et al, 1991) to dissolve the deposited cystine. Corneal grafts may be required (Kayser-Kupfer et al, 1986).

DEFECTS OF AMINO ACID METABOLISM

Homocystinuria

Homocystinuria is one of several hereditary diseases that resemble Marfan's syndrome, but with different signs and metabolic abnormalities. Patients are normal at birth, and an affected infant may fail to thrive but diagnosis is often delayed until late childhood when the lens subluxes. Unlike Marfan's syndrome the lens is microspherophakic and subluxes in a downward direction (*Figure 9*). Forty per cent of patients show biochemical improvement with high doses of pyridoxine and the rest may respond to betaine supplements. Early management may prevent or delay lens dislocation and mental retardation.

Figure 6. Cornea verticillata, the corneal deposits are subepithelial (inset).

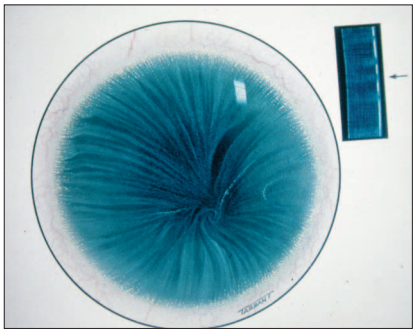


Figure 7. Pale fundus with the choroidal circulation showing in Refsum's disease.

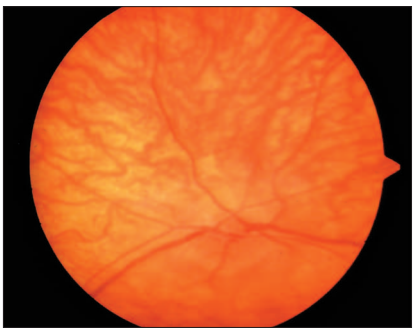


Figure 8. Cystine crystals are deposited in all layers of the corneal tissue and cause photophobia.

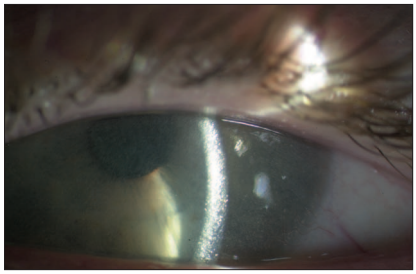
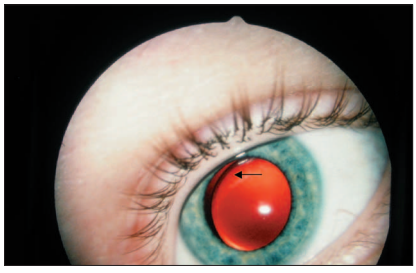


Figure 9. Homocystinuria: notice the small lens (microspherophakia) dislocated downwards.



Albinism

In albinism melanocytes are unable to synthesize melanin. Two main clinical variants exist, both of which have several subgroups and can be inherited in a variety of ways. In ocular albinism the inability to synthesize melanin is limited to the eye. In oculocutaneous albinism, however, the hair, skin and eyes all lack pigmentation to a variable degree (*Figure 10*).

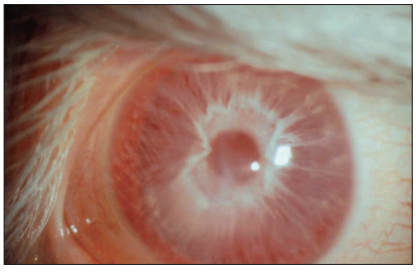
Nystagmus and reduced vision are almost always present but other features, in addition to pigment deficiency, may include photophobia, iris translucency, myopia, astigmatism, squint and macular hypoplasia. The VEP shows typical contralateral predominance as a result of the chiasmal misrouting. Infants with albinism of all types are typically slow to see. Vision starts to improve as the child grows but typically remains subnormal. Most of these children, however, attain sufficient vision to progress well with their lives.

Management is symptomatic for photophobia, refractive errors and squint, in addition to genetic counselling, low visual aids, and special educational and psychological services (Taylor, 1997).

Neonatal tyrosinaemia

The most important manifestations of this condition (also known as Richner–Hanhart disease) are those affecting the eye. They include pseudodendritic ulcers that may occur as early as 2 weeks of age. These lesions may result in corneal scarring. Other ocular features include glaucoma. The cutaneous lesions are painful keratoses that occur on the peripheral pressure-bearing areas of the palms and soles. Fifty per cent of children have neurological features (Driscoll et al, 1988).

Figure 10. Oculocutaneous albinism, notice the white eyelashes and the diaphanous iris.



DEFECTS OF CARBOHYDRATE METABOLISM

Galactosaemia

Galactosaemic cataract is important to recognize in the neonatal period because its severe associations can be prevented by early restriction of galactose intake. Unfortunately, even with good dietary compliance, many patients have neuropsychological problems. This is an autosomal recessive deficiency of the galactose-1-phosphate uridyl transferase causing hepatocellular damage and mental retardation.

The classic oil droplet cataract appears early (*Figure 11*); it is not a real cataract but a refractive change caused by dulcitol accumulation in the lens. Early diagnosis and galactose-free diet can reverse lens changes and improve prognosis.

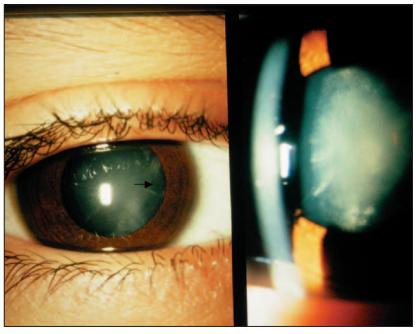
Galactokinase deficiency

Galactokinase deficiency is autosomal recessive and has been associated with nuclear, zonular and posterior cortical cataracts. Bilateral cataracts occur in the first year of life. Unlike galactosaemia, however, systemic disease is usually absent. Heterozygotes are at increased risk for pre-senile cataracts (Stambolian et al, 1986).

DISORDERS OF STEROL METABOLISM

Early onset cataract is a main feature of this group of diseases that includes mevalonic aciduria, Conradi Hunermann syndrome, cerebrotendinous xanthomatosis, steroid sulphatase deficiency and Smith Lemli Opitz syndrome.

Figure 11. Oil droplet cataract in galactosaemia (a) under diffuse light and (b) slit beam.



Smith Lemli Opitz syndrome is caused by deficient 7-dehydrocholesterol reductase in the cholesterol synthesis chain. Internal organ and brain malformations are common. Ocular manifestations include congenital cataracts, strabismus, glaucoma, optic atrophy and microphthalmia. Treatment with cholesterol appears to improve weight gain and growth in these patients and may improve development and behaviour but the prognosis depends on the severity of internal malformations. HM

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