THE EYE AND LIVER DISORDERS

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SUMMARY

There are ocular changes associated with a wide spectrum of congenital, familial and acquired liver diseases and disorders. The early identification of ocular changes may aid diagnosis of the underlying liver condition. This is particularly important in conditions where there are effective treatments which can arrest hepatic damage. It is also of considerable value in patients who have untreatable disorders because identification of the correct diagnosis may offer prognostic information and spare the patient unnecessary invasive investigation. This article discusses the ocular findings in selected liver diseases and reviews the current literature on the subject. The principles of investigation and diagnosis and treatment are described. Data on the incidence and prevalence of ocular involvement in liver conditions are included where such figures are available. The potential transmission of viral hepatitis following corneal grafting is discussed.

EYELIDS IN LIVER DISEASE

Cutaneous eyelid xanthelasma are a feature of longstanding cholestasis, particularly in cases of primary biliary cirrhosis. Xanthelasma were reported in 17% of cases of primary biliary cirrhosis in one recent series.[1]

THE CONJUNCTIVA IN LIVER DISEASE

Hyperbilirubinaemia causes a yellow discolouration of skin and mucosa (jaundice). Jaundice is not usually clinically apparent until bilirubin concentrations exceed 50 umol/l. The conjunctiva is one of the most sensitive areas to detect jaundice, particularly in patients with heavy skin pigmentation.

The combination of jaundice and conjunctival haemorrhage in association with fever, aseptic meningitis, gastroenteritis and acute renal failure occurs in leptospirosis (Weil's disease).[2] Systemic tetracyclines are of proven benefit in the treatment of anicteric leptospirosis.[3] Penicillin is of questionable efficacy in treating the icteric forms of this spirochaetal infection.[4,5] Leptospirosis occurs in patients exposed to infected rodent urine such as sewage workers.

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Keratoconjunctivitis sicca is particularly common in primary biliary cirrhosis, affecting approximately 50% of patients.[6,7] Keratoconjunctivitis sicca is also common in chronic active hepatitis, affecting 35% of patients.[6] Pingueculae are seen in many cases of adult Gaucher's disease.[8]

CORNEAL SIGNS IN LIVER DISEASE

Asymptomatic corneal changes have been described in Wilson's disease, primary biliary cirrhosis, chronic active hepatitis and Alagille's syndrome. Corneal clouding combined with hepatomegaly is a feature of several types of mucolipidoses and mucopolysaccharidoses.

(i) *The cornea in Wilson's disease*

This is an autosomal recessive condition characterised by abnormalities in copper metabolism. Copper accumulation causes chronic liver and central nervous system disease. Chronic deposition of copper in the liver typically presents with cirrhosis, jaundice, splenomegaly, bleeding oesophegeal varices or ascites in a child under the age of ten. Chronic central nervous system deposition tends to affect the basal ganglia resulting in spasticity, rigidity, tremor and dysarthria.

The almost pathognomic ocular sign is the Kayser Fleischer ring; this is a yellow, green, brown or red deposit of copper in the region of Descemet's membrane in the peripheral cornea. It is interesting to note that Kayser-Fleischer rings regress after successful reduction of total body copper with penicillamine.[9] Copper is deposited in the lens in Wilson's disease and this may lead to cataract formation.

The Kayser Fleischer ring is virtually always found in patients who have neurologic manifiestations of Wilson's disease, and is also often found in other patients who have Wilson's disease but no neurologic manifestations.[9] The serum caeruloplasmin level is usually markedly reduced. Treatment includes reduction of total body copper (using penicillamine) as well as treating liver failure.

(ii) *Descemet's membrane infiltrates in non-Wilsonian chronic liver disease*

The presence of a pigmented peripheral corneal ring in the

absence of neurologic disease is not necessarily pathognomic of Wilson's disease. This has been demonstrated by one paper which described peripheral corneal rings in 3.7% of cases of primary biliary cirrhosis and in one case of non-Wilsonian chronic active hepatitis.[10] Other case reports have described pigmented corneal rings in chronic active hepatitis,[11] and in severe jaundice.[12]

(iii) Other abnormalities of Descemet's membrane in liver disease

Alagille's syndrome (hepatic ductular dysplasia, cholestasis, peripheral pulmonary stenosis, posterior embryotoxon and characteristic skeletal changes) is a relatively recently described autosomal dominant condition. Several ocular abnormalities and variations have been described including hypertelorism, squint, refractive errors, band keratopathy, keratoconus, Axenfeld's anomaly, chorioretinal changes, and anomalous optic discs.[13,14,15]

Posterior embryotoxon is particularly common, occurring in 89% of cases.[13] This is a congenitally prominent ending of Descemet's membrane at the peripheral cornea (and is not a metabolic deposit). It has been suggested that the presence of posterior embryotoxon and prolonged neonatal jaundice may be specific for arteriohepatic dysplasia. Further work is required to prove this hypothesis. If it is correct it may spare the jaundiced neonate with Alagille's syndrome from a diagnostic laparotomy.[16]

(iv) *Hepatomegaly and central corneal clouding: the mucopolysaccharidoses and mucolipidoses*

Muscopolysaccharidoses and mucolipidoses are both inherited lysosomal enzyme deficiencies. The deficiency leads to the accumulation of the mucopolysaccharides (now called glycoseaminoglycans) or mucolipidoses which the deficient enzyme normally metabolises.

The accumulation of intracellular material causes hepatosplenomegaly, mental retardation, skeletal dysplasia, coarse skin and ocular changes, with varying prevalence depending on the subtype of mucopolysaccharidoses/lipidoses involved and the age at which the patient is examined. There are at least six classes of mucopolysaccharidoses and ten classes of mucolipidoses, each distinguished by clinical, genetic and biochemical manifestations.

Increased glycoseaminoglycans (G.A.G.) urinary excretion is found in mucopolysaccharidoses but not in mucolipidoses. Further diagnosis of the sub-type depends on the clinical phenotype and identification of the deficient enzyme in cultured skin fibroblasts, cultured amniotic cells, peripheral leukocytes or conjunctival biopsy. Allogeneic bone marrow transplant may cure the biochemical defect in selected cases of mucopolysaccharidoses.[17]

The prevalence of clinical corneal clouding at any one time depends on the type of storage disease, the age of the patient and the method of examination used. (Flashlight or ophthalmoscopic examination may miss opacities readily seen using a slit lamp).

Severe corneal clouding within the first few years of life is typical of Hurler's (MPS I-H) and Maroteaux-Lamy syndromes (MPS VI), whereas clouding may commence at any age from birth to the teenage years in Scheie's syndrome (MPS I-S).[18,19]

Corneal clouding is found much less frequently in the other mucopolysaccharidoses. Clouding is seen in about 10% of cases of Morquio's syndrome (MPS IV), occurring after the age of ten; in a small number of older patients with the milder phenotypes of Hunter's syndrome (MPS II), and rarely in Sanfillipo syndrome (MPS III).[20,21,22]

Corneal clouding is found in type IV mucolipidosis in all cases from infancy;[23] in type III mucolipidosis mild corneal clouding is found in all cases by age ten.[24,25] Mild corneal clouding is seen in 40% of cases of type II mucolipidosis, and in less than 20% of type I mucolipidosis and GM-1 gangliosidosis.[26,27,28]

Corneal opacities may be treated by corneal grafting (penetrating keratoplasty) if severe. The ultimate visual acuity may be limited by the presence of simultaneous retinopathy, optic nerve disease, cataract or glaucoma as well as recurrence of corneal clouding in the corneal graft.[22]

GLAUCOMA IN LIVER DISEASE

The mucopolysaccharidoses may be complicated by glaucoma. Acute and chronic angle closure glaucoma has been described in Maroteaux Lamy (VI) and Scheie's (I-S) syndromes.[29,30] Open angle glaucoma has been reported in Maroteaux Lamy (VI) and Hurler's (I-H) syndromes.[29,31,32] There is one intriguing case report of open angle glaucoma in Hurler's syndrome (I-H) in which the intraocular pressure returned to normal levels following bone marrow transplant.[32]

THE LENS IN LIVER DISEASE

Liver disease associated with paediatric lens opacities is a feature of galactosaemia, Zellwegger's hepatocerebrorenal syndrome, neonatal adrenoleukodystrophy, and neonatal haemolytic jaundice syndrome. Cerebrotendernous xanthomatosis may be complicated by cataracts, usually in an older child or young adult.

Prolonged use of systemic adrenocorticosteroids for immunosupression (e.g. following liver transplantation) may be complicated by cataract formation.

(i) *Galactosaemia*

Classic galactosaemia is an autosomal recessive defect of galactose metabolism due to a deficiency of the enzyme galactose-1-phosphate uridyl transferase. The resultant accumulation of galactose leads to cataracts, hepatocellular damage (with cirrhosis and ascites), renal tubular acidosis (with aminoaciduria) and mental retardation. Severe cases present in infancy with diarrhoea and vomiting after commencing milk feeding, and later develop jaundice and cataracts. The diagnosis is confirmed by finding galactosuria and the demonstration of deficient levels of the enzyme galactose-1-phosphate uridyl transferase in red blood cells.

Early diagnosis followed by a galactose-free diet and tight biochemical control prevents cataract formation and improves systemic prognosis. The ophthalmologist may

play an important role by diagnosing galactosaemia, treating galactosaemic cataracts and by detecting new lens opacities. The development of new lens opacities may be a sensitive index of inadequate biochemical control.[33]

(ii) *Zellwegger's cerebro-hepato-renal syndrome*

Zellwegger's cerebro-hepato-renal syndrome is a lethal autosomal recessive neonatal peroxisomal disorder related to neonatal adrenoleukodystrophy and neonatal Refsum disease.[34] Peroxisomes are absent in Zellwegger's syndrome and multiple metabolic disturbances and systemic malformations are found. These affect the central nervous system (severe psychomotor retardation, epilepsy, deafness), liver (hepatomegaly and neonatal cirrhosis), and kidneys (cortical renal cysts). There is characteristic skeletal dysplasia, and ocular involvement is frequent. Ocular changes include epicanthic folds, corneal clouding, cataract, glaucoma, nystagmus and retinopathy indistinguishable from retinitis pigmentosa. Recent work suggests that retinopathy is a relatively constant feature of Zellwegger's syndrome.[35]

Diagnosis is based on clinical features and confirmed by biochemical findings. These include plasmalogen deficiency, bile acid synthesis defects and elevated coprostanic and pipecolic acid levels.[36] Recent work suggests that rectal biopsy may be used to detect peroxisomal disorders at an early stage.[37] Zellwegger's syndrome is untreatable.

(iii) *Neonatal adrenoleukodystrophy*

Neonatal adrenoleukodystrophy is an autosomal recessive peroxisomal disorder related to Zellwegger's syndrome. Affected infants have abnormal facies, hypotonia, hepatomegaly and pigmentary retinopathy. Optic atrophy and cataract are occasionally seen. Diagnosis is confirmed by finding peroxisomal deficiency with raised very long chain fatty acids in skin and fibroblasts, brain and adrenal cortex in patients whose disability begins in the neonatal period.[38] Neonatal adrenoleukodystrophy is untreatable.

(iv) *Autosomal dominant neonatal jaundice syndrome*

Heterochromia, corectopia, myopia, microphthalmos, cataracts and dyschromatopsia are frequently seen in autosomal dominant congenital haemolytic jaundice.[39]

(v) *Cerebrotendernous xanthomatosis*

This rare autosomal recessive defect of bile acid synthesis is due to a lack of hepatic C24 cholesterol hydroxylation. It presents in the second decade with neurologic signs (paresis, dementia, cerebellar ataxia, peripheral neuropathy), tendon xanthomas, cataracts, premature atherosclerosis, endocrine deficiencies and pulmonary dysfunction. Diagnosis is based on clinical features and is confirmed by raised plasma cholestanol levels. Oral chenodeoxycholic acid replacement arrests progression and may reverse some manifestations of the disease.[40]

RETINAL INVOLVEMENT IN LIVER DISEASE

Several liver disorders are due to systemic conditions which affect the retina to a greater or lesser extent. Thus many of the mucopolysaccharidoses are associated with pigmentary retinopathy and two of the sphingolipidoses manifest macular "cherry red spot". Primary biliary cirrhosis may be associated with treatable night blindness due to malabsorption of vitamin A. Immunosuppression following liver transplantation may be associated with opportunistic retinal and choroidal infections.

(i) *Pigmentary retinopathy with liver disease*

Retinal pigmentary changes morphologically identical to those of other retinitis pigmentosa syndromes affect the majority of cases of Hurler's (I-H), Scheie's (I-S), Hunter's (II) and Sanfillipo's (III) syndromes; but is not a feature of Morquio's (IV) or Maroteaux Lamy syndromes.[22,41] The pigmentary retinopathy seen in Zellwegger's syndrome and Neonatal Adrenoleukodystrophy has already been mentioned above.

(ii) *Perimacular deposits and liver disease*

Grey perimacular deposits of complex lipids are seen in several of the sphingolipidoses. The fovea is unaffected but appears unusually red and prominent against the surrounding pale infiltrated perimacular. This appearance is frequently described as a 'cherry red spot'. A cherry red spot appearance with hepatomegaly is also a feature of von Gierke's glycogen storage disease.

The sphingolipidoses are a group of rare inherited lysosomal enzyme deficiencies. The deficiency leads to the accumulation of the sphingolipid which the deficient enzyme normally metabolises. There are at least ten variants of sphingolipidoses, but only two have combined hepatic and ocular manifestations: Niemann-Pick disease and generalised gangliosidoses.

Niemann-Pick disease is a heterogenous group of disorders where sphingomyelin is deposited in the reticuloendothelial cells, central nervous system and the parenchyma of many organs. The condition is diagnosed by family history, characteristic physical findings and the demonstration of Sudan black staining histiocytes with foamy cytoplasm. Sphingomyelinase deficiency may be demonstrable in some subtypes. There are several subpopulations with varying hepatosplenomegaly, jaundice, mental retardation, delayed motor maturation, deafness, tremor, epilepsy and athetosis.

Cherry red macular spots are frequently seen in this condition, and have been described in 20%-60%[42,43] of cases. The variation in incidence between studies may be explained by the existence of several subtypes of Niemann-Pick disease. Subtle corneal and lens opacities have also been reported in one recent study of Niemann-Pick disease subtype A. Optic atrophy occurs in the later stages of Niemann-Pick disease.

Generalised gangliosidoses is a sphingolipidoses variant where ganglioside is deposited in the central nervous system and mucopolysaccharide is deposited in the viscera. Diagnosis is based on characteristic physical findings and the demonstration of deficiency of Ã-galactosidase in per-

ipheral blood leukocytes or fibroblasts cultured from skin biopsy specimens. Babies with generalised gangliosidoses have an appearance similar to Hurler's syndrome with hepatosplenomegaly, mental retardation, skeletal dysplasia and ocular changes.

Generalised gangliosidoses may easily be confused with Hurler's syndrome because of the similarity of the skeletal dystrophy. The ocular findings in the two conditions are, however, quite distinct. Patients with generalised gangliosidoses have no corneal clouding (unlike Hurler's syndrome) and may have a cherry red macular spot (also unlike Hurler's syndrome).[44]

There are eight different types of glycogen storage disease. Only type 1, von Gierke's disease, is associated with ocular signs. This autosomal recessive deficiency of glucose-6-phosphatase has a characteristic presentation with massive hepatosplenomegaly, renal enlargement, myopathy, short stature, obesity and extensor xanthomas. Multiple bilateral paramacular retinal deposits have been described in 60% of cases in one short series.[45]

(iii) *Retinal vitamin A deficiency and liver disease*

Deficiency of fat soluble vitamins may follow chronic cholestasis because of malabsorption. Chronic deficiency of vitamin A and resultant disturbance of retinal rod photoreceptor function is common in advanced primary biliary cirrhosis. This can be prevented by adequate vitamin A replacement therapy. Established night blindness may be reversed if replacement therapy is given sufficiently early and at correct dosage.[46] There is a case report of severe visual field restriction in a case of primary biliary cirrhosis which reverted to near normal after liver transplantation, despite failure to respond to oral vitamin A prior to transplantation.[47]

NEURO-OPHTHALMIC INVOLVEMENT IN LIVER DISEASE

Liver disease may be associated with neuro-ophthalmic disorders. These manifestations may be sensory (affecting the optic nerve) or motor. These ocular motility disorders may be subdivided into cranial nerve palsies, gaze palsies, internuclear ophthalmoplegia and nystagmus.

(i) *Optic nerve involvement in liver disease*

Optic atrophy has been described in all forms of mucopolysaccharidoses except the mild phenotypes of Maroteaux Lamy.[22] Optic atrophy may be multifactorial in the mucopoysaccharidoses; it may be secondary to pigmentary retinopathy, or consecutive to chronic papilloedema due to hydrocephalus.

(ii) *Cranial nerve palsy in liver disease*

Wernicke's encephalopathy is a confusional state associated with ocular cranial nerve palsies, ataxia and nystagmus. It is seen in chronic thiamine deficiency, typically in cirrhotic alcoholics with a poor diet. It is an important diagnosis as early replacement of thiamine in adequate doses may save the patients life and reverse some of the manifestations.

One recent post mortem study discovered histologic changes identical to those seen in Wernicke's encephalopathy in many alcoholics who died with only some or none of the manifestations of Wernicke's encephalopathy.[48] This study emphasised that encephalopathy is often underdiagnosed, and therefore not treated.

(ii) *Gaze palsy in liver disease*

Dorsal midbrain syndrome (synonym Parinaud's syndrome) has been described in Niemann-Pick disease,[49] kernicterus and Wilson's disease.[50] Signs of the dorsal midbrain syndrome include vertical gaze palsy, light-near pupillary dissociation, convergence retraction nystagmus, upper eyelid retraction, skew deviation and unstable fixation.

Horizontal gaze palsy is seen occasionally in Wilson's disease.

(iii) *Internuclear ophthalmoplegia in liver disease*

Internuclear ophthalmoplegia is an occasional feature of Korsakoff's psychosis and hepatic coma.[50]

(iv) *Nystagmus and liver disease*

Nystagmus is a non-specific sign seen in hepatic and Wernicke's encephalopathies.

VIRAL HEPATITIS FOLLOWING CORNEAL TRANSPLANTATION

The possibility of acquiring Hepatitis B following corneal transplantation has long been recognised, although it is a rare event.[51] Properly performed sophisticated testing of serum from prospective donors has helped avoid this complication. It appears that the risk of acquiring cytomegalovirus from penetrating corneal grafts is negligible, and the risk can be ignored in patients who are not systemically immunocompromised.[52] There are little data on the transmission of hepatitis C or hepatitis non A/ non B/C virus at the time of corneal transplantation.

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