REVIEW ARTICLE

# Ophthalmological Pointers to Hepatic Disorders in Children

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**Abstract:**

The value of ophthalmological examination is often overlooked when we deal with disorders of hepatobiliary system. There is a wide spectrum of genetic, metabolic and other acquired disorders in infants and children that have ocular changes along with hepatic involvement. If the disease course is insidious then these findings may be noted in adolescence or early adulthood in several such conditions. Some ocular findings are very suggestive of the underlying etiology giving the clinician an opportunity for early diagnosis and intervention. Where the condition is untreatable, decision regarding palliative measures, prognostic counselling and genetic counselling for future pregnancies can be offered earliest to the caregivers. The article attempts to discuss the ophthalmological findings of several such disorders manifesting in infancy and childhood. Pediatricians, ophthalmologists and even physicians dealing with adult medicine should be aware of these findings.

**Keywords:** Child, Diagnosis, Eye diseases, Liver, Retinal, Corneal

## Introduction:

Eyes of an infant are the windows looking through which we can have diagnostic clues about a wide spectrum of congenital, familial and acquired hepatic disorders. In case of treatable conditions it provides the opportunity to stop the disease progression (ex: Wilson's disease) and even in case of untreatable conditions it provides prognostic information saving the patient from unnecessary invasive investigation [1]. The eye is the fourth most common system affected by genetic ocular diseases with mutations of more than 200 different loci identified so far [2]. The presentation of a patient may be with signs and symptoms of a metabolic disease, the ocular findings explored on subsequent ophthalmological examination or primarily an ocular symptom may give rise to suspicion of a specific underlying genetic/ metabolic disorder [3]. Hereditary oculo-systemic disorders as well as metabolic disorders usually have symmetrical bilateral involvement, first raising the doubt in an observant parent at around 2 months of age of the infant due to lack of fixation. Some ocular involvements are easily recognised as in cataracts in galactosemia but sometimes it may be difficult as in peroxisomal diseases where fundoscopic examination may be normal in the neonatal period but electroretinogram (ERG) and visual evoked responses are found to be abnormal giving clues about the disorder [3]. Here we are going to describe the paediatric disorders affecting both the organs - liver and eyes.

## A. Eye lid involvement:

Xanthelasma, deposition of fatty plaques over inner canthus of mostly upper eyelid, is a feature of hyperlipidemia and prolonged cholestasis. Primary biliary cirrhosis, although a rare entity in children and adolescents, is a chronic autoimmune cholestatic condition with guarded prognosis is associated with this finding.

## B. Orbital changes:

Frontal bossing with shallow nasal bridge is a feature of many of the lysosomal storage diseases

(mucopolysaccharidoses and mucolipidoses) while hypertelorism is sometimes seen in the patients with generalised gangliosidosis [4].

**C. Conjunctival Features:**

**a. Jaundice:**

Bilirubin deposition causes a visible yellow discolouration of elastin component of conjunctival tissue particularly with higher range of serum bilirubin levels (>2 mg/dL).

**b. Leptospirosis (Weil's disease):**

Leptospirosis, a zoonosis, acquired through exposure to infected urine of carrier mammals, presents with fever, headache, body ache, features of aseptic meningitis and in complicated cases may have jaundice, bleeding tendency and acute kidney injury [5]. Ocular features may consist of conjunctival chemosis and subconjunctival haemorrhages or uveitis in late stages [6].

**c. Keratoconjunctivitis sicca:**

Keratoconjunctivitis sicca, dryness of conjunctival and corneal surfaces, is associated with autoimmune diseases. Though rare in children, 25% of patients with primary biliary cirrhosis have keratoconjunctivitis sicca [7].

**d. Lysosomal Storage Diseases:**

Minor tears and conjunctival anomalies are common in these conditions [8]. Bulbar conjunctival aneurysms are frequently seen in the mucolipidoses and pingueculae are features of adult Gaucher's disease [9]. Conjunctival cytological studies are useful in the diagnosis of mucolipidosis type IV [10].

**e. Secondary Vitamin A deficiency in liver disease:**

In chronic liver disorders due to malabsorption of fat soluble vitamins there is secondary vitamin A deficiency which ultimately leads to retinal rod photo receptor dysfunction causing nightblindness, conjunctival and corneal xerosis, bitot's spot, xerophthalmia etc. Established nightblindness may be reversed if replacement therapy is given sufficiently early and at correct dosage [11]. 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 [12].

**D. Cornea: Few Words on Kayser-Fleischer Ring and Corneal Clouding:**

Asymptomatic peripheral corneal opacities are seen in chronic hepatobiliary disorders while progressive central corneal opacification is characteristics of several mucolipidoses and mucopolysaccharidoses.

**a. Wilson's disease:**

Wilson's disease, an autosomal recessive disorder with a prevalence of 1 in 30,000 (as reported from USA), is characterised by defect in copper metabolism and excretion resulting in copper deposition in the liver and several other extra-hepatic tissues, generally manifests in the first two decades of life [13].

Kayser-Fleischer (KF) ring (Fig. 1), a bilateral golden brown/yellow/bright green/ruby coloured ring located in the peripheral cornea, beginning at Schwalbe's line and extending less 5 mm onto the cornea, produced as a result of excess circulating copper deposition in Descemet's membrane, is a pointer of Wilson's disease [14,15]. It appears superiorly first, then inferiorly and later becomes circumferential [15]. It is not pathognomonic of Wilson's disease as similar pigmented peripheral corneal ring have been observed in severe jaundice, primary biliary cirrhosis and non-Wilsonian chronic active hepatitis [16, 17].

**Fig. 1: A 6 years old child with bilateral brown coloured circumferential KF ring visible with naked eye**

**b. Alagille Syndrome:**

Alagille syndrome, an autosomal dominant condition with paucity of interlobular bile ducts, is the result of mutations in the human Jagged 1 gene on chromosome 20p12 [18]. The patients have a distinctive facial appearance (prominent forehead, deep-set eyes, hypertelorism, straight nose, small pointed chin etc.) [19]. Posterior embryotoxon is found in more than 80% cases. 10% of general population also have this ocular sign implying a jaundiced infant with posterior embryotoxon does not always indicate Alagille syndrome and it is prudent not to overlook treatable extra hepatic biliary atresia in these situations [8]. Other common ocular abnormalities of Alagille syndrome are microcornea, iris anomalies, diffuse hypopigmentation of fundus, retinal pigment granularity and optic disc anomalies [20]. Optic disc drusen is a useful pointer in diagnosing this condition [21].

**c. Syndromes with Hepatomegaly and central corneal opacification:**

Mucopolysaccharidoses and mucolipidoses, inherited lysosomal enzyme deficiencies, are characterised by hepatosplenomegaly, intellectual disability, skeletal dysplasia, coarse skin and ocular changes, mostly corneal clouding (Fig. 2). The prevalence of clinical corneal clouding depends on the type of storage disease, the age of

**Fig. 2: A 4 years old child with mucopolysaccharidosis with corneal clouding**

the patient and the method of examination used. Flashlight or ophthalmoscope examination may underdiagnose it making a slit lamp examination mandatory in all suspected cases [1].

Severe corneal clouding within 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) [22,23]. Corneal clouding is less frequent in the other mucopolysaccharidoses. Clouding is seen in about 10% of cases of Morquio's syndrome [MPS IV], and rarely in Sanfillipo syndrome (MPS III) [24].

Corneal clouding is found in all type IV mucolipidosis cases since infancy and all type III mucolipidosis cases by age ten [25]. Mild corneal clouding is seen in 40% cases of type II mucolipidosis and in less than 20% type I mucolipidosis and GM-1 gangliosidosis [26, 27, and 28]. The ultimate visual outcome depends upon presence of simultaneous retinopathy, optic nerve disease, cataract or glaucoma as well as recurrence of corneal clouding in the corneal graft [24].

**E. Uveal Involvement:**

**a. Glaucoma:**

It is seen in mucopolysaccharidoses. Acute and chronic angle closure glaucoma has been described in Marotreaux Lamy (VI) and Scheie's (I-S) syndromes [29, 30]. Open angle glaucoma was reported in Maroteaux Lamy (VI) and Hurler's (I-H) syndromes [29, 31]. One case report of open angle in Hurler's syndrome demonstrated normalisation of intraocular pressure following bone marrow transplant [31].

**b. Uveitis :**

Uveitis has been reported in autoimmune hepatitis and leptospirosis. Even a case report suggested uveitis as the presenting feature of autoimmune hepatitis [32].

**F. Lens: Cataracts in Children with Hepatic Disorders:**

Liver disease with cataract formation (Fig. 3) is a feature of galactosemia, Zellweger syndrome and cerebrotendinous xanthomatosis.

**Fig. 3: Bilateral mature cataract seen in a child with galactosemia**

**a. Galactosemia:**

Classical galactosemia, an autosomal recessive defect of galactose metabolism due to a deficiency of the enzyme galactose-1-phosphate uridyl transferase/galactokinase/isomerise, is characterised by reduction of galactose by aldose reductase to galactitol. Polyol accumulation causes cataract formation due to increased intracellular fluid causing lens swelling, increased membrane permeability and electrolyte abnormalities [33].

**b. Zellweger syndrome:**

Disorders of peroxisomal malfunction include Zellweger syndrome and neonatal adreno-leukodystrophy [34, 35]. Zellweger's cerebro-hepato-renal syndrome is a lethal autosomal recessive neonatal peroxisomal disorder related to neonatal adrenoleukodystrophy and neonatal Refsum disease [36]. Epicanthic folds, corneal clouding, cataract, glaucoma, nystagmus and retinopathy mimicking retinitis pigmentosa are pointers of this condition. Recent works have shown that retinopathy is relatively consistent stigmata of Zellweger syndrome [37].

**c. Neonatal adrenoleukodystrophy:**

Affected infants have abnormal facies, hypotonia, hepatomegaly and pigmentary retinopathy. Optic atrophy and cataract may also be present. 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]. A characteristic “leopard spot” fundal appearance is very much suggestive of this disorder [39].

**d. Autosomal dominant neonatal jaundice syndrome:**

Heterochromia, corectopia, myopia, micro-phthalmos, cataracts and dyschromatopsia are frequently seen in autosomal dominant congenital haemolytic jaundice [40].

**e. Cerebrotendinous Xanthomatosis:**

This rare autosomal recessive condition is characterised by defect in bile acid synthesis due to mitochondrial sterol 27-hydroxylase deficiency. The clinical spectrum of this disease consists of tendon xanthomas, juvenile cataracts, neurological abnormalities and premature atherosclerosis. The earliest presentation of cerebrotendinous xantho-matosis may be bilateral juvenile cataracts with

chronic diarrheoa [41]. Optic neuropathy has also been reported [41]. Diagnostic confirmation is done by elevated plasma cholestanol concentrations.

**f. Drug induced cataract following hepatic transplantation:**

Following liver transplantation there is need of prolonged immunosuppression and the most common agent used for this purpose is corticosteroid. This might lead to features of steroid toxicity among which posterior subcapsular cataract is a prominent one.

**G. Retina – The "Often Missed One":**

Many metabolic disorders affecting liver affect the retina also. Changes in Zellweger syndrome and neonatal adrenoleukodystrophy have already been discussed.

**a. Pigmentary Retinopathy: Mucopolysaccharidoses**

Most systemic mucopolysaccharidoses affect retina to some extent. Retinal pigmentary changes morphologically identical to those of other retinitis pigmentosa syndromes are seen in majority of cases of Hurler's syndrome (I-H), Scheie's (I-S), Hunter's (II) and Sanfillipo's (III) syndrome; But it is not a feature of Morquio's (IV) or Maroteaux Lamy syndromes [24]. Electroretinographic testing in these patients appears most suggestive of rod-cone degeneration [42].

**Pigmentary Retinopathy: Abetalipoproteinemia**

It is an autosomal recessive defect of hepatic beta-lipoprotein that presents in small children as chronic malabsorption, progressive ataxia, cardiac abnormalities and pigmentary retinopathy. It is crucial to detect it early as the retinopathy can be arrested by vitamin A and E supplements [43]. Angioid streaks with secondary subretinal neovascular membrane formation have also been described in abetalepoproteinemia [44].

**b. Perimacular Retinal Deposits: Sphingolipidoses**

Sphingolipidoses are rare goups of autosomal recessive lysosomal enzyme defects. There are at least ten sphingolipidoses variants but only three can affect both liver and eye: Niemann pick disease, acute neuronopathic Gaucher's disease and generalised gangliosidosis.

- **Niemann Pick Disease:**

It is a heterogenous group of diseases in which sphingomyelin is deposited in reticuloendothelial cells, central nervous system and many other organs. Hepatosplenomegaly, icterus, epilepsy, intellectual disability, delayed motor milestones, deafness, extrapyramidal movement disorders etc. are seen in this condition. In patients with classical Niemann Pick disease, 20%-60% have "cherry red spots" (Fig. 4) in the macula [45]. Optic atrophy is often a long term sequelae [46]. Subtle corneal and lens opacities have also been described [46].

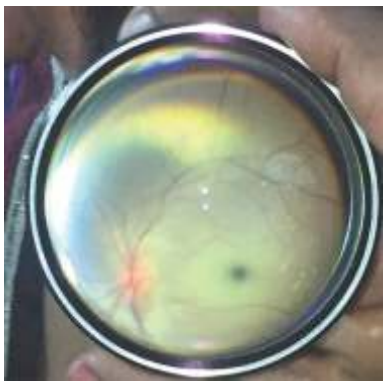

**Fig. 4: Indirect ophthalmoscopy examination showing cherry red spot in a patient with Tay Sachs disease**

- **Gaucher's disease:**

This disorder is characterised by glucocerebroside deposition in liver, spleen, bone marrow and to some extent, neural tissues. Macular cherry red spots are frequently seen in acute neuropathic

Gaucher's disease (type II) – the most severe form. Retinal vascular disease has also been reported in Gaucher's disease [47].

- **Generalised Gangliosidosis:**

It is a sphingolipidosis variant in which ganglioside is deposited in the central nervous system. This condition is very similar to Hurler's syndrome (mucopolysaccharidosis I-H) in presentation i.e hepatosplenomegaly, intellectual disability, hypotonia and skeletal dysplasia. Diagnosis is made by demonstration of beta-galactosidase deficiency.

Patients with generalised gangliosidosis do not usually have corneal clouding (as do patients with mucopolysaccharidosis type I-H), and they frequently have a cherry red macular spot (unlike mucopolysaccharidosis type I-H) [4].

**Perimacular Retinal Deposits : Glycogen Storage Disease :**

There are at least eight different types of Glycogen Storage Disease (GSD). Only GSD type I /von Gierke's disease has ocular signs. Multiple bilateral perimacular retinal deposits were described in 60% of cases in one short series [48].

**About "cherry red spots":**

This term describes the ophthalmoscopic finding of the retina in neurometabolic disorders such as Tay-Sach's disease, as described by Warren Tay [49]. This fundal appearance also accompanies other neuronal lipid storage disorders, including Sandhoff's disease (GM 2 type II), Gangliosidosis (GM 1 type I and II), Farber's disease, mucolipidosis type III, and Metachromatic Leukodystrophy (MLD) [50]. It often follows central retinal artery occlusion, which shows a pale retina as a result of reduced blood flow. The colour of the fovea, however, results from the pigment epithelium and choroid. The absence of ganglion cells at the fovea gives rise to red spot surrounded by white diseased cells. Thus, the "cherry red spot" could appropriately be renamed the "perifoveal white patch".

**H. Antiphospholipid syndrome secondary to Hepatitis C: Ocular signs:**

Hepatitis C is one of the causes of antiphospholipid syndrome which may affect liver and eyes both. Ocular signs of this condition are: in the anterior segment: conjunctival vessel abnormalities, episcleritis, limbal keratitis, and filamentary keratitis. Posterior segment findings may include vitritis, retinal detachment, retinal vein occlusions, and retinal haemorrhages [1].

**I. Involvement of the Nerves supplying the Eye:**

Liver disease in children can affect the sensory or motor nerve supply of eye.

**Optic nerve involvement:**

MLD, a deficiency state of lysosomal enzyme arylsulphatase A, shows storage of metachromatic complex lipids in the Retinal Ganglion Cells (RGC) and in the optic nerve, leading to optic atrophy [51]. Optic atrophy has been described in all forms of mucopolysaccharidosis except the mild phenotype of Maroteaux Lamy [24]. It may be secondary to pigmentary retinopathy or consecutive to chronic papilloedema due to hydrocephalus [1]. Profound optic atrophy is usually present in Zellweger syndrome and neonatal adrenoleukodystrophy [35].

**Conclusion:**

If we consider all the diseases involving both liver and eyes, ocular signs and symptoms are often subtle except for clinical hyperbilirubinemia and severe corneal pathologies. Posterior segment findings are often missed. Infectious, metabolic, genetic, syndromic causes of liver dysfunction

with ophthalmological findings are to be kept in mind while dealing with an infant or a child with hepatobiliary dysfunction or hepatomegaly or hepatosplenomegaly. These disorders claim that a paediatrician and an ophthalmologist, instead of working alone, should therefore discuss their clinical findings and share their opinions regarding the possible diagnosis as early identification and treatment of correctible conditions as well as palliative measures and genetic counselling in case of untreatable disorders are extremely important for the families of the affected patient.

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